Neuropsychological Outcomes in Children Treated with Surgery for Brain Tumour

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Declaration

This thesis is my original work and does not incorporate any material previously submitted for a degree at any University or other educational institution without acknowledgment. To the best of my knowledge it does not contain any material previously published or written by another person except where due reference is made in the text.

This research project was formally approved by the Victoria University Psychology Department Ethics Committee and the Royal Children's Hospital Ethics in Human Research Committee. These ethical guidelines have been adhered to in the production of this report.

Mia Rowe, August 2004

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Abstract

Brain tumours are the second most common form of cancer in children. The majority of children treated for brain tumour survive, but they can experience a number of neurological and neuropsychological sequelae. A range of tumour, treatment, and psychosocial factors cumulatively and interactively determine long-term sequelae in these children. There is a paucity of research on neuropsychological outcomes, and the determinants of these outcomes, in children treated for brain tumour with surgery-only. This is because they represent a minority of children treated for brain tumour. Research has focused on children treated with radiotherapy and chemotherapy where the effects can be devastating. The present study examined neuropsychological outcome in children treated with surgery-only to identify risk factors for poor outcome, to determine sequelae according to tumour location, and to explore the process of recovery over a one-year period. Twenty-two children, 12 with Posterior Fossa tumours (PF) and 10 with Supratentorial tumours (ST) were assessed one-year post-surgery. A subset of 16 of these children (PF = 10, ST = 6) were assessed again two-years post-surgery. The results of this study indicated that for this sample the presence of hydrocephalus was the best predictor of poor outcome while the relationship of outcome to tumour volume and overall severity of cumulative neurological events was less clear. The PF group generally performed more poorly than the ST group on neuropsychological outcome measures at one-year. Both groups had a mixed pattern of change from one-year to two-years, with evidence of decline as well as improvement on individual neuropsychological measures. At both time points these groups demonstrated specific areas of deficit relative to the normal population. Overall, the PF group were impaired on measures of sustained attention, visuo-motor skills, and behavioural outcome. Only social competence was impaired in the ST group. Both groups tended to function well on measures of attentional control, verbal fluency, verbal learning and memory, and academic achievement. These findings indicate that radiotherapy and chemotherapy are not the only causes of morbidity in children treated for brain tumours. Children treated with surgery-only can experience neuropsychological problems which are determined by a range of factors including tumour location and neurological complications.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter One – Introduction

1.1 Brain Tumours in Childhood

Brain tumours are the second most common type of cancer in childhood following leukaemia (Australian Institute of Health and Welfare (AIHW) & Australian Association of Cancer Registries (AACR), 2002). In children solid tumours most frequently develop in the central nervous system and are the leading cause of death due to cancer (AIHW & AACR, 2002). The survival rate has improved dramatically over the last three decades due to advances in treatment, and has continued to improve over recent years (Rosenfeld & Ashley, 2000; Smith & Gloeckler Ries, 2002). Over half of all children diagnosed with brain tumour survive for at least five years after diagnosis, after this length of time tumour recurrence is much less likely (American Brain Tumor Association, 1998). For instance, a 10 year follow-up study of children diagnosed with brain tumours found that 84% of recurrences occurred within 3 years of initial diagnosis and that 100% of recurrences occurred within 4.5 years (Hoppe-Hirsch, Lellouch-Tubiana, Sainte-Rose, Pierre-Kahn, & Hirsch, 1990).

The survival rate varies according to tumour type, and the 4 year survival rate for low-grade tumours is as high as 90% (Gajjar et al., 1997). With improvements in the survival rate greater attention has been given to the morbidity of surviving children. Brain tumours can cause a range of sequelae by virtue of the impact of their growth on healthy tissue and surrounding structures. The variation in tumour type, location, and growth rate are some of the primary factors that determine the type of symptoms experienced. Apart from the range of neurological effects, children treated for brain tumours often experience neuropsychological changes including cognitive, academic, behavioural, and emotional difficulties. Research has also highlighted the impact of particular tumour treatments on long-term neuropsychological outcome. Advances in our understanding of the effect of these variables on outcome led to changes in treatment protocols in an effort to maximise survival with minimal sequelae.

1.2 Epidemiology & Aetiology

In Australia brain tumours are the second most common type of cancer in children under fifteen (AIHW & AACR, 2002). Childhood brain tumours are nevertheless a low-incidence condition. The incidence of brain tumours in Australian children between the ages of 5 and 14 is about 2 per 100,000. This rate is slightly higher for the age range 0 to 4 years, at 3.6 per 100,000, and currently stands at 2.3 per 100,000 for people aged 15 to 19 years (AIHW & AACR, 2002). At the Royal Children's Hospital (RCH), Melbourne, Australia, about 50 children were diagnosed and treated for brain tumours in the year 2000. In Australian children tumours of the brain and central nervous system are the most common cause of death due to cancer, and the mortality rate is 0.8 per 100,000 for children aged 0 to 19 years (AIHW & AACR, 2002).

Brain tumours occur slightly more frequently in males than females across the lifespan. In 2000, males comprised 55% of all children in the State of Victoria diagnosed with brain and central nervous system tumours (Giles & Thursfield, 2002). Brain tumours are more frequent in people under 20 years and over 70 years, although they occur across all age groups (American Brain Tumor Association, 1998; Strother et al., 2002). The types of brain tumours that usually present in childhood are different in nature to those that typically present in adulthood in terms of malignancy, pathology, and location.

For the most part, the aetiology of brain tumours is unknown. There is some evidence that brain tumours are the result of an alteration in genetic structure, caused by environmental and/or hereditary factors (Bondy, Wiencke, Wrensch, & Kyritsis, 1994). Paediatric brain tumours can result from familial diseases such as neurofibromatosis (type 1 and 2) and tuberous sclerosis. However, these syndromes account for less than 10% of paediatric brain tumours (Strother et al., 2002). The development of brain tumours has been associated with exposure to radiation (including radiation therapy used to treat cancer) and certain chemical agents (American Brain Tumor Association, 1998).

1.3 Brain Tumour Classification

A brain tumour can be defined as a large group of excess cells within the brain, which form a mass and serve no function. The cells are often abnormal and fast growing. They can invade the surrounding healthy tissue, disrupting the function of healthy structures, and sometimes spread to other parts of the central nervous system. Brain tumours can be classified according to their malignancy, location, and pathology.

1.3.1 Malignancy

Tumours that arise from within the brain are referred to as primary tumours, because the brain is the primary site of the tumour. Brain tumours can also originate from cancer cells arising elsewhere in the body, and these types of tumours are known as secondary or metastatic tumours. Primary tumours vary in their degree of harmfulness; they can be benign or malignant. Benign tumours are the most harmless tumours and are not considered a cancer. The margins of a benign tumour are well defined, they are very slow growing, and they seldom spread elsewhere. Despite being slow growing the expansion of benign tumours can be harmful or life-threatening because of their proximity to important brain structures and increased intracranial pressure.

Malignant (cancerous) brain tumours are more invasive than benign tumours. They lack clearly defined borders thereby invading surrounding tissue, they tend to grow rapidly, and may spread to other parts of the brain or spine – though they rarely spread elsewhere within the body. Metastatic brain tumours are malignant by definition because they grow from cancer cells that have spread (metastasised) from cancer elsewhere in the body and invaded healthy brain tissue.

A standard clinical practice is to grade the degree of tumour malignancy from I to IV (American Brain Tumor Association, 1998). A grade I tumour is the most benign and usually only requires treatment with surgical resection. As the classification moves from grade II to IV the tumour cells become increasingly abnormal in

appearance, are more invasive, grow more rapidly, and have a greater tendency to recur. Therefore, grade IV is the most malignant grade of tumour and the most life-threatening (American Brain Tumor Association, 1998).

This thesis is exclusively concerned with primary brain tumours, as paediatric brain tumours are predominantly primary and not metastatic in origin. Therefore the use of the term brain tumour in the ensuing discussion refers to primary brain tumours only.

1.3.2 Location

Brain tumours develop in different areas within the brain, and sequelae can vary depending on the location of the tumour. When differentiating tumours according to their location within the brain, an elementary distinction is made between tumours that arise above the tentorium (supratentorial tumours) and those that arise below the tentorium (infratentorial tumours). A membrane known as the meninges surrounds the brain and spinal cord. The tentorium is a segment of the meninges that lies between the cerebral hemispheres and the cerebellum and separates them (See Figure 1.1). Therefore the supratentorium is defined as the area above the tentorium. This area is also referred to as the cerebrum, and includes the cerebral hemispheres, diencephalon, lateral ventricles, and the third ventricle (See Figure 1.1). The infratentorium is defined as the area below the tentorium. This area is also referred to as the posterior fossa because it is bounded inferiorly by the posterior fossa of the cranium. The posterior fossa contains the cerebellum, brainstem, and fourth ventricle (See Figure 1.1).

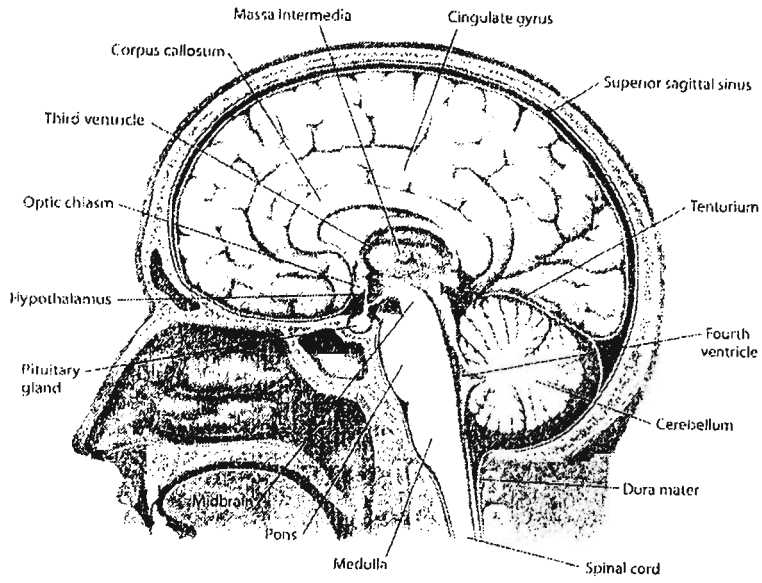

Figure 1.1 Midsagittal section of the brain and brainstem (from Gazzaniga, Ivry, & Mangun, 1998, p. 63)

1.3.3 Pathologic Classification

Brain tumours are classified by their pathologic characteristics in addition to their anatomical location. There are a range of pathologic classification systems developed for tumours of the nervous system based on the morphology and histologic cell-of-origin (Strother et al., 2002). Where tumours are composed of heterogenous cells, these classification schemes pertain to the predominant cell type of the tumour. The World Health Organisation (WHO) developed one of the more commonly used classification schemes in use, which has undergone two major revisions since it was first published in 1979. The first revision was published in 1993 followed by the most recent revision published in 2000 (Kleihues et al., 2002). The main categories of tumours in this classification system are derived on the basis of morphology, and include tumours such as astrocytic tumours, ependymal tumours, and tumours of the meninges. Tumours within the WHO categories vary in terms of their grade and location.

In contrast to brain tumours of adulthood, the majority of paediatric brain tumours develop in the posterior fossa, they are mainly primary tumours, and are more likely

to be of low grade (Lanzkowsky, 2000; Plowman & Brada, 1996). About 70-80% of childhood brain tumours are gliomas, meaning they originate from glial cells (Lanzkowsky, 2000). Astrocytomas and ependymomas are two types of gliomas common in children.

Astrocytomas arise from astrocyte cells (found in glial tissue) and range in malignancy from Grade I (Pilocytic Astrocytoma) to Grade IV (Glioblastoma Multiforme). In childhood astrocytomas predominantly develop in the supratentorium and represent 25-40% of all paediatric brain tumours (Strother et al., 2002). A further 10-20% of paediatric brain tumours are cerebellar astrocytomas (Strother et al., 2002). Cerebellar astrocytomas are typically Grade I cystic tumours that are easily resected (American Brain Tumor Association, 1998). The survival rate for low grade astrocytomas ranges from 69-100% following complete resection (Strother et al., 2002).

Ependymomas arise from ependymal cells that line the ventricles and central canal of the spinal cord, and represent 5-10% of paediatric brain tumours (Strother et al., 2002). Ependymomas vary in malignancy and findings suggest that half (Lanzkowsky, 2000) to two-thirds (Plowman & Brada, 1996; Strother et al., 2002) of paediatric ependymomas develop in the posterior fossa. Like ependymomas, choroid plexus tumours also develop in the ventricles, but are less common than ependymomas in children. They can be benign (choroid plexus papilloma) or malignant (choroid plexus carcinoma).

Medulloblastomas are the most common malignant brain tumour in childhood and represent about 20-30% of all paediatric brain tumours (Lanzkowsky, 2000). Medulloblastoma is the term for a *primitive neuroectodermal tumour* (PNET) that arises in the posterior fossa. PNETs may develop in the supratentorium but are relatively rare in children (Strother et al., 2002). Medulloblastomas grow rapidly, invade surrounding tissue, and often spread outside the primary tumour bed (Strother et al., 2002).

Brain stem gliomas account for a further 10-20% of paediatric brain tumours (Strother et al., 2002) and are the third most common tumour to develop in the

posterior fossa after medulloblastomas and astrocytomas. The majority of brain stem gliomas are highly malignant and have a poor prognosis (Strother et al., 2002).

There are several other types of less common paediatric brain tumours, but the final one of note here is the meningioma. Meningiomas develop in the meninges that surround the brain and spinal cord and they tend to be benign (American Brain Tumor Association, 1998). They represent up to 6% of brain tumours in children (Lanzkowsky, 2000).

1.4 Clinical Presentation: Common Symptoms

Symptoms of brain tumours may develop slowly, with gradual changes in functioning going unnoticed, resulting in a delay between the onset of symptoms and the diagnosis of brain tumour. This is often the case for midline tumours that tend to lack focal neurological signs (Rosenfeld & Ashley, 2000). The clinical presentation at diagnosis is variable and the tumour may cause focal neurologic signs or more general symptoms that are not localising. Symptoms that are often observed include: signs of increased intracranial pressure (IICP), seizures, motor and sensory disturbance, cognitive and behavioural change, endocrine and growth disturbance, and various other focal symptoms (Rosenfeld & Ashley, 2000). Focal neurological signs tend to present earlier than signs of IICP in the case of supratentorial tumours, whereas the reverse is more often true in the case of posterior fossa tumours (Bannister, 1992).

Some common non-localising symptoms such as headaches, nausea, vomiting, lethargy, papilloedema, visual disturbances, and altered mental state are caused by IICP (Bannister, 1992). IICP can result from growth of the tumour, hydrocephalus, or cerebral oedema. Brain tumour growth will eventually cause IICP because the skull can not expand to accommodate the expansion of the tumour. However, in infants the head may expand and the sutures can split to better accommodate this growth (Rosenfeld & Ashley, 2000).

IICP is also caused by hydrocephalus. Hydrocephalus is a disruption in the production and absorption of the fluid which normally flows in and around the brain (cerebrospinal fluid) resulting in an excess of fluid (Anderson, Northam, Hendy, & Wrennall, 2001). This disruption can occur when the flow of cerebrospinal fluid is obstructed by the growth of the tumour in or near a ventricle (obstructive hydrocephalus). Hydrocephalus may also occur as a result of the accumulation of cerebrospinal fluid because of the tumours effect on the production or absorption of cerebrospinal fluid (communicating hydrocephalus).

Finally, IICP may result from cerebral oedema, which is the accumulation of excess fluid in the inter-cellular spaces in the tissue surrounding the tumour. The excess fluid results in swelling of the brain tissue, which in turn increases pressure in the skull. If severe enough IICP can lead to herniation. Herniation occurs when pressure causes the displacement of brain tissue into a different compartment within the skull (Simon, Aminoff, & Greenberg, 1999). For example, supratentorial brain tissue may be displaced inferiorly through the gap in the tentorium and into the posterior fossa. Cerebellar tissue can herniate into the foramen magnum (the hole at the base of the skull) toward the brainstem. If these types of herniation remain untreated they can lead to coma and death by causing compression of the brainstem.

Focal neurological symptoms (that are dependent on the location of the tumour) typically include some form of motor or sensory disturbance. Supratentorial tumours may manifest as seizures, although this occurs more commonly in adults (Strother et al., 2002). Such tumours may also cause visual disturbance, hemiparesis, hemisensory loss, cognitive deficits, and personality change. Typical focal signs of a cerebellar tumour include ataxia, incoordination, poor motor skills, and cranial neuropathy.

When a brain tumour is suspected it is common clinical practice at the RCH to perform a magnetic resonance image (MRI) of the brain to determine the anatomic location, the extent of the tumour, and possibly the type and grade of the tumour (Rosenfeld & Ashley, 2000). It is also useful for detecting the presence of brain and spinal metastases.

1.5 Treatment of Brain Tumours

The aim of treatment is to reduce the morbidity and mortality associated with brain tumours. The standard treatment for brain tumours in children includes surgical resection (removal), radiotherapy, and chemotherapy, and they are often used in combination.

1.5.1 Surgery

Most children with brain tumours require neurosurgery. The primary reason for neurosurgery is to resect as much of the tumour as possible. Surgery is also performed to take a biopsy of the tumour in order to establish the histologic diagnosis. This is necessary when the tumour is inoperable but the diagnosis needs to be established in order to proceed with other therapies. Some tumours are inoperable because their location deep within the brain makes the risks associated with neurosurgery too great. Tumour characteristics such as size, number, and degree of infiltration may also render neurosurgery too difficult or risky. Surgery does not improve the prognosis of children with certain tumours, such as infiltrative brain stem gliomas, and because the MRI is usually diagnostic surgical biopsy is not always required (Strother et al., 2002).

The procedure used to resect a tumour is a craniotomy, whereby an incision is made in the scalp, a piece of skull over the tumour is removed, and then the meninges are opened to allow access to the tumour (American Brain Tumor Association, 1998). During a stereotactic craniotomy the neurosurgeon is guided by three-dimensional images (stereotaxy) created using computers (American Brain Tumor Association, 1998). Stereotactic surgery may be performed with a head frame to hold the head in place, or without one (frameless stereotaxy).

Surgical resection is performed for the majority of paediatric brain tumours, with an attempt to remove as much tumour as possible. The extent of the resection is dependent on the amount of tissue that can be safely removed. A complete surgical resection is often achieved for tumours with well defined borders (Strother et al.,

2002). Complete resection (sometimes with insertion of a shunt) is usually the only treatment required for benign or low grade tumours. Incomplete resections are performed when the boundaries of the tumour are imperceptible, or when complete removal would be too detrimental to surrounding brain tissue (such as in the brain stem). Treatment of higher grade tumours and those that are not completely resected almost always involves follow up radiotherapy and/or chemotherapy.

1.5.2 Radiotherapy

Radiotherapy is usually used when a tumour is inoperable, after an incomplete resection, or when a complete resection is achieved but the tumour is of high grade and likely to grow back. Therefore it is primarily used in the treatment of malignant tumours. Radiotherapy affects both normal cells and tumour cells by interrupting the cell cycle. Irradiated cells are unable to divide and reproduce, but tumour cells are particularly vulnerable because normal cells are more capable of self-repair (American Brain Tumor Association, 1998).

The most common form of radiotherapy used for paediatric brain tumours is a procedure where external beams of radiation are directed at the tumour using a linear accelerator (a device that creates ionising radiation). These beams may be directed at the whole central nervous system (whole-brain radiotherapy), or more often are directed to conform to the tumour's shape (conformal radiotherapy). Radiotherapy is usually delivered in fractions (doses) for five days a week for six weeks (American Brain Tumor Association, 1998). Radiotherapy usually begins 1-2 weeks after surgery unless post-operative complications occur.

Radiotherapy is known to have detrimental effects, particularly on the developing brain. Attempts to reduce the harmful effects of radiotherapy have led to the use of conformal radiotherapy rather than whole brain irradiation to spare healthy brain tissue from unnecessary radiation. The deleterious effects of radiotherapy are even greater for children who undergo it at a very young age while the brain is still rapidly developing (Rosenfeld & Ashley, 2000). The rate of brain growth is most rapid under the age of three and development slows further after six years of age (Strother

et al., 2002). If very young children require radiotherapy the total dose is reduced, and the need for radiotherapy is often delayed with the use of chemotherapy and second surgery.

1.5.3 Chemotherapy

Chemotherapeutic agents are drugs that kill actively dividing cells. Tumours respond differently to chemotherapy depending on their histologic type, and some do not respond to chemotherapy at all (Rosenfeld & Ashley, 2000). Chemotherapeutic drugs may be delivered orally but are mostly delivered by injection. The injection routes may be intravenous, intra-arterial, intrathecal (into the central lumen of the spinal cord), and intraventricular (into the ventricles) amongst other methods (American Brain Tumor Association, 1998). Chemotherapy is generally given in courses with up to 8 weeks between each course, which means treatment can be ongoing over many months (Lanzkowsky, 2000). Chemotherapy has a variety of side-effects due to the affect of the agents on normal cells (such as damage to bone marrow). Recovery is often assisted with a bone marrow transplant or stem cell transplant. Chemotherapy is rarely used by itself, although this may be indicated in the case of disseminated tumours because of the difficulty avoiding damage to healthy tissue using surgery or radiotherapy. Chemotherapy alone may also be indicated in the case of optic nerve gliomas because surgery and radiotherapy have a detrimental effect on vision. Chemotherapy is also used when benign tumours regrow.

1.6 Complications of Brain Tumours and their Treatment

As mentioned above, brain tumours can cause a variety of neurological complications, some of which require specific treatment. For instance, IICP sometimes requires treatment in addition to tumour resection. If the IICP is caused by hydrocephalus it can be relieved by the insertion of a shunt or a third ventriculostomy. This requires surgery and can be done prior to, during, or after surgical resection of the tumour. A shunt is essentially a catheter to drain cerebro-spinal fluid into a body cavity where it is absorbed, the most common being a

ventriculo-peritoneal shunt. A third ventriculostomy is an opening made in the floor of the third ventricle to allow cerebro-spinal fluid to drain outside the brain for reabsorption.

The pressure caused by cerebral oedema can result from the tumour itself, or may be caused by surgery or radiotherapy. The standard treatment for cerebral oedema is corticosteroid treatment, such as dexamethasone (American Brain Tumor Association, 1998). Like oedema, seizures are a common symptom in children with brain tumours that result either from the brain tumour or surgical resection of the tumour. Antiepileptic drugs are prescribed depending on the type of seizure. If resection of the tumour relieves seizures medication is ceased.

Unfortunately successful treatment of brain tumours does not always relieve pre-operative symptoms of brain tumours and many survivors have to live with neurological, neuropsychological, and hormonal changes (Strother et al., 2002). Further, a variety of complications can occur peri-operatively or post-operatively that result in other sequelae. These include haemorrhage, infection, shunt malfunction, hypothalamic disturbance, hormonal problems, hemiparesis, and sensory impairment. Treatment ranges from further surgery or medication to rehabilitation from a range of health professionals.

A rare complication to occur following the removal of posterior fossa tumours in children is the phenomenon of mutism and dysarthria. Following surgery patients have a short interval of normal speech (1-2 days), followed by a period of mutism (1 day to 6 months), after which there is a severe dysarthria (1-3 months) which eventually resolves completely (Catsman-Berrevoets et al., 1999). The development of this complication is more likely following: hydrocephalus at presentation, medulloblastoma, tumours adjacent to the fourth ventricle, large tumour size, splitting of the entire inferior vermis, or post-operative oedema of the pontine tegmentum (Catsman-Berrevoets et al., 1999; Dailey, McKhann, & Berger, 1995; van Dongen, Catsman-Berrevoets, & van Mourik, 1994).

Chapter Two – Neuropsychological Outcomes After Tumour Treatment

2.1 Factors Affecting Outcome

Childhood brain tumours interrupt the maturation process of the developing brain and thereby interrupt normal brain function. Brain tumours and their treatment may disrupt developing functions as well as interfere with pre-existing functions, leaving many children with functional sequelae that persist across their lifetime. A large proportion of people that survive childhood brain tumour are left with some form of cognitive deficit on testing (Glauser & Packer, 1991). Estimates based on the literature reveal this proportion is as low as 40% and as high as 100% (Glauser & Packer, 1991). Neuropsychological sequelae include: intellectual deficits, language and visuo-spatial problems, attention, memory and learning difficulties, deficits of executive functioning, academic problems, and emotional and behavioural difficulties. Other tumour sequelae include a range of physical, sensory, and motor impairments, such as speech difficulties, fatigue, endocrine dysfunction, ataxia, hemiparesis, visual impairment, and hearing loss.

A range of risk factors for poor outcome have been identified and these factors compound over time to influence the long term neuropsychological outcome in children with brain tumours. These include tumour characteristics, treatment approach, medical complications, and demographic variables. Within the individual child the effects of the brain tumour itself cannot be isolated from the functional impact of these other variables, making it difficult to predict the type and severity of sequelae on the basis of brain tumour characteristics alone. Indeed, the literature has failed to reveal distinct neuropsychological profiles of paediatric brain tumour survivors because of the heterogeneity of the samples studied (Ris & Noll, 1994).

Tumour characteristics such as the location, histological diagnosis, degree of infiltration, rate of growth, and size are parameters that determine the impact a

tumour will have on healthy brain tissue, and therefore its effect on neuropsychological outcome. One of the main tumour variables known to influence neuropsychological sequelae is tumour location. It is widely understood that supratentorial tumours result in cognitive deficits of a different nature to posterior fossa tumours. The relationship between regions of the brain and their function is better understood for the supratentorium because the neuropsychological literature has traditionally focused on disorders and lesions of the cerebrum. For instance, at the most simplistic level it is well established that the left hemisphere is dominant for language functioning in most individuals, while the right hemisphere is predominantly involved in visuo-spatial processing. The neuropsychological function of different anatomical areas within the posterior fossa is not as well understood even at this basic level, although some brain tumour studies have attempted to address this question (Riva & Giorgi, 2000).

Treatment variables are the other major factor implicated in the compromise of cognitive function. Neurosurgery invariably damages healthy brain tissue, even though care is taken to choose the least harmful path to the tumour and avoid damage to critical areas of the brain. The literature that has examined outcome following radiation therapy has repeatedly indicated that this therapy results in significant neurocognitive sequelae (Copeland, deMoor, Moore, & Ater, 1999; Mulhern, Hancock, Fairclough, & Kun, 1992; Packer, Meadows, Rorke, Goldwein, & D'Angio, 1987), while the literature on chemotherapy reveals mixed findings. The outcome of surgical resection, radiotherapy, and chemotherapy will be discussed in more detail in the following section.

Medical complications and their treatment, as described in the previous section, have also received some attention in the literature. Hydrocephalus, seizures, meningitis, and hormone dysfunction are all known to have neuropsychological sequelae of their own, as these are all conditions that can occur independently of brain tumours (Anderson et al., 2001; Yeates, Ris, & Taylor, 2000). The literature on brain tumours and other childhood disorders indicates that demographic variables can also influence functional outcome. These variables include age at diagnosis, sex, familial factors (including family adjustment to illness and socio-economic status), and premorbid characteristics. Younger age at diagnosis has frequently been found to be an

indicator of poorer long-term outcome (for example see Anderson et al., 2001; Chapman et al., 1995; Dennis, Spiegler, Hetherington, & Greenberg, 1996). Nevertheless, a range of variables effect the long term neuropsychological outcome in children with brain tumours and often it is the interaction of these variables that best explains the resultant cognitive impairment (Carlson-Green, Morris, & Krawiecki, 1995).

2.2 Sequelae of Tumour Treatment

Brain tumours are predominantly treated by surgery, with adjuvant radiotherapy and/or chemotherapy for malignant tumours. The advent of radiotherapy in the treatment of brain tumours led to a significant improvement in survival rate. However, reduced mortality has resulted in a greater number of survivors who pose new treatment challenges due to their significant sequelae.

2.2.1 Radiotherapy

Early studies determined that a significant proportion of children treated with radiotherapy and chemotherapy were left with intellectual impairment, learning disabilities, or other cognitive deficits (Duffner, Cohen, & Thomas, 1983; Duffner, Cohen, Thomas, & Lansky, 1985; Ris & Noll, 1994). This has been confirmed by several other studies which revealed that cognitive outcome was significantly worse for those treated with radiotherapy than those treated without radiotherapy (Copeland et al., 1999; Lannering, Marky, Lundberg, & Olsson, 1990; Moore, Ater, & Copeland, 1992; Pfefferbaum-Levine et al., 1984; Riva, Pantaleoni, Milani, & Belani, 1989). Further, they discovered that these cognitive deficits become apparent some time after radiotherapy, and that cognitive functioning continued to deteriorate for up to 10 years after treatment (Hoppe-Hirsch et al., 1990; Packer et al., 1987).

The factors that appear most important in determining outcome after radiotherapy are young age at treatment and the radiotherapy technique. Several studies found that younger age at the time of radiotherapy was associated with poorer neuropsychological outcome (Chapman et al., 1995; Hoppe-Hirsch et al., 1990;

Moore et al., 1992; Mulhern et al., 1992). This has led to changes in treatment protocol whereby radiotherapy is avoided in very young children, or at the very least its administration is delayed in order to allow the immature brain to develop. Radiotherapy technique also has an impact on the severity of sequelae. Radiotherapy to the whole-brain results in more severe deficits and greater deterioration over time than radiotherapy restricted to a focal area, such as the posterior fossa (Hoppe-Hirsch et al., 1995; Mulhern et al., 1992). Therefore, the more of the brain that is irradiated the worse the long-term outcome is. Some argue that reducing the dose of radiotherapy benefits long-term outcome (Palmer et al., 2001) but a recent, large, prospective study has shown this to have no effect (Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001).

2.2.2 Chemotherapy and Surgery

Research on chemotherapy is not as prolific because its usefulness as a treatment has only been realised more recently. The literature on chemotherapy is also less conclusive with respect to its contribution to neuropsychological deficits. While some chemotherapeutic agents have not been consistently demonstrated to have effects on cognition, others have reasonably well established effects. In particular methotrexate has been frequently implicated as having a deleterious effect on cognition. Methotrexate, vincristine, and cis-platinum, amongst other chemotherapeutic drugs, can have both acute and long-term neurological and cognitive effects (Packer et al., 1987).

The effects of chemotherapy are dependent on various factors, including: dose, method of administration, and adjuvant radiotherapy (Packer et al., 1987). Some studies have found that methotrexate used in conjunction with radiotherapy has a radiopotentiating effect, causing greater damage to the central nervous system and hence resulting in more significant neuropsychological deficits than radiotherapy alone (Glauser & Packer, 1991; Ris & Noll, 1994). While a number of studies have implicated methotrexate as a cause of cognitive deficits others have not. A large and well-controlled study found no effect of chemotherapy on cognition when almost half of the chemotherapy sample had received intrathecal methotrexate (Anderson,

Smibert, Ekert, & Godber, 1994). This study was based on a sample of children with acute lymphoblastic leukaemia who did not have the confounding effects of central nervous system damage caused by brain tumours and surgery. A large prospective longitudinal study that followed a sample of paediatric cancer patients for up to 11 years post-diagnosis found no deleterious effects of chemotherapy on cognition (Copeland, Moore, Francis, Jaffe, & Culbert, 1996). They compared patients receiving intrathecal chemotherapy with patients not receiving central nervous system treatments on a comprehensive range of neuropsychological measures. This study also included children who did not undergo cranial radiotherapy and was therefore free of the possible confounding effects. Further, there have been other recent studies that also found chemotherapy had no impact on cognitive, academic, or behavioural functioning, whether used in conjunction with radiotherapy (Dennis et al., 1996; Palmer et al., 2001) or only in conjunction with surgery (Copeland et al., 1999).

The number of treatment modalities used in the treatment of brain tumour is a factor that affects outcome (Carlson-Green et al., 1995). Neuropsychological outcome is worse in those treated with multiple therapies, this is most probably because multiple therapy samples are likely to include more patients treated with radiotherapy. Notwithstanding, tumour size, histological diagnosis, malignancy, and medical complications also confound the neurocognitive effect of treatment.

Children treated with surgery alone usually have a better neuropsychological outcome than those treated with radiotherapy. The remaining question is whether these children differ from normal children? Most of the literature examining this question does not focus on surgery alone, but instead makes comparisons between groups that have received radiotherapy and those that have not. Therefore, children in the non-radiotherapy groups have often received chemotherapy in addition to surgery. Several of these studies show that these non-radiotherapy children differ from healthy children in at least some cognitive and affective domains (Copeland et al., 1999; Levisohn, Cronin-Golomb, & Schmahmann, 2000; Moore et al., 1992). Copeland et al. (1999) found that scores may decline over time even without receiving radiotherapy. The few studies that have focused on surgery only, have revealed a range of cognitive, behavioural, and emotional impairments in these

children (Beebe, Ris, & Holmes, 2001; Karatekin, Lazareff, & Asarnow, 2000; Riva & Giorgi, 2000; Riva et al., 1989). The way in which children treated with surgery only differ from normal children and the factors that determine these differences will be discussed in the ensuing sections.

2.2.3 General Surgery-Only Outcomes

Much of the brain tumour literature does not make the distinction between supratentorial and posterior fossa tumours and instead neuropsychological sequelae are examined for the group as a whole. This is probably due to difficulty obtaining large samples and an interest in exploring functioning relative to the normal population.

Neuropsychological outcome is generally better for children treated with surgery-only (Lannering et al., 1990; Moore et al., 1992), although there are always exceptions to this finding (Dennis et al., 1992). Moore et al. (1992) found that their surgery-only group performed better than those that received radiotherapy on every measure, however this difference was only significant for three areas.

Surgery appears to improve most areas of cognitive functioning compared to pre-surgical performance (Bordeaux et al., 1988). Pre-surgical functioning is probably affected by the neurological deficits that precipitate diagnosis. Overall surgery-only children tend to perform relatively normally in most areas. Moore et al. (1992) only found differences between these children and normative data on visuo-spatial skills. Similarly Bordeaux et al. (1988) found that psychomotor speed, fine motor speed, and visuo-motor construction were impaired, while performance was normal in other areas. Carpentieri et al. (2003) found evidence of impairment in a greater number of areas: PIQ, language, visuo-spatial abilities, motor skills, and memory. In summary, these studies found that surgery-only patients were comparable to normative data in terms of IQ, VIQ, academic achievement and executive functioning, whereas the areas of greatest difficulty were mainly within the visuo-spatial and motor domains.

Changes in behaviour and adjustment following surgery for brain tumour may be amongst the most significant sequelae these children experience. Meyer and Kieran (2002) found that 56% of children presented with significant psychological adjustment problems, and that 38% had sufficient symptoms to warrant a diagnosis in two or more domains of psychological adjustment. Rates of depression, anxiety, disruptive behaviour disorder, and academic problems were much higher for these children than in the general population. The literature including children treated with adjuvant therapy often reports elevated levels of emotional, behavioural, or social dysfunction (Carlson-Green et al., 1995; Lannering et al., 1990; Mulhern, Carpentieri, Shema, Stone, & Fairclough, 1993; Vannatta, Gartstein, Short, & Noll, 1998) and there is some evidence that these problems are not a result of treatment with radiotherapy (Vannatta et al., 1998).

2.3 Anatomy and Function of the Cerebellum

The cerebellum is located in the posterior cranial fossa and its appearance is much like a small cerebrum (Nolte, 1999). It lies over the brainstem at the level of the pons and forms the roof of the fourth ventricle. Relative to the other infratentorial structures it is a large structure that occupies a significant proportion of the posterior fossa. The cerebellum is uniform and systematic in structure. The cerebellum has two hemispheres divided by a longitudinal medial section known as the vermis. The area adjacent to the vermis is known as the intermediate (or paravermal) zone. It is considered a distinct area from the lateral hemispheres because it differs in terms of its connections and function. Each hemisphere is divided into the anterior and posterior lobe by the primary fissure. The flocculonodular lobe is separated from the rest of the cerebellum by the posterolateral fissure. The flocculus comprises the lateral portion of this lobe (Nolte, 1999).

The cortex is comprised of three distinct cell layers: the molecular layer containing axons and dendrites, a single layer of Purkinje cells (large neurons), and the granular layer made up of many granule cells. Contained within the white matter in the medullary centre of each side of the cerebellum are the deep cerebellar nuclei. They receive input from the cerebellar cortex and send output via the peduncles. The

cerebellum is attached to the brainstem via three (bilateral) peduncles: the middle, inferior, and superior peduncle (Nolte, 1999). The middle peduncle is the largest and consists almost exclusively of afferent pathways to the cerebellum, while the superior peduncle is composed of the major efferent projections from the cerebellum. The cerebellum also receives projections from the spinal cord and brainstem via the inferior cerebellar peduncle. The three main sources of external input to the cerebellum are the spinal cord, the vestibular nerve and nuclei, and the cerebral cortex. The cerebellum receives afferent fibres from the cerebral cortex via pontine nuclei, which form a very large pathway that projects contralaterally to the cerebellar cortex. The cerebellum projects afferents to the cerebral cortex via the thalamus (Nolte, 1999).

The lateral hemispheres receive most of their input from premotor, somatosensory, and association areas of the cerebral cortex. The lateral hemispheres are thought to be involved in planning voluntary movements, particularly the types of movements that are skilled and required to be performed rapidly, precisely, and eventually automatically. The intermediate zone is involved in correcting and adjusting limb movements by comparing the performance of the limb with the commands from the motor cortex. The vermis is concerned with the regulation and adjustment of posture as well as stereotyped movements. The intermediate zone and vermis tend to receive most of their input from the motor cortex of the precentral gyrus and the spinal cord. The flocculus and vermis both receive vestibular input and they also play a role in the control of eye movements. If the flocculus is damaged vertigo and disequilibrium occur. Therefore, as a whole, the cerebellum is implicated in equilibrium, muscle tone, motor learning, integration, planning, and control (Nolte, 1999).

It is well established that the cerebellum is involved in motor control and regulation, the role that the cerebellum plays in cognition, emotion, and behaviour is less well understood although there is sufficient evidence to implicate it in supporting some of these functions. As Schmahmann has argued at some length, even the anatomical evidence points to this given the large corticopontocerebellar pathway connecting the cerebral cortex with the cerebellum (Schmahmann, 1991, 2001a, 2001b; Schmahmann & Sherman, 1998). Most pertinent to this point is the fact that this pathway contains projections from the associative areas of the frontal, temporal, and

parietal cortices and the paralimbic and autonomic areas (Schmahmann, 1991). This provides evidence that cerebellar projections are not restricted to sensorimotor regions because associative areas process information from multiple sensory modalities and subserve cognitive functioning.

These corticopontocerebellar pathways are reciprocal, with both feedforward and feedback pathways, with the anatomical evidence indicating that the cerebellum projects efferents to these association areas via the thalamus. The feedforward limb to the cerebellum is comprised of the corticopontine pathway, which projects from the cerebral cortex to the ventral pons, the pons then projects to the cerebellar cortex via the pontocerebellar path (Schmahmann, 2001b). The feedback pathway from the cerebellum begins with the cerebellar cortex projecting to the deep cerebellar nuclei, which project to the red nucleus, which then projects via the thalamus to the cerebral cortex (Schmahmann, 2001b). The anatomical connections between the cerebral cortex and pons (the corticopontine pathway) are better understood than the particulars of the pontocerebellar pathway. However, associative input appears to have a predilection for the rostral pons which in turn projects to the posterior lobe, whereas sensorimotor input projects to the caudal pons which projects to the anterior lobe (Schmahmann, 2001b). Therefore, the posterior lobe is more likely to mediate cognitive functioning while the anterior lobe has more of a sensori-motor role.

There is also evidence that regions of the frontal lobes project to medial pontine nuclei which projects to superior portions of the cerebellar cortex (involving both the anterior and posterior lobe), while temporal and parietal areas tend to project to nuclei in the lateral pons that then projects to inferior cerebellar cortex of the posterior lobe (Desmond, 2001). This evidence suggests that different supratentorial regions may have a predilection for particular areas of the cerebellar cortex. It may also be the case that functions are localised within the cerebellum according to the recency of evolutionary development of the anatomic areas to which it is connected (Schmahmann, 1991).

On the basis of the evidence that the cerebellum is reciprocally connected with areas outside the sensori-motor regions of the cerebral cortex, Schmahmann proposed that the cerebellum is involved in cognition, emotion, motivation, and behaviour

(Schmahmann, 2001b). Dolan (1998) also argued that the anatomical evidence supports such a role for the cerebellum. For instance, the cerebellum contains the majority of the brain's neurons and is connected to the central nervous system on a number of levels. However, assuming this role in higher-order functioning is true several pertinent questions remain to be clarified, such as whether the cerebellar mechanisms that regulate motor function also regulate cognitive function as Schmahmann (1991) once suggested. Alternatively, does it support a broad range of cognitive functions and what is the relationship between deficits in these functions and the anatomical regions of the cerebellum?

2.4 Cerebellum and Cognition

Evidence from clinical observations following damage to the cerebellum and neuroimaging studies has provided support for its role in a range of neuropsychological functions and has also shed some light on the above questions. Cerebellar abnormalities have been found in patient groups with severe disturbances of cognition and affect, such as autism (Courchesne, 1991) and schizophrenia (for review see Daum & Ackermann, 1995). Early clinical observations of cerebellar damage identified deficits in speech production and in more recent times the phenomenon of cerebellar mutism has been documented. Cerebellar mutism occurs following the resection of cerebellar tumour, most often in the paediatric population (Dailey et al., 1995; van Dongen et al., 1994). The onset of mutism occurs 12 – 96 hours post-surgery which is transient lasting 1 day to 6 months (Catsman-Berrevoets et al., 1999; Pollack, 2001; van Dongen et al., 1994). The period of mutism is followed by a severe dysarthria that resolves completely after 1 – 6 months. Risk factors for developing mutism and subsequent dysarthria include midline tumour location (particularly large tumours), vermal incision, medulloblastomas over 5 centimetres in diameter, and bilateral oedema within the cerebellar peduncles (Catsman-Berrevoets et al., 1999; Dailey et al., 1995; Pollack, 2001). Not all children with midline cerebellar tumours develop this syndrome, but a review of the literature indicated that it occurs in at least 10% of such cases (Pollack, 2001).

Clinical observations have shown that this syndrome extends beyond difficulties with speech and incorporates a range of other symptoms including: oral pharyngeal motor apraxia causing reduced oral intake, oculomotor apraxia, difficulty initiating complex voluntary movements, incontinence, emotional lability, and personality changes (Dailey et al., 1995; Pollack, 2001). Neuropsychological investigation of these patients demonstrated deficits on formal tests of attention span, recent memory, and problem solving during the phase where speech and affect were recovering (Pollack, 2001). This syndrome is often referred to as 'posterior fossa syndrome', 'cerebellar mutism', or 'cerebellar mutism with subsequent dysarthria'.

2.4.1 Cerebellar Cognitive Affective Syndrome

While the posterior fossa syndrome was the first cerebellar syndrome to implicate the cerebellum in neurobehavioural function, another syndrome has been identified to further support this point, namely the 'cerebellar cognitive affective syndrome' (CCAS, Schmahmann, 2001a; Schmahmann & Sherman, 1998). CCAS was first described by Schmahmann and Sherman (1998) following their prospective analysis of adult patients with disease confined to the cerebellum. This study identified four main areas of deficit in patients with cerebellar disease, namely: executive, visuo-spatial, language, and personality/affective changes. More specifically deficits of executive functioning included difficulty with planning, set shifting, verbal fluency, abstract reasoning, and working memory. Visuo-spatial deficits were characterised by a difficulty with visuo-spatial organisation and memory, while the types of language and linguistic deficits observed were agrammatism, dysprosodia, and mild anomia. Finally, personality and affective changes manifested as disinhibited or inappropriate behaviour and a flattening of affect (Schmahmann, 2001a; Schmahmann & Sherman, 1998).

The overall effect of these difficulties was a reduction in general intellectual ability. However, remote episodic and semantic memory were intact, and only mild deficits in new learning were detected. In addition, traditional cortical syndromes such as aphasia, apraxia, and agnosia were generally not detected. CCAS has also been observed in a paediatric population (Levisohn et al., 2000). In children CCAS does

not have to occur in conjunction with cerebellar mutism because CCAS can result from a variety of lesion sites and not simply from midline lesions as is the case for cerebellar mutism.

The nature and severity of CCAS symptoms observed in a given individual was related to disease variables including the anatomical location of the disease. Acute disease onset, large or bilateral disease, or pancerebellar disorders were all associated with more severe and generalised symptoms of CCAS (Schmahmann, 2001a). Symptoms in those with unilateral lesions tended to resolve. Smaller lesions or anterior lobe lesions were associated with the least pronounced cognitive symptoms, namely mild deficits in executive function and visuo-spatial ability. Lesions of the posterior lobe tended to produce the full cognitive symptom complex of CCAS as described above. Vermal lesions were most frequently associated with prominent affective disorders. These findings point towards a sensori-motor role for the anterior lobe while the posterior lobe appears to have greater involvement in cognition. The vermis was implicated in affect regulation, which is interesting when considering that cerebellar mutism results from vermal lesions and often involves emotional lability and personality change. The fact that lesions of these regions produce cognitive, behavioural, and affective impairments that typically occur in patients with lesions of cortical areas indicates that the cerebellum plays a modulating role in these functions and is further evidence that the anatomical pathways between the cerebellum and cerebral cortex are not restricted to sensori-motor functions.

Schmahmann (2001a) postulated that the modulating role undertaken by the cerebellum remains constant across different types of input whether that be motor, cognitive, or affective input. He argues that the cerebellum is responsible for regulating things such as speed, consistency, accuracy, and appropriateness of its various input, and thus coordinating performance across different domains of functioning. Schmahmann labels this idea the 'dysmetria of thought' hypothesis because just as damage to the cerebellum causes dysmetria or instability of motor function, it also causes dysmetria (instability) of cognitive, behavioural, and affective functions as manifested in CCAS.

On the basis of the anatomical evidence that reciprocal pathways connect the cerebellum with the cerebral cortex it is quite conceivable that the cerebellum may have a role in cognitive functioning beyond motor related cognition and such a role has been preliminarily supported by the observation of the above syndromes. However, recent reviews of the adult literature over the last decade have disagreed about whether there is sufficient evidence to support a role for the cerebellum in cognitive processes outside of motor planning and learning (Daum & Ackermann, 1995, 1997; Daum, Snitz, & Ackermann, 2001; Justus & Ivry, 2001). While some assert that there is sufficient evidence to implicate the cerebellum in at least some areas of cognition (Justus & Ivry, 2001) others have dismissed this research on the grounds of methodological weaknesses and inconsistency (Daum et al., 2001). They purport that it is difficult to draw conclusions from the research because studies use patients with pathologies of differing severity and have poorly matched controls. They argue that future research needs to utilise broader test batteries and use a variety of tasks within cognitive domains to elucidate any potential deficits of specific functions.

Nevertheless, the reviews concur that the cerebellum is strongly and consistently implicated in motor learning, which includes: classical conditioning, procedural learning, acquisition of motor skills, habituation, and visuomotor adaptation (Daum & Ackermann, 1995, 1997; Daum et al., 2001; Justus & Ivry, 2001). They also agree that the evidence is equally as strong for temporal processing, more specifically the regulation of timing in motor processes and the perception and estimation of time (Hetherington, Dennis, & Spiegler, 2000).

Of the remaining neuropsychological research support has certainly been stronger for some domains of cognition over others, and the cumulative evidence most strongly points towards a cerebellar role in specific frontal/executive functions and visuo-spatial skills, consistent with some of the symptom complex of CCAS (Daum et al., 2001; Justus & Ivry, 2001). These reviews found that deficits in language, attention, and memory were detected in some studies but the evidence was insufficient to draw conclusions from and therefore unable to support some of Schmahmann and Sherman's (1998) original findings. While the adult literature has overwhelmingly investigated various aspects of cognition, an association between posterior fossa

lesions and neuropsychiatric symptomatology has been found by one group (Pollak, Klein, Rabey, & Schiffer, 1996) in support of the affective dysregulation observed in CCAS.

A number of studies utilised verbal fluency tasks and despite methodological flaws in some of these studies, impairment on this task has been one of the most consistent findings. A recent study addressed previous methodological weakness by including matched controls and covarying for motor impairment and dysarthria (Leggio, Silveri, Petrosini, & Molinari, 2000). No differences were found for semantic fluency tasks but deficits on phonemic fluency tasks were highly significant. The different cerebellar pathology groups did not differ, but there was a tendency towards poorer performance for those with right focal damage.

Clearly some patients with cerebellar diseases experience cognitive deficits as a direct result of cerebellar compromise. Recent neuroimaging evidence has also elucidated specific deficits related to cerebellar damage. For instance, the cerebellum has been implicated in verbal working memory (Desmond, 2001). Previous evidence suggests that the phonological store and articulatory loop are independent processes, and neuroimaging research has implicated temporal/parietal areas in the phonological store process and associated the articulatory control process with the frontal lobes (Desmond, 2001). Using neuroimaging Desmond (2001) found activation in the inferior and superior cerebellar cortex during a verbal working memory task. The inferior cerebellar cortex receives projections from the temporal-parietal regions, and it was inferred that activation in this area reflected the phonological store component of working memory. The articulatory loop was thought to be reflected in the activation of superior portions of the cerebellar cortex because that region receives projections from frontal areas (Desmond, 2001). The importance of these pathways in cognitive functioning is further supported by the phenomenon of crossed cerebellar diaschisis, which is the reduction of cerebellar metabolism observed following contralateral frontal lobe damage, and recovers in parallel with frontal lobe recovery (Desmond, 2001).

2.5 Posterior Fossa Tumours

The cerebellum occupies a large proportion of the posterior fossa and for this reason a significant number of posterior fossa tumours arise from the cerebellum, hence the terms are used interchangeably in the brain tumour literature. Traditionally the posterior fossa has been thought of as unimportant to the integrity of cognitive functioning, and while the role of the cerebellum in cognition is becoming increasingly elucidated, the outcomes for children with posterior fossa tumours are not as well understood, particularly for those treated with surgery-only. Early in the tumour literature cerebellar tumours were not thought to influence intellectual functioning unless they were treated with chemotherapy or radiotherapy (Duffner et al., 1983). Further, much of the research focussed on children with medulloblastomas because of their prevalence and the use of aggressive treatment they necessitated. There is now enough evidence to show that cognitive deficits do occur in children treated for posterior fossa tumours that are not attributable to treatment effects. As yet no consistent cognitive profile for surgery-only children has been described, but the current literature is reviewed below.

2.5.1 Intellectual, Language, and Visuo-spatial Outcomes

The measurement of IQ has frequently been used in outcome studies to indicate decline in function and this is not always a reliable indicator of neuropsychological deficits, particularly in the surgery-only population. Of the small number of surgery-only studies the results vary as to whether the tumour groups differ from the normal population. Most of the studies report no difference in IQ scores (Ater et al., 1996; Mulhern et al., 1999; Riva & Giorgi, 2000; Steinlin et al., 2003). In children treated with radiotherapy the length of time between treatment and assessment is often related to subsequent IQ score, such that a longer period of elapsed time is associated with poorer IQ, and this decline in IQ is known to continue for at least 10 years (Hoppe-Hirsch et al., 1990). However, no decline was detected in a surgery-only group compared with their baseline assessment two years prior (Packer et al., 1989) and when assessed up to 18 years after treatment no differences were found between the surgery-only children and normative data (Steinlin et al., 2003).

When IQ differences have been found they tend to indicate a greater decrement in PIQ and FSIQ than VIQ (Beebe et al., 2001; Riva et al., 1989). Despite the reduction in IQ found in these studies the mean IQ scores still fell within the 'average' range. This differential impairment of PIQ and VIQ has also been observed in medulloblastoma survivors treated with radiotherapy, with greater impairment of PIQ (Dennis et al., 1996). This group also found that PIQ impairment was related to age at diagnosis but remained relatively stable over time, while VIQ did not vary as a function of age at diagnosis but tended to decline over time. Children treated with radiotherapy for posterior fossa tumours consistently fare worse than children treated with surgery in terms of IQ (Mulhern et al., 1999; Riva et al., 1989). This impairment of FSIQ appears to be related to the amount of white matter loss, which is greater in children treated with radiotherapy than surgery-only (Mulhern et al., 1999).

Riva and Giorgi (2000) have proposed that language and visuo-spatial functions are lateralised to the contralateral hemisphere of the cerebellum after finding that children treated for left-sided cerebellar tumours performed more poorly on PIQ while children treated for right-sided tumours experienced greater deficits on VIQ and poorer performance when formulating sentences. This pattern of contralateral lateralisation has been found in children who were also treated with adjuvant therapy (Scott et al., 2001). Riva and Giorgi (2000) also found that a language disorder (associated with mutism) developed in some children following vermal lesions that was not simply a problem with speech production and was distinct from mutism with subsequent speech disturbances. Language and visuo-spatial functions have not been examined in great depth in the surgery-only literature, but it is of note that one group found that the Rey Figure Copy was the most significantly affected function, even compared with the Delay trial, which may reflect visuo-spatial and organisational difficulties (Steinlin et al., 2003). Furthermore, deficits in naming and comprehension have been found in surgery-only children (Riva & Giorgi, 2000) and expressive language and word finding problems were detected in children treated with surgery, some of whom received chemotherapy (but not methotrexate; Levisohn et al., 2000).

2.5.2 Attention and Executive Function Outcomes

The literature consistently demonstrates attentional difficulties in children treated for posterior fossa tumours by surgery-only. However, they vary in terms of the particular facet of attention that is affected. Selective attention, divided attention, and processing speed/time based attention are most commonly found to be impaired (Akshoomoff & Courchesne, 1992; Riva & Giorgi, 2000; Riva et al., 1989; Steinlin et al., 2003). The two studies that measured sustained attention had opposing results (Riva et al., 1989; Steinlin et al., 2003). Akshoomoff and Courchesne (1992) found that children treated for cerebellar tumours (2/5 received radiotherapy) were able to maintain focussed attention but were impaired on a selective attention task. They found that these children were able to selectively attend to the environment but they had difficulty with their response speed. That is, it was their ability to rapidly and accurately shift their attention that was impaired, and it was not as a result of motor control problems. The anatomical basis for attentional difficulties may be due to reciprocal connections with the frontal lobes and/or the proximity to the ascending activating system.

Further support that frontal functions are disrupted by cerebellar damage comes from the finding of executive impairments in cerebellar tumour patients. Two surgery-only studies found deficits of verbal fluency, which is consistent with the adult literature in this area (Riva & Giorgi, 2000; Steinlin et al., 2003). These studies also found design fluency to be impaired, but not necessarily to the same extent. Impairments were also detected on the Wisconsin Card Sorting Test with children making high numbers of perseverative errors (Riva & Giorgi, 2000) or generally performing poorly on the test compared to their own level of intellectual ability (Karatekin et al., 2000). Importantly, Karatekin et al. (2000) were able to demonstrate that children with temporal lobe tumours did not perform as poorly as children with cerebellar lesions which suggests that poor performance was due to lesion location. Executive deficits in children treated for cerebellar tumour were also found on other tasks including the Stroop test and the Rey Complex Figure (Steinlin et al., 2003). Animal ablation studies have also demonstrated inflexibility and working memory difficulties following cerebellar lesions (Mandolesi, Leggio,

Graziano, Neri, & Petrosini, 2001). Although poorly understood, there is enough preliminary evidence from the surgery-only literature to suggest that the cerebellum forms part of the distributed system that underlies executive functioning.

2.5.3 Memory and Learning Outcomes

Memory and learning in children treated surgically for posterior fossa tumour is not very well understood. Three of four studies found memory deficits to occur in these children, but each study examined different aspects of memory and the findings remain to be replicated. One study found that semantic memory (as measured by vocabulary), immediate memory (digit span), and visual memory (Rey Figure) were abnormal (Steinlin et al., 2003). The second study found auditory sequential memory to be affected, particularly in children who had right cerebellar tumours, and visual sequential memory was affected in children who had left cerebellar tumours (Riva & Giorgi, 2000). The third study found that memory was one of only two cognitive domains to be impaired in these children as assessed by the verbal and nonverbal selective reminding tests (Ater et al., 1996). The fourth study (using selective reminding and the Rey Figure) found memory function was relatively well preserved and did not deteriorate over time (Packer et al., 1989). Additional evidence for memory deficits comes from a study that included some children who had chemotherapy (not methotrexate) in addition to surgery found that the recall of the Rey Figure was abnormal in a proportion of children and that a third of them had verbal memory deficits (Levisohn et al., 2000).

2.5.4 Visuo-motor Outcomes

Difficulties with visuo-motor skills might be expected in children with posterior fossa tumours given the cerebellum's role in motor control and regulation. As discussed above children (surgery-only) have been found to be slow on time based tasks and processing speed was impaired in two studies (Riva & Giorgi, 2000; Steinlin et al., 2003). Impairments of fine motor speed and dexterity were found to be one of the main problems in these children, although there was no evidence of deterioration over time (Ater et al., 1996; Packer et al., 1989). Others have found

that simple reaction time was not affected, even in children treated with radiotherapy for medulloblastoma (Riva et al., 1989). Visuo-motor integration deficits were found in a study including children treated with chemotherapy (Levisohn et al., 2000) but were not apparent on the same test in a surgery-only study (Beebe et al., 2001). However, this surgery-only study did find that adaptive motor skills were significantly impaired (Beebe et al., 2001). Deficits in visuo-motor skills may result in handwriting difficulties but handwriting has not been assessed in the surgery-only population. Writing disabilities were reported in 45% of children treated (including chemotherapy and/or radiotherapy) for medulloblastoma (Hoppe-Hirsch et al., 1990).

2.5.5 Academic Outcomes

There is little research into academic outcomes for children treated surgically for posterior fossa tumour, and there is also a lack of detailed information regarding academic outcomes in the wider brain tumour literature, although studies that have investigated academic achievement found deficits in at least one academic area (Mulhern et al., 1992). Children (surgery-only) assessed within a year of surgery were found to have normal reading skills (Wide Range Achievement Test) but a significant impairment of mathematics and spelling skills (Beebe et al., 2001). Two studies using the same test found that these children had normal academic skills on assessment around the time of diagnosis (Ater et al., 1996; Packer et al., 1989), although one did report relatively poorer mathematical ability than reading or spelling ability (Packer et al., 1989). When followed up two years later there was no decline in the performance of surgery-only children, while there was evidence of decline in IQ and academic skills in the children treated with radiotherapy (Packer et al., 1989). They concluded this decline was due to the effects of radiotherapy rather than other factors such as age at diagnosis. Although decline in academic performance is often associated with a decline in IQ, this is not always the case as academic and learning problems have been found in children with normal IQ's (Duffner et al., 1983; Duffner et al., 1985).

Long-term decline in academic ability has also been reported in children treated with surgery and adjuvant therapy for medulloblastoma (Hoppe-Hirsch et al., 1990). Five

years after treatment only 40% of children were functioning at a normal academic level while 26% of children were classified as having 'complete failure' academically and were attending special schools. They also found 35% of these children had dyslexia. Ten years after treatment only 11% were functioning at a normal level and 60% were attending special schools. While there is no long-term follow up of surgery-only children, Packer et al. (1989) found that at two years post-surgery 7/9 children remained in a regular classroom while the remaining two required special help.

2.5.6 Social and Behavioural Outcomes

Emotional and behavioural disorders have been found in as many as 47% of children five years after treatment (surgery/chemotherapy/radiotherapy) for posterior fossa tumours and up to 78% of children ten years after treatment (Hoppe-Hirsch et al., 1990). Three surgery-only studies have examined behavioural and social outcomes in children. Beebe et al. (2001) used two formal measures: the Achenbach Child Behaviour Checklist and the Vineland Adaptive Behaviour Scales. They found that these children presented with a significant number of internalising behaviour problems relative to normative data, but the externalising and total behaviour problem scales were not different. Of the Vineland domains there were significant differences on the Communication, Socialisation, and the overall Adaptive Behaviour Composite while only Daily Living skills was not significant. Interestingly, an effect of lesion location was found for the Adaptive Behaviour Composite with children who had lesions restricted to the vermis performing more poorly than those who had hemispheric or mixed vermis and hemispheric lesions. Overall a number of these children were clearly presenting with social, emotional, and behavioural problems as reported by parents.

While Steinlin et al. (2003) did not conduct formal behavioural assessment they did identify special behavioural problems in one-third (8) of their sample. These children presented with obvious behavioural or psychiatric problems during testing and/or from their history including selective mutism, phobia, and uncontrolled temper tantrums. All but one of these children had vermal lesions. It is quite

possible these authors would have identified other children with behavioural problems if formal measures were used.

Riva and Giorgi (2000) also identified social, emotional, and behavioural problems in children with vermal lesions who did not present with mutism (all five children had incisions in the lower part of the vermis). One child presented with the behavioural profile of autism with disinhibited behaviour. The other four children shared a similar presentation of contact avoidance, displaying irritability, difficulty being around others, avoidance of physical and eye contact, monotonous speech, and decreased speech output.

It is evident that children treated with surgery-only are at risk for affective, behavioural, and social problems that range from mild to severe. Two of the surgery-only studies ascribed these behavioural problems (except for one child) to the location of the lesion, namely damage to the vermis. Levisohn et al. (2000) also found deficits of affect regulation in two-thirds of children with extensive vermis damage (not treated with methotrexate or radiotherapy). None of the children without extensive vermis damage experience affective problems. Although affective and behavioural disturbances appear to be related to vermal lesions in many of these children, they are not always associated with posterior fossa syndrome (Levisohn et al., 2000; Riva & Giorgi, 2000).

Social, emotional, and behavioural disturbances are not consistently associated with vermal lesions (Beebe et al., 2001; Steinlin et al., 2003) and it is likely that factors other than tumour location are responsible for determining these outcomes. For example, the psychological impact of the illness experience may in itself produce emotional sequelae. The child's functional status may impact on the child's emotional state if they are experiencing failure at school or on a social level. Mulhern, Carpentieri, Shema, Stone, and Fairclough (1993) examined the factors associated with behavioural problems in children diagnosed with brain tumour (including a range of tumour locations and treatments). They found that brain tumour location, functional status, and particular demographic variables were predictive of poor psychological outcome.

The adult literature has also provided evidence of social, emotional, and behavioural changes following cerebellar damage. For instance, one study reported neuropsychiatric symptoms in patients with structural abnormalities of the posterior fossa (Pollak et al., 1996). Pompili et al. (2002) assessed quality-of-life in adults who had been treated with surgery-only for cerebellar pilocytic astrocytoma during childhood. These adults differed from controls on every dimension of quality-of-life that was assessed except for one (sex life). The dimensions they differed on were: energy, leisure, cognition, socialising, work, symptoms, depression, well-being, memory, family, and adolescence. While they were unable to identify the cause of these differences, this study indicates that children treated with surgery-only experience psychological and psycho-social sequelae and that these sequelae may persist into adulthood.

2.5.7 Summary

The literature makes it clear that children treated for posterior fossa tumours with surgery-only fare much better than those treated with radiotherapy. There are, however, very few studies examining surgery-only outcomes. The surgery-only studies that do exist have provided evidence of neuropsychological sequelae, but the profile of impairment is not consistent from study to study. For instance, a reduction in IQ scores has been found in some studies but others report that IQ is most often unaffected. There is some evidence of impairment in some visuo-spatial and language functions and occasionally children experience a severe language disorder associated with vermal lesions. One study proposed that cognitive functions are lateralised to the cerebellar hemispheres in a pattern contralateral to cerebral hemisphere lateralisation (Riva & Giorgi, 2000). This has been replicated in children treated with surgery and adjuvant therapy (Scott et al., 2001).

Attentional difficulties are a common finding, particularly deficits of selective attention, divided attention, and processing speed. Similarly the literature presents evidence for executive deficits on a number of different tests. Most studies examining memory found evidence for impairment in this domain. In addition, there was some indication that academic skills might be affected (even in the absence of IQ

decline), particularly in mathematics. As expected several studies have provided evidence for deterioration of motor skills. Finally, behavioural and affective changes were a frequent finding with severe presentations often associated with vermal lesions. Social, emotional, and behavioural sequelae appear to evolve from a range of compounding factors, and are not always determined by tumour location.

Levisohn et al. (2000) conducted a study of children treated with surgery-only or surgery and chemotherapy (not methotrexate) to investigate CCAS in the paediatric population. Their results were consistent with Schmahmann and Sherman's (1998) original findings of deficits in executive function, visuo-spatial skills, expressive language, and affect modulation. At this stage evidence from the surgery-only literature more strongly supports the presence of executive and behavioural/affective problems, expressive language difficulties seem to occur in a minority, and there is insufficient evidence for visuo-spatial difficulties.

2.6 Supratentorial Tumours

There is less debate about whether tumours in the supratentorium are likely to impair or alter neuropsychological functioning because the mechanisms by which lesions may impact on cognitive functioning are better understood for the supratentorium than the posterior fossa. Tumours in different locations within the supratentorium would be expected to produce different types of deficit. There is also an argument that the *severity* of deficit is dependent on location, for instance that children treated for hemispheric tumours have a worse outcome than those treated for ventricular tumours (Dennis et al., 1992). However, very few studies have made comparisons between different tumour locations within the supratentorium. This may be due to the difficulty obtaining sufficient numbers of children with tumours in the various locations, particularly as the majority of childhood brain tumours are located in the posterior fossa. Research is also limited in terms of understanding the neuropsychological consequences of supratentorial tumours treated with surgery-only. This research is even more scarce than it is for posterior fossa tumours, despite the fact that there are a number of low grade tumours that can develop in the supratentorium during childhood that often only require surgical resection. Most of

the literature that examines outcomes for children with supratentorial tumours compares and contrasts them with children treated for posterior fossa tumours. Hence, the following discussion will focus on the comparison between the different tumour locations and will include some of the literature on adjuvant therapy.

2.6.1 Comparison of Surgery-Only Outcomes

Only one study has examined the differences between tumour location in any detail (Ater et al., 1996). This study included children with malignant tumours, but the assessment was conducted prior to radiotherapy or chemotherapy. Children with cerebral hemisphere tumours fared worse than children with tumours in any other location (midline, posterior fossa, or brain stem). Relative to the normal population they experienced a higher incidence of deficits in PIQ, attention, memory, motor, and academic skills. In fact, their performance as a group was only comparable to norms on VIQ and language measures. Children with midline tumours experienced a higher incidence of memory, motor, and attention problems than normal children, while those with posterior fossa tumours were impaired on the memory and motor domains. The brain stem tumour group were comparable to the normal population on all domains (Ater et al., 1996). Another study assessing children at a similar stage in treatment reported no patterns of deficit associated with supratentorial versus posterior fossa tumour location (Carpentieri et al., 2003).

Children with temporal lobe tumours have been found to have average IQs and normal performance on an executive task (WCST; Karatekin et al., 2000). In addition language skills tend to improve post-operatively in children with left temporal lobe tumours with no evidence of new deficits (DeVos, Wyllie, Geckler, Kotagal, & Comair, 1995). Nevertheless, the neuropsychological outcome for children with temporal lobe tumours is not always uncomplicated as case studies have shown (Frayne, Leathem, & O'Keefe, 1999).

2.6.2 Comparison of Surgery/Chemotherapy/Radiotherapy Outcomes

It is more common for tumours to be treated with some form of adjuvant therapy than to be treated with surgery-only. For this reason there is more literature on outcomes for children receiving such treatment, some of which have made comparisons between different tumour locations. Several reviews have concluded that brain tumour studies generally find that intellectual ability is worse affected in children with supratentorial tumours (Duffner, Jackson, & Cohen, 1996; Glauser & Packer, 1991; Mulhern et al., 1992; Ris & Noll, 1994). It is possible that these differences are due to the inclusion of craniopharyngiomas in the supratentorial group. Children with these tumours tend to have a poor outcome and when they were excluded from a supratentorial group the posterior fossa group was found to be worse off than the supratentorial group (Ris & Noll, 1994). Some studies have found no difference between the two locations in terms of intellectual functioning (Lannering et al., 1990; Yule, Hide, Cranney, Simpson, & Barrett, 2001).

Research into other cognitive domains has also yielded mixed results. A comparison between third and fourth ventricle tumours found no effect of tumour location on focussed attention, selective attention, and working memory tasks and performance was better predicted by treatment with radiotherapy (Dennis, Hetherington, & Spiegler, 1998). Differences in functioning that occur as a result of tumour location are not necessarily cognitive in nature. Lannering et al. (1990) found no differences between groups on cognitive, visual, or motor functioning, but discovered that supratentorial location was related to poor psychological/emotional outcome and to a moderate-severe level of total disability. In another study children treated for brain tumour had poor social competence and increased behavioural problems compared to controls (Mulhern et al., 1993). However, these authors found that non-hemispheric tumours better predicted poor social competence.

2.7 Identification of Predictive Factors

Understanding the factors that influence neuropsychological outcome in children treated for brain tumour is complicated by the many events that occur during the

course of diagnosis, treatment, and recovery. Brain tissue is not only subject to damage caused directly by the tumour and its surgical removal, it is also vulnerable to other treatment factors, medical complications, family factors, and demographic variables. Research on factors predicting outcome following surgery for brain tumours is scarce, but a number of studies have examined these factors in mixed treatment groups.

2.7.1 Age Effects

Age at diagnosis and/or treatment is one of the most commonly investigated risk factors and might be expected to influence the recovery of intellectual functioning as demonstrated in other conditions (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000). A fairly consistent association exists between age at radiotherapy and outcome, with younger age being associated with poorer neuropsychological outcome (Chapman et al., 1995; Hoppe-Hirsch et al., 1990; Kao et al., 1994; Lannering et al., 1990; Reimers et al., 2003). Sometimes this relationship only holds for particular neuropsychological measures such as VIQ (Dennis et al., 1992), or conversely PIQ (Dennis et al., 1996). In a study assessing a broader range of neuropsychological abilities this relationship only held for PIQ, FSIQ, and motor skills of children treated with radiotherapy (Moore et al., 1992). While younger age has been associated with worse neuropsychological outcome it has also been associated with better ten year survival (Hoppe-Hirsch et al., 1990). A handful of studies have found no relationship between younger age at diagnosis/radiotherapy and IQ (Yule et al., 2001), overall disability (Lannering et al., 1990), or behavioural problems (Holmquist & Scott, 2002; Mulhern et al., 1993) which may in part be due to short follow-up periods. Two of the three studies examining age in children who were not treated with radiotherapy found no relationship between age and outcome (Moore et al., 1992; Steinlin et al., 2003). The third study found that younger children had less neuropsychological deficits, but this relationship was confounded with tumour type as younger children were less likely to have medulloblastomas (Levisohn et al., 2000).

2.7.2 Demographic and Family Variables

Sex differences have been infrequently examined but generally appear to be unrelated to outcome (Dennis et al., 1991; Mulhern et al., 1993; Reimers et al., 2003). Other demographic variables such as low socio-economic status, single parent status, and younger mother at time of birth have been associated with problem behaviours and adaptive behaviour deficits (Carlson-Green et al., 1995; Mulhern et al., 1993). Family factors also contribute to poor behavioural outcome when the family has difficulty in terms of coping strategies, stress levels, and family environment (Carlson-Green et al., 1995).

2.7.3 Medical Factors

Aside from tumour location and treatment type there are a range of other tumour and treatment related factors that compromise neurological functioning in children with brain tumours. Medical variables are sometimes examined in isolation but a number of studies have also attempted to look at their cumulative effect. Tumour size is one factor that is rarely assessed, but it has been investigated in one study (surgery-only for posterior fossa tumours) and was found to have no influence on neuropsychological outcome (Steinlin et al., 2003). Another recent study looked at tumour grade and found that it was not related to IQ (Reimers et al., 2003). Hormone status is another infrequently considered variable which was only found to be related to poor serial order memory in older children with impaired hormone function (Dennis et al., 1992). Seizures might also be expected to influence neuropsychological outcome, but has been found to be unrelated to memory functioning (Dennis et al., 1991) or behavioural problems (Mulhern et al., 1993).

Hydrocephalus is a condition that can result in neuropsychological sequelae in itself, particularly in patients requiring a shunt (Anderson et al., 2001; Fletcher, Brookshire, Landry, & Bohan, 1996; Fletcher, Dennis, & Northrup, 2000). As hydrocephalus is a common occurrence in brain tumour patients it would be reasonable to expect that it contributes to overall neurological and neuropsychological impairment. A number of studies have examined the role of hydrocephalus as a risk factor for poorer outcome

and results have been inconclusive. Hydrocephalus was not shown to be related to disability level or behavioural problems (Lannering et al., 1990; Mulhern et al., 1993). Hydrocephalus requiring a shunt was a predictor of intellectual ability in one study (Reimers et al., 2003) but not in another (Yule et al., 2001). However, the latter study found that the most powerful predictor of intellectual ability was instead the duration of symptoms of IICP prior to surgery (Yule et al., 2001). Children who presented within four months of the onset of headache and/or vomiting had a better outcome than those who presented later.

Many authors have considered it more useful to examine the combined effects of neurological insult on outcome, a logical approach given that outcome is dependent on the cumulative and interactive effects of neurological events (Ater et al., 1996). The range of events that comprise composite scores are generally comprehensive, including: IICP, seizures, meningitis, obtundation, neurological deficits, deterioration in neurological status, subdural fluid collection, repeat craniotomy, sensory abnormalities, and peri-operative complications. However, the relationship of outcome to these events is often only studied at one time point (pre-operative, peri-operative, or post-operative). Analysis of pre-operative factors has not yielded any significant relationship with neuropsychological functioning (Beebe et al., 2001), memory (Dennis et al., 1991), or extent of disability (Lannering et al., 1990). There may be a greater influence of peri-operative factors on outcome as greater complications have been associated with poorer intellectual functioning (Kao et al., 1994) and more severe neuropsychological outcome (Chapman et al., 1995). Adverse peri-operative factors were also associated with younger age at treatment in these studies, and may partly explain poorer outcomes for younger children receiving radiotherapy. Hoppe-Hirsch et al. (1995) found that those with post-operative complications were at greater risk for deterioration in IQ.

The only study to examine the influence of these three time points in a surgery-only sample (posterior fossa tumours) found no relationship between any of the time points and a range of neuropsychological measures (Beebe et al., 2001). It is possible that medical factors at each time point alone are not sufficient in themselves to explain much of the variance in outcome scores, and need to be considered in combination with each other or in association with other factors. For instance,

Carlson-Green et al.(1995) found that illness variables in association with demographic or family variables predicted academic achievement and intellectual ability respectively.

2.7.4 Neurological Severity Score

Ater et al. (1996) are the only group to have considered the combined effects of pre-, peri-, and post-operative events on neuropsychological outcome. They developed a scoring procedure to quantify the severity of events at each of these three time points, and also included the quantification of pre-existing neurological deficits. The scores from each of the four categories are summed to form a composite 'neurological severity score' (NSS) with higher scores indicating greater overall severity of neurological events. They correlated the NSS with neuropsychological assessments conducted prior to surgery or within three months of surgery for astrocytoma, but prior to any adjuvant therapy. Each NSS only included events that occurred prior to the child's assessment. They found significant correlations between the NSS and FSIQ, PIQ, visuo-spatial skills, attention, and memory. Correlations between the NSS and VIQ, language skills, motor skills, and academic skills were not significant. Ater et al. (1996) concluded that the overall severity of neurological events had more impact than tumour location on subsequent neuropsychological abilities around the time of diagnosis. This is a very important finding, especially considering how infrequently the impact of these factors is considered.

While this research was significant in elucidating the contribution of neurological events to brain tumour sequelae it had some methodological inadequacies and left some questions unanswered. This study was problematic in that almost half of the neuropsychological data was collected retrospectively. Nearly two-thirds of the sample underwent testing prior to surgery and the remaining third were tested within three-months of surgery, thus the NSS has been shown to be strongly associated with neuropsychological deficits that are apparent within three months of these neurological events. However, it remains to be shown whether the NSS is an effective tool for predicting long-term outcome. Potentially any relationship between the NSS and outcome will be more difficult to find in a study of long-term outcome

when presumably many of the children in the Ater et al. (1996) study were experiencing the acute effects of neurological events (entered into the NSS) at the time of neuropsychological assessment. Nevertheless, this is the most promising method of identifying whether neurological events are underlying risk factors for poor medium- to long-term outcome.

2.8 The Present Study

2.8.1 Rationale

Brain tumours and their treatment can have a marked impact on a child's functioning and development. A range of tumour, treatment, and psychosocial factors cumulatively and interactively determine long-term sequelae. Tumour location and treatment are frequently considered the major factors determining neuropsychological outcome. This is particularly true of children treated with radiotherapy that has been shown to have devastating effects on cognitive functioning. However, the impact of neurological events related to the tumour and treatment are often overlooked in the literature and a handful of studies indicate that they contribute to neuropsychological outcome in their own right. Neurological events and medical complications may be particularly important in determining sequelae in children treated with surgery-only because their recovery is not compounded by chemotherapy or radiotherapy. Only one study has examined the impact of these events on medium-term outcome in a surgery-only sample (Beebe et al., 2001). For the purposes of the present study the definition of short-term is less than a year (usually within months) of surgery, medium-term outcome is around one-year post-surgery, and long-term is two-years post-surgery and beyond.

Our knowledge of neuropsychological sequelae in children only requiring surgery is poor for two reasons. Firstly they represent a minority of children treated for brain tumour. Second the effects of radiotherapy and some chemotherapeutic agents are so dramatic that the vast majority of research has focused on outcomes for patients who have undergone these treatments rather than surgery alone. Due to the scarcity of this research we know little about the sequelae of posterior fossa tumours compared

with supratentorial tumours in children treated with surgery-only. An extensive review of the literature failed to find a study that has compared medium- or long-term neuropsychological sequelae of posterior fossa tumours with that of supratentorial tumours in children treated with surgery-only.

Considering that most children treated with surgery alone survive, it is necessary to advance our understanding of medium- to long-term neuropsychological outcomes and the factors that play a role in determining outcomes in order to provide better information and patient care. The present study will prospectively examine the medium- to long-term sequelae of children treated with surgery-only, and compare the outcome of children with posterior fossa tumours to that of supratentorial tumours. The present study also has the advantage of examining these outcomes from one- to two-years post-surgery in order to understand the nature of recovery in these groups. In addition this study will examine the contribution of tumour and treatment related factors on sequelae in an attempt to establish a useful method for predicting outcome. It is in the position to test the capacity of the NSS to predict deficits over time and to compare the utility of using a composite measure of severity (NSS) rather than individual disease variables. Two further advantages of the present study include:

- The use of a comprehensive range of neuropsychological tests to measure outcome
- The Royal Children's Hospital is the primary hospital for treatment of paediatric brain tumours with a catchment area covering the states of Victoria and Tasmania.

2.8.2 Aims and Hypotheses

The present study aims to identify risk factors for poor outcome by investigating the relationship of different neurological variables with neuropsychological outcome, and to determine whether individual disease variables predict outcome as well as a composite measure (NSS). This study also aims to determine the neuropsychological impact of surgery to treat brain tumours in two difference locations and to delineate

the process of recovery over a one year period. More specifically the aims and hypotheses of this study are:

Aim One

To explore the relationship between the NSS and neuropsychological outcome at one-year post-surgery for brain tumour.

Hypothesis One

It is predicted that a higher NSS will predict poorer cognitive and behavioural functioning in children one-year post-surgery.

Aim Two

To explore the relationship of tumour volume and hydrocephalus with neuropsychological outcome at one-year post-surgery.

Hypothesis Two

On the basis of the literature it is predicted that larger tumour volume and the occurrence of hydrocephalus will each predict greater cognitive impairment.

Aim Three

To characterise the cognitive and affective functioning of children who have undergone surgery for a posterior fossa tumour and contrast this with the cognitive and affective functioning of children treated for supratentorial tumours at one-year post-surgery.

Hypothesis Three

It is expected that children with posterior fossa tumours will have a distinctly different profile of neuropsychological deficits to children with supratentorial tumours.

Hypothesis Four

It is predicted that each tumour location group will have a profile of deficits that distinguish them from the normal population at one-year post-surgery.

Aim Four

To explore the nature of recovery from one-year to two-years post-surgery in a subset of children treated by surgery-only for brain tumour.

Hypothesis Five

It is predicted that each tumour location group will have a profile of deficits that distinguish them from the normal population at two-years post-surgery.

Chapter Three – Methodology

3.1 Participants

Children (and their parents) presenting at the Royal Children's Hospital (RCH), Melbourne, Victoria, for diagnosis and treatment of a brain tumour were recruited within one-year of diagnosis. The children were aged 6 to 18 at the time of assessment.

Children were recruited according to the following inclusion criteria:

1. The child as diagnosed with a brain tumour in the posterior fossa or supratentorium, treated by surgical resection, and not requiring adjuvant therapy (radiotherapy or chemotherapy).
2. The child was to continue to receive follow up treatment from the RCH
3. The child had no history of premorbid neurological or psychiatric problems not associated with the tumour
4. The child's gross developmental level was not more than two years delayed (or their IQ was not below 70 on initial testing)
5. At least one parent was a competent speaker of English
6. The child was English speaking
7. This was their first presentation for treatment of tumour

Children with brainstem tumours or those being placed on palliative care were excluded from this study. Children with a diagnosis of craniopharyngioma, tuberous sclerosis, or neurofibromitosis were also excluded.

At the commencement of the present study twelve children meeting the above criteria had already been recruited as part of a larger study being conducted at the RCH, investigating the development of cognitive and learning difficulties in children treated for a brain tumour. There were four children who met the above criteria,

were diagnosed within the past year, and had not been recruited by the larger project. The parents of these children were contacted by telephone and invited to participate in the present study as it was nearing one-year since the child's diagnosis. Subsequently, parents of children with newly diagnosed brain tumours were contacted in person (when possible) and invited to participate.

A total of 23 participants were contacted. Twenty-two families agreed to enrol in both the present study and the larger study and one family declined. Of the 22 children there were 13 girls and 9 boys. All 22 children were assessed one-year post-surgery. The age range for the total sample at the one-year assessment was 6.1– 17.3 years (M = 11.9, SD = 3.0). A subset of 16 children was also seen for assessment two-years post-surgery. The remaining 6 children did not undergo the two-year assessment because: two were living interstate, two had assessments due after completion of this study, one had a recurrence requiring radiotherapy, and one did not reply to correspondence. The assessments were conducted at one-year (median = 12.06 months) and two-years (median = 23.82 months) post-surgery plus or minus three months. The total sample was divided into two groups according to tumour location at both assessment time points. These groups are described below.

3.1.1 Posterior Fossa Group

Twelve children were diagnosed with posterior fossa tumours, 7 girls and 5 boys, aged 6.1 – 17.3 years (M = 11.0, SD = 3.5) at the one-year assessment. The tumour pathology was: pilocytic astrocytoma = 11 and choroid plexus papilloma = 1. There were 10 children who also underwent assessment two-years post-surgery, 5 girls and 5 boys aged 6.8 – 18.5 years (M = 12.2, SD = 3.8).

Of this group, tumours were located in the following regions: midline = 8, midline extending into the left hemisphere = 1, left cerebellopontine angle = 2, and fourth ventricle = 1.

3.1.2 Supratentorial Group

Ten children were diagnosed with supratentorial tumours, 6 girls and 4 boys, aged 9.5 – 15.5 years (M = 12.9, SD = 1.9) at the one-year assessment. The tumour pathology was: astrocytoma = 3, pilocytic astrocytoma = 3, meningioma = 2, ependymoma = 1, and dysembryoplastic neuroepithelial tumour (DNET) = 1. There were 6 children who also underwent assessment two-years post-surgery, 4 girls and 2 boys aged 11.9 – 16.4 years (M = 14.5, SD = 2.0).

Of this group tumours were located in the following regions: posterior right frontal = 1, left medial temporal = 2, left parietal = 1, left parieto-occipital = 2, right parietal = 1, left lateral ventricle adjacent to the foramen of Munro = 2, and right lateral wall of the third ventricle = 1.

Initial analyses revealed no statistically significant differences between the tumour location groups in terms of age, sex, or SES at either assessment time point.

3.2 Materials

Neurological Severity Score: The Neurological Severity Score (NSS) was calculated retrospectively for each patient using information contained in the patient records at the RCH. The NSS is a measure developed by Ater et al.(1996) to quantify the severity of a brain tumour patient's overall neurological status during the peri-surgical period. The items reflect complications that could potentially result in brain injury and hence reduced neuropsychological functioning. The NSS ranks the severity of neurological events and medical complications occurring within four categories (time periods): pre-existing deficits, events leading up to diagnosis, events during surgery, and post-operative complications due to surgery. A score ranging from 0 – 3 is given for each of the four categories according to the number and severity of medical problems. A score of zero within a category indicates no symptoms, deficits, or events. The overall score (the NSS) is obtained by adding up the ratings for each category, with a higher score reflecting greater overall severity of neurological events. The typical range for the NSS is 0 – 11, except in the case of

complicated courses whereby extra points may be scored in the case of multiple problems within a category. This did not occur in the present study.

Neurological Severity Score from Ater, Moore, Francis, Castillo, Slopis, & Copeland (1996)

SCORE A. Events prior to diagnosis

0__Mild symptoms not affecting mental status, without abnormality on neurological examination

1__Mild neurological symptoms and signs not affecting function performance status

2__Onset of seizures controlled by anticonvulsants; significant neurological deficit resulting in loss of developmental milestones

3__Near-herniation requiring emergency ventriculostomy, respiratory arrest, status epilepticus > 1 hr, cerebellar fits with posturing; surgery done as emergency procedure because of signs of impending herniation (if more than one of these severe events occur, the score should be multiple)

SCORE B. Pre-existing neurological deficits

0__None

1__Pre-existing known borderline intelligence

2__Pre-existing neurological deficit from head trauma, central nervous system infection, or other (eg, mental retardation caused by meningitis in earlier childhood, Down's syndrome, etc.); pre-existing visual or auditory impairment (for known pre-existing mental retardation, score 3 = mild, 4 = moderate, 6 = severe)

SCORE C. Perioperative events

0__Biopsy only without any complication; no change between preoperative and postoperative neurological status

1__Craniotomy with open biopsy or attempted surgical resection; uneventful postoperative recovery with discharge in < 1 week

2__Postoperative period complicated by persistent fever, headache, or vomiting; hydrocephalus requiring shunting; syndrome of inappropriate secretion of antidiuretic hormone (SIADH) leading to seizures or requiring desmopressin (DDAVP); new neurological deficit not present preoperatively

3__*Impending herniation postoperatively requiring preoperative mannitol or second surgical resection; hypotension during surgery due to bleeding; postoperative central nervous system haemorrhage or infarction; not awakening postoperatively for > 24 hours; postoperative meningitis caused by identified organism (if more than one of these severe events occur, the score should be multiple)

SCORE D. Postoperative events, due to surgery

0__After discharge, neurological status continues to improve, no further seizures, not receiving anticonvulsants or dexamethasone after 1 month postoperatively

1__Same as above, but receiving anticonvulsant and/or tapering doses of dexamethasone > 1 month postoperatively, no generalised seizures

2__Continued poorly controlled seizures; significant neurological deficits affecting performance status, eg, hemiparesis, severe ataxia, visual impairment, hearing deficit

3__Persistent mutism, somnolence, or hypothalamic dysfunction (temperature instability, hyperphagia, disordered thirst)

_____**Total score**

* Note: In original paper this was designated a 4, but close examination of the methodology suggests that this is a typographical error and should be 3, as used in the present study.

Tumour Volume: Three-dimensional measurements of tumour size were available from the MRI reports of 12 children, which were multiplied to calculate tumour volume (because of the differing shapes of the tumours these volumes are necessarily approximate). For two of these children two measurements were provided of both the solid and cystic components of the tumour, in which case the largest measurement was used to calculate tumour volume. Four children had two-dimensional measurements of tumour size on their MRI reports. The average of these two measurements was used to estimate the third measurement required to calculate tumour volume. This method of estimation was used on the basis that in those 12 children with a complete set of measurements the three measurements were very similar to each other, indicating that most tumours in this sample were roughly spherical in shape.

Hydrocephalus: Hydrocephalus was retrospectively rated as present or absent on the basis of medical records and/or medical imaging. If there was evidence of hydrocephalus, even if only mild or unilateral, it was rated as present. It was not possible to do an analysis of the severity of hydrocephalus or hydrocephalus requiring a shunt as there was not a sufficient number of children in these groups to conduct statistical analysis and severity was not always clearly described.

Socio-Economic Status: The measure of socio-economic status used was Daniel's (1983) "occupational prestige" scale. This is an Australian developed instrument for measuring socio-economic status normed on an Australian sample. The prestige scale provides a ranking between 1.0 and 7.0 for a wide range of professions. A lower ranking indicates higher prestige. The parents of each child were asked what their main occupation was. Those not currently working were asked their main occupation when they were working. The occupations of both parents were rated on the prestige scale and the ranking for the parent with the higher prestige score was used.

Intelligence: Standardised intellectual assessment was conducted using the Wechsler Intelligence Scale for Children – 3rd Edition (WISC-III; Wechsler, 1992) or the Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III; Wechsler, 1997). The

WISC-III comprises thirteen subtests, three of which are optional. The ten primary subtests and the two optional subtests Digit Span and Symbol Search were administered. Digit Span was used as a measure of immediate auditory attention and Symbol Search as a measure of processing speed. The WAIS-III is comprised of fourteen subtests, three of those optional. The ten primary subtests and the two optional subtests Symbol Search and Letter-Number Sequencing were administered. The Freedom from Distractibility Index (FDI) was calculated from the Arithmetic and Digit Span subtests of the WISC-III. When the WAIS-III was used the Working Memory Index was calculated from the Arithmetic, Digit Span, and Letter-Number Sequencing subtests and used as a substitute for the FDI.

Sustained Attention: The Conners' Continuous Performance Test (CPT; Conners, 1995) was administered as a measure of sustained attention. It is a computerised task that requires the participant to press a button as soon as a letter appears on the screen with the exception of the letter X. Individual letters are presented briefly (250 milliseconds) on the screen and the rate of presentation (the inter-stimulus interval) is varied systematically throughout the test. The CPT runs for approximately fourteen minutes. A number of scores are obtained from this test based on speed and response time. Those used in this study are: Omissions (the number of targets/letters not responded to), Commissions (the number of non-targets/X's responded to), and Reaction Time (the mean response time for all targets). High scores represent poor performance on these measures. A low score for Reaction Time also represents poor (slow) performance. The computer software automatically scores the data using age based norms.

Verbal Learning and Memory: The Children's Version of the California Verbal Learning Test (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994) was used to test verbal learning and memory. The CVLT-C is a list of fifteen words that can be classified according to three semantic categories (fruit, clothing, playthings). The list of words is read aloud by the examiner and the child is asked to recall as much of the list as they can. This is done for a total of five trials and immediately followed with a new 'interference' list (list b). The child has only one trial to recall words from the interference list before they are asked to recall words from the first list without hearing it again (short-delay free recall trial). A long-delay free recall trial is

conducted approximately twenty minutes later where the child is again asked to recall words from the first list last presented to them over twenty minutes earlier. The CVLT-C was scored on computer software (Fridlund & Delis, 1994), which calculates age-based norms for a number of scores including: trial 1 recall, trial 5 recall, short-delay free recall, and long-delay free recall. For participants that were 18 years of age the Adult Version of the California Verbal Learning Test, Research Edition (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) was used. The CVLT is a list of sixteen words that can be classified according to four semantic categories (spices/herbs, fruits, tools, clothing). The administration and scoring is identical to that of the CVLT-C.

Visual Memory and Organisation: The Rey-Osterrieth Complex Figure Test (Spreen & Strauss, 1998) assesses a range of cognitive functions including visuo-spatial skill, memory, organisation, and planning. The child is instructed to copy a picture of the complex geometric figure as best they can. They are then asked to draw the figure from memory thirty-minutes later. It is a test of incidental memory, as the child is not warned that it is a memory test. An accuracy score is calculated for the copy and recall trials which was originally developed by Osterrieth and later modified by Taylor as described in Spreen and Strauss (1998). The normative data used for the accuracy scores were those of Kolb and Whishaw (1990). An organisational score for the copy trial was not calculated due to the lack of adequate norms for this age range.

Verbal Fluency: The Controlled Oral Word Association Test (COWAT; Spreen & Strauss, 1998) is a test of verbal fluency measuring the ability to generate words according to a search strategy. The most common version of the COWAT was used, which requires the child to generate words beginning with a specific letter (F, A, and S) and is thus essentially a test of phonetic fluency/executive function. The child has one minute to orally generate as many words as they can for the given letter. The child is not allowed to say proper nouns or use the same word with a different ending (eg. run, runs, running). The number of correct responses is tallied for each letter and for the three letters combined. The normative data for children aged 7-13 was obtained from the Neuropsychological Assessment of the School-Aged Child while norms for children 14 years and over were derived from the Delis-Kaplan Executive

Function System (Delis, Kaplan, & Kramer, 2001). The children who were aged 6 years at the time of assessment were administered the verbal fluency test from the NEPSY (Korkman, Kirk, & Kemp, 1998). This test requires children to generate words according to two semantic categories (animals and food or drink) and is a test of executive function. The child has one minute for each category and a scaled score is derived from the total number of different words produced. This was administered to 3 children at the one-year assessment and no children at two-years. COWAT norms for this age group were not available.

Academic Skills: The Wechsler Individual Achievement Test (WIAT; The Psychological Corporation, 1992) screen was used to assess basic academic achievement. It comprises three tests: single word reading, spelling, and mathematics reasoning. The child is asked to read/spell/calculate material of increasing difficulty until they complete the test or the discontinue criteria are met. Age normative data were obtained from the WIAT manual.

Visuo-Motor Integration: The Developmental Test of Visual-Motor Integration (VMI; Beery, 1997) is a measure of visuo-motor integration, visual perception, and motor skills. It is a series of 24 geometric designs that progressively increase in difficulty. The child was required to copy each geometric design as best they could in the blank square below the design. The scoring procedure from the 4th Edition, Revised manual (Beery, 1997) was followed, whereby a score of one or zero was awarded to each copy. Standard scores were also calculated from this manual.

Handwriting Speed: The Australian Handwriting Test (Wallen, Bonney, & Lennox, 1996) measures speed of handwriting. The participant is required to write 'The quick brown fox jumps over the lazy dog' as many times as they can in three minutes. They are provided with a lined A4 sheet of paper with the sentence 'The quick brown fox jumps over the lazy dog' printed at the top. The instructions given are: "Write this sentence as many times as you can until I say stop. It doesn't have to be neat, I just want you to write as quickly as you can. Any questions? Begin." The total number of letters written during the time limit is counted; this total is divided by three to provide the average number of letters written per minute. A scaled score can then be obtained based on this average, the child's sex, and their current school year.

Behavioural Adjustment: The Child Behaviour Checklist (CBCL; Achenbach, 1991) is a questionnaire designed to assess the child's current social, emotional, and behavioural status. The questions are designed to assess children from age 4 to 18 years. The parent is required to complete questions about the child's activities, socialisation, and schooling which form the three competency scales: activities, social, school. The parent is also required to rate their child's behaviour on 113 statements using a three-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true). These responses form the 8 problem scales: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behaviour, and Aggressive Behaviour. Most of the 113 problem scale questions are also divided according to whether they reflect an internalising or externalising coping style. The CBCL was scored on computer software (Arnold & Jacobowitz, 1993), which calculates age appropriate T scores for the 3 competency and 8 problem scales. T scores are also calculated for the internalising and externalising factors, the total problem scale, and the total competence scale. High T scores indicate higher levels of problem behaviour for the problem scales and the internalising and externalising factors. Low T scores indicate clinical problems for the competency scale.

Adaptive Behaviour: The Vineland Adaptive Behaviour Scales – Survey Form (Sparrow, Balla, & Cicchetti, 1984) is a structured interview conducted with the parent to determine the child's level of adaptive behaviour on four domains. The four domains are: Communication, Daily Living Skills, Socialisation, and Motor Skills. Each domain is composed of questions that are divided into subdomains. Communication is divided into Receptive, Expressive, and Written; Daily Living Skills is divided into Personal, Domestic, and Community; Socialisation is divided into Interpersonal Relationships, Play and Leisure Time, and Coping Skills; and Motor Skills is divided into Gross and Fine. The optional measure of Maladaptive Behaviour (Part 1) was also administered. This comprises 27 questions about unusual, antisocial, and inappropriate behaviours.

Each domain has up to 92 questions ordered in terms of developmental level of difficulty. The interviews were begun at the developmental questions corresponding

to the child's chronological age. Questions were not read directly from the form but asked in a general manner, if an appropriate response was not elicited further probing was required. The parents responses were coded into one of five options: Yes, usually; Sometimes or partially; No, never; No opportunity; and Don't know. These responses are scored 0, 1, or 2, then summed to produce a score for each subdomain. The subdomains were added to produce the domain score. Standard scores were then obtained for the domain scores. A standard score was also calculated for the Adaptive Behaviour Composite (ABC) – the sum of the domain standard scores.

Medical and Developmental History: A specially developed questionnaire covering medical history, developmental information, school details, and family information was also given to the parents to complete to ensure that this relevant background information was collected (See Appendix One).

Other: As part of the larger study the parents were given instruments to assess Family Functioning and Family Burden of Illness, but these will not be reported in this thesis as this data is beyond the scope of the present study.

Table 3.1 Summary of neuropsychological domains and test scores used for analysis

Domain	Measure of	Test Used
Attention and Executive	Sustained Attention: Inattentiveness	Conners' CPT Omissions
	Sustained Attention: Impulsivity	Conners' CPT Commissions
	Sustained Attention: Processing Speed	Conners' CPT Reaction Time
	Attentional Control	Wechsler FDI
	Executive Function	Verbal Fluency Rey Figure Copy
Memory and Learning	Visual Memory	Rey Figure Delay
	Verbal Memory	CVLT Trial 1 CVLT Trial 5 CVLT Short-Delay CVLT Long-Delay
Visuo-Motor Skills	Visuo-Motor Speed	Wechsler Coding Subtest Handwriting Speed
	Visuo-Motor Integration	VMI
Functional Outcome	Behaviour	CBCL Competence CBCL Internalising CBCL Externalising Vineland ABC
	Academic	WIAT Reading WIAT Mathematics WIAT Spelling

3.3 Procedure

The present study was designed to assess participants at two time points: one-year and two-years after initial surgery to remove the brain tumour. As part of the protocol for the larger study these families were also offered assessments at the time of diagnosis (where possible) and three-years after surgery. The test protocol and procedure were identical for both studies, except that a short-form of the WISC-III

was administered at the two-year assessment to participants enrolled in the larger study only. The short-form WISC-III was also administered at all assessments conducted at diagnosis and three-years post-surgery.

Eligible children and their parents were contacted, when possible, during the initial admission for diagnosis and treatment of brain tumour. They were advised of the study and invited to participate by the neurosurgical or neuro-oncology consultant/nurse, or by the researcher from psychology, and with their agreement they were enrolled into the study. These families were contacted by telephone almost one-year and two-years after their initial admission to arrange assessment times. At each contact point families could choose whether they wished to continue to participate in the study.

At the commencement of the present study parents of eligible children that were not recruited at the time of diagnosis were contacted by telephone as it approached one-year since their initial admission. The study was explained to them, they were invited to participate, and upon agreement an appointment was arranged for the one-year post-surgery assessment. They were also contacted by telephone prior to the two-year assessment to arrange an appointment time.

The assessment procedure was identical for both the one-year and two-year assessments. At the commencement of the first appointment the project was again explained, the plain language statement and written consent forms were offered, and any questions were answered. The assessment began with the researcher conducting a short semi-structured interview with the parent(s) about their child's progress and any ongoing cognitive, academic, medical, social, emotional, or behavioural difficulties they may have been experiencing (approximately 20 minutes; See Appendix Two). The parent(s) then left the room and a one-to-one assessment of the child's intellectual and neuropsychological status was conducted. The parent(s) were asked to complete the Achenbach Child Behaviour Checklist (15-20 minutes), a general questionnaire (10 minutes), and sign a consent form to allow the research report to be put into the child's medical record.

The child's intellectual functioning was assessed using the WISC-III following the standard administration procedure as described in the manual (Wechsler, 1992). The full version (excluding Mazes) was administered in most instances. However, five participants were administered a short-form of the WISC-III at their two-year assessment. In these instances the assessment was conducted prior to the commencement of the present study, and administration of the short-form was protocol for the two-year assessment. The short-form consisted of the following subtests: Information, Coding, Similarities, Arithmetic, Block Design, Digit Span, and Symbol Search. Only one participant was outside of the WISC-III age range and was administered the WAIS-III at both assessments. The standard administration procedure was followed as described in the manual (Wechsler, 1997).

The Rey-Osterrieth Complex Figure Test was administered using an A4 size sheet of paper with the figure taking up most of the top 13 centimetres of the page. The standard administration procedure from Spreen and Strauss (1998) was followed using coloured pens that were changed upon the completion of a section of the drawing (resulting in 3-5 different colours used per drawing). The delayed recall test was conducted thirty-minutes after the initial copy was completed.

The CVLT-C or CVLT was administered according to the procedure in the manual after the copy of the Rey-Osterrieth Complex Figure was completed. Administration involved the presentation of five learning trials, the interference list, the short-delay free-recall trial, and after twenty-minutes the long-delay free-recall trial. The cued recall trials were omitted.

The CPT was administered during the delay period of the Rey-Osterrieth Complex Figure and CVLT-C/CVLT. Each child was read the instructions from the screen, and allowed to read the instructions themselves, before completing the 'standard practice'. Following the standard practice they completed the actual test. The delayed recall trials of the Rey-Osterrieth Complex Figure and CVLT-C/CVLT were administered (respectively) immediately after the CPT was completed.

The COWAT was administered according to the procedure described by Spreen and Strauss (1998). When the child paused for 15 seconds or more the basic instructions were repeated.

The Australian Handwriting Test was then administered according to the instructions outlined in the Materials section.

The WIAT screen was administered in the standard order (reading, mathematics, spelling) according to the procedure in the manual and using the standard forms. Finally, the VMI was administered following the instructions in the manual and the child was asked to stop drawing once the discontinue criteria were met. For both the VMI and Australian Handwriting Test a grey lead pencil was used and erasers were not allowed.

Following cognitive assessment of the child one parent was asked to complete the Vineland Adaptive Behaviour Scales with the researcher. The standard administration procedure from the manual was followed.

Each assessment was conducted on one day and the measures were administered in a fixed order, as described above. The overall duration of the actual testing was about two and a half hours. In the course of testing at least two breaks were given and more were offered as needed. Following each assessment the researcher wrote a summary report of the child's performance at that assessment to provide to the family. Due to time constraints some children were unable to complete all tests. Some children were too young to complete the Conners' CPT or the handwriting speed test. Further, some parents did not complete all of the items on questionnaires due to time restraints or parental failure to complete all items.

While the neuropsychological assessments were conducted prospectively, the NSS was calculated retrospectively. The NSS was calculated based on the close examination of medical records and rated on the NSS form. This was the standard procedure for calculating the NSS used by Ater et al. (1996). There was most variation in symptomatology for the category 'Events prior to diagnosis'. Prior to scoring the NSS a decision was reached regarding the types of symptoms that would

meet criteria for a score of 1 or 2 points based on the expert judgement of a Neurologist. For example, ataxia or sensory loss would receive a score of 2 because they would result in loss of developmental milestones whereas intermittent convergent squint or papilloedema would only receive a score of 1 because by themselves they were not considered to affect functional performance. The researcher calculated the NSS for all 22 children in consultation with an experienced Clinical Neuropsychologist whenever necessary. A convenient sample reflecting a range of NSSs were checked for inter-rater reliability (N = 6). A Neurologist and Neuro-oncology Nurse independently evaluated these six protocols and the agreement was perfect on five out of six. On the sixth case the NSSs differed by one point.

3.4 Research Ethics Approval

The Victoria University Psychology Department Ethics Committee granted ethics approval for the present study on the 2nd August 2001. Documenting evidence is attached (See Appendix Three). The larger study being conducted at the RCH (Stargatt, Anderson, & Rosenfeld, 1999), of which the present study is a part, received ethics approval from the RCH Ethics in Human Research Committee on the 8th June 1999. Documenting evidence is attached (See Appendix Four).

Plain language statements and consent forms were given to the parent(s) of each participant prior to testing. Participant plain language statements and consent forms were also given to children over 12 years of age. All of the parents and children over 12 years agreed to participate in the study and signed the consent forms.

Chapter Four – Results

4.1 Data Screening

The Kolmogorov-Smirnov Test of Normality was conducted with all variables (neuropsychological domain variables, NSS, and tumour volume). For Hypothesis One and Two Part A (tumour volume) these tests were conducted for the group as a whole. They were conducted by group for Hypothesis Two Part B (hydrocephalus) and Hypothesis Three to Five (tumour location). The presence of extreme scores and outliers were detected using boxplots. All extreme scores were recoded closer to the mean of the group being studied by giving them a value one unit further from the mean than the next most extreme case, as suggested by Tabachnick and Fidell (1996). Doing this helps to minimise the effect of extreme scores while still upholding the effect under investigation. This technique is conservative in that it reduces the likelihood of detecting statistically significant differences between the groups. Outliers that were impacting on the normality of variables were also recoded using this procedure.

There was very little data missing from the variables under investigation (34 of the total 462 scores at one-year and 7 of 336 scores at two-years). This data was replaced as it appeared to be missing randomly; it was missing across the range of variables, it was missing equally between the groups at 1 year, and at 2 years slightly more was missing from the posterior fossa group which approximately reflected the proportions of children in each group at that time point. Missing data was replaced using the mean score of the group under investigation after recoding extreme values and outliers (this is a conservative technique). Normality was reassessed following these procedures.

4.2 Analysis of IQ

Independent-samples t-tests revealed no significant differences between the children treated for posterior fossa tumour (PF) and the children treated for supratentorial tumour (ST) in terms of FSIQ, VIQ, or PIQ at the one-year assessment (See Table 4.1). There were also no significant differences between the groups on FSIQ at the two-year assessment. Of the children that completed a full IQ test at two-years (half of each group N = 8) there were no VIQ or PIQ differences between the PF and ST groups. There were also no differences between the groups and normative data on any of the IQ measures at one-year and two-years.

Table 4.1 Mean IQ scores by tumour location at one-year

Tumour Location	FSIQ	VIQ	PIQ
PF	96.00 (12.62)	97.17 (13.47)	95.42 (13.05)
ST	103.20 (13.65)	101.60 (13.88)	104.90 (13.49)

An initial analysis was done to determine whether IQ scores of the whole sample at one-year were related to the three prediction variables (NSS, tumour volume, and hydrocephalus) and hence whether it might account for some of the variance in relationships found between these predictors and neuropsychological outcome. FSIQ, VIQ, and PIQ were not significantly related to any of these prediction variables, although a small, positive correlation was found between these three scores and tumour volume. A small positive correlation was also found between VIQ and the NSS.

Further analysis was conducted to determine the strength of relationship between FSIQ, VIQ, and PIQ at one-year with the neuropsychological outcome variables. Pearson's correlations were conducted for all variables except CVLT Trial 5 which did not meet criteria for normality. A Spearman's rank order correlation was conducted for this variable.

The strength of relationship was defined according to Cohen's (1988) guidelines, where:

- small r = .10 to .29
- medium r = .30 to .49
- large r = .50 to 1.0

A number of significant correlations were found, and most variables had a moderate or large relationship with at least two of the IQ measures (See Table 4.2). Coding and Freedom from Distractibility (FDI) were strongly correlated with all three IQ scores, which would be expected given they are from the WISC-III/WAIS-III and at least in part form two of the IQ indices. Small or no relationships were found between IQ scores and CPT Commissions, Rey Figure Delay, CVLT Trial 1, and CBCL Internalising.

Table 4.2 Moderate and large correlations between IQ scores and neuropsychological variables at one-year

	FSIQ	VIQ	PIQ
CPT Omissions+	-.47*	-.49*	-.35
CPT Reaction Time+	.58**	.61**	.42*
FDI	.83**	.73**	.74**
Verbal Fluency	.65**	.66**	.49*
Rey Figure Copy	.46*	.33	.49*
CVLT Trial 5	.51*	.50*	.37
CVLT Short-Delay	.37	.39	.18
CVLT Long-Delay	.37	.39	.23
Coding	.75**	.51*	.83**
VMI	.63**	.44*	.70**
Handwriting Speed	.35	.31	.31
CBCL Competence	.60**	.54**	.52*
CBCL Externalising+	-.36	-.23	-.41
Vineland ABC	.67**	.75**	.46*
WIAT Reading	.75**	.81**	.52*
WIAT Maths	.80**	.79**	.63**
WIAT Spelling	.66**	.76**	.40

* Correlation is significant at the 0.05 level (2-tailed)

**Correlation is significant at the 0.01 level (2-tailed)

\+ Note: High scores indicate deficits

4.3 Hypothesis One: Relationship Between Neurological Severity Score and Neuropsychological Outcome at One-Year

Two outliers were identified in the neuropsychological variables at one-year (in Coding and CBCL Competency) and were recoded according to the procedure described above (section 4.1). CVLT Trial 5 was the only variable not to meet

criteria for normality. This was included in the analysis for Hypothesis 1 because non-parametric tests were employed.

Given that the NSS is an ordinal measurement Spearman's rank order correlations (non-parametric) were conducted between the NSS and the 21 variables measured at the one-year assessment. Differences between the tumour location groups on the NSS were explored using a Mann-Whitney U Test. The groups did not differ in terms of the NSS.

The NSS values ranged from 2 – 6 (Median = 4, Interquartile Range = 3.00 – 5.25). Of the 21 neuropsychological variables only CBCL Externalising correlated significantly with the NSS. There was a moderate, negative relationship between the two variables ($\underline{r}$ = -.48, $\underline{n}$ = 22, $\underline{p}$ = .025). There was also a moderate, negative relationship between the NSS and CVLT Trial 1 ($\underline{r}$ = -.35, $\underline{n}$ = 22, $\underline{p}$ = .107). A number of small correlations were also found with the variables CPT Commissions, CPT Reaction Time, FDI, Rey Figure Copy, Rey Figure Delay, CVLT Trial 5, Handwriting Speed, CBCL Competence, CBCL Internalising, Vineland ABC, WIAT Maths, and WIAT Spelling (See Appendix Five, Table 1). No relationship was found between the NSS and CPT Omissions, Verbal Fluency, CVLT Short-Delay, CVLT Long-Delay, Coding, VMI, or WIAT Reading.

4.4 Hypothesis Two: Relationship Between Tumour Volume and Neuropsychological Outcome at One-Year

Outliers and normality were assessed as described for Hypothesis One. Preliminary analyses were conducted to ensure no violation of the assumptions of linearity and homoscedasticity. Pearson's correlations were conducted between tumour volume and the 20 variables meeting criteria for normality. A Spearman's rank order correlation was conducted for CVLT Trial 5 because it did not meet criteria for normality. Differences between the tumour location groups in terms of tumour volume were explored using an independent samples t-test.

Tumour volume measurements were available for a subset of 16 patients (n = 8 PF, 8 ST). Two of these children had ST meningiomas and were excluded from the analysis on the basis that these extra-cerebral tumours do not exert the same disruptive effect on brain and brain systems as intra-cerebral tumours. Tumour volume ranged from 1.0 – 216 cubic centimetres (M = 82.32, SD = 66.85). There was no significant difference in tumour volume for the PF group (M = 93.6, SD = 48.54) and the ST group (M = 67.25, SD = 88.56; t(12) = .72, p = .487).

There was a strong, positive correlation between tumour volume and CBCL Competence (r = .54, n = 14, p = .047). There was a moderate, positive correlation between tumour volume and Rey Figure Copy (r = .41, n = 14, p = .144), CVLT Short-Delay (r = .34, n = 14, p = .228), and CVLT Long-Delay (r = .30, n = 14, p = .305). A number of small correlations were also found with the variables CPT Omissions, CPT Commissions, CPT Reaction Time, FDI, Verbal Fluency, Rey Figure Delay, CVLT Trial 1, CVLT Trial 5, CBCL Externalising, Vineland ABC, WIAT Reading, WIAT Maths, WIAT Spelling (See Appendix Five, Table 2). Coding, VMI, Handwriting Speed, and CBCL Internalising had no relationship with tumour volume.

4.5 Hypothesis Two: Relationship Between Hydrocephalus and Neuropsychological Outcome at One-Year

Extreme values or outliers requiring recoding were found for the following 12 variables: Verbal Fluency, Rey Figure Copy, CVLT Trial 1, CVLT Trial 5, CVLT Short-Delay, CVLT Long-Delay, Coding, VMI, CBCL Competence, CBCL Internalising, Vineland ABC, and WIAT Mathematics. After recoding outliers CVLT Trial 5 and CBCL Internalising did not meet the criteria for normality and were excluded from the MANOVAs.

Four one-way between-groups MANOVAs were planned, one for each neuropsychological domain (See Table 3.1), to examine differences between children who experienced hydrocephalus and those that did not. The assumptions of MANOVA were checked before performing the analyses. The variables within each

domain met criteria for linearity and multivariate normality and no multivariate outliers were detected. A problem with multicollinearity was found between CVLT Short-Delay and CVLT Long-Delay. Thus CVLT Short-Delay was excluded from the MANOVA.

The four MANOVAs were conducted excluding CVLT Trial 5 and CVLT Short-Delay from the Memory and Learning Domain and CBCL Internalising from the Functional Outcome Domain. As part of the MANOVAs Levene's Test of Equality of Error Variances and Box's Test of Equality of Covariance Matrices were performed. The assumption of homogeneity of variance-covariance matrices was met for all domains. The VMI variable was significant on Levene's Test and hence results from the MANOVA were interpreted with caution for this variable.

Of the three variables excluded from the MANOVAs, Mann-Whitney U Tests were used to evaluate the two that violated the assumption of normality (CVLT Trial 5 and CBCL Internalising). An independent samples t-test was used for the variable that violated the assumption of multicollinearity (CVLT Short-Delay). Differences between the tumour location groups in terms of hydrocephalus could not be explored formally because cell frequencies were too small to conduct a Chi-square test. Notwithstanding, inspection of the data strongly indicated an association between hydrocephalus and tumour location.
Thirteen children had hydrocephalus and 9 did not (See Table 4.4).

Table 4.3 Frequency of hydrocephalus by tumour location

	Hydrocephalus	**No Hydrocephalus**	**TOTAL**
PF % of total	**10** 45.5%	**2** 9.1%	**12**
ST % of total	**3** 13.6%	**7** 31.8%	**10**
TOTAL	**13**	**9**	**22**

Due to the small sample size this study was not statistically powerful enough to detect significant differences, thus moderate and large effect sizes were reported to explore trends in the data. A moderate effect size was defined as a partial eta squared of .06 to .13 and a large effect size was defined as a partial eta squared of .14 and above (Cohen, 1988).

There were no statistically significant differences between children who had hydrocephalus and those who did not on the combined neuropsychological variables within each domain at one-year post-surgery. However, a large effect size was found for the Attention/Executive, Memory/Learning, and Functional Outcome domains.

4.5.1 Attention and Executive: Hydrocephalus Compared With No Hydrocephalus

In the Attention and Executive domain no significant differences were found and there was a large effect size for the combined dependent variables: $F(6, 15) = .95$, $p = .487$; Wilks' Lambda = .72; partial eta squared = .28. An examination of the individual variables showed that Verbal Fluency had a large effect size: partial eta squared = .17. A moderate effect size was found for CPT Reaction Time: partial eta squared = .06. An inspection of the mean scores indicated that the hydrocephalus group performed more poorly on these measures than the group without hydrocephalus (See Figure 4.1).

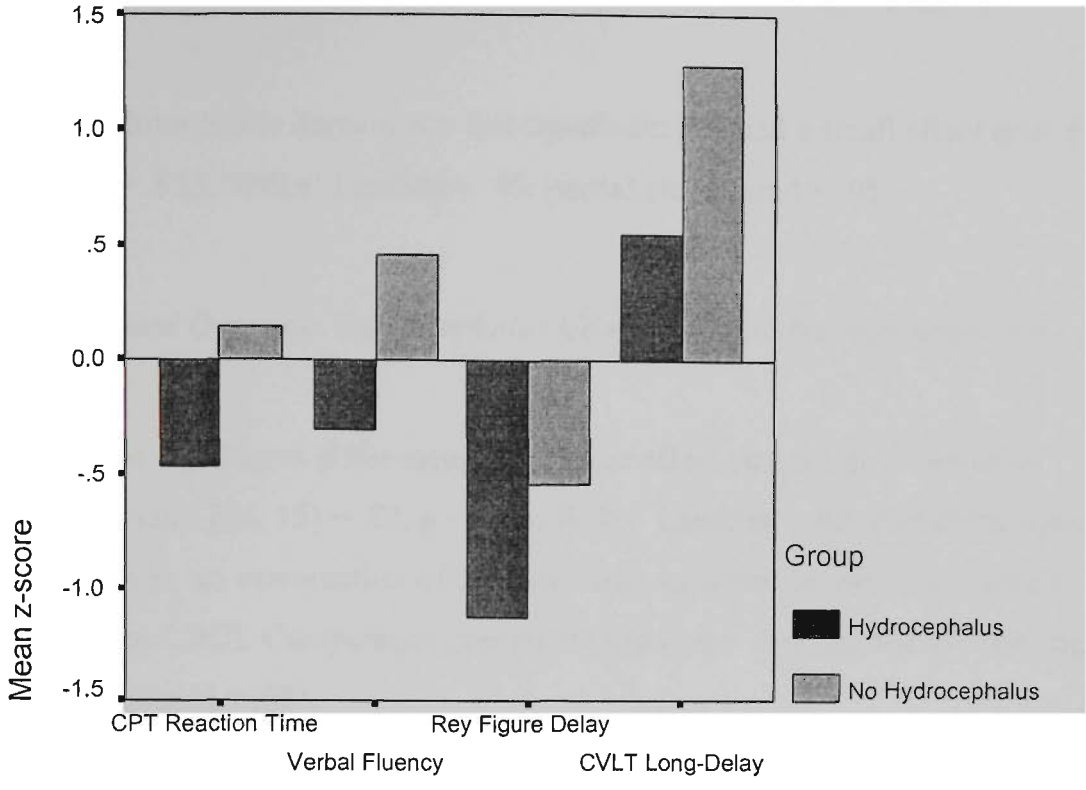

Figure 4.1 Means for hydrocephalus groups on neuropsychological variables with moderate or large effect sizes

4.5.2 Memory and Learning: Hydrocephalus Compared With No Hydrocephalus

While there were no significant differences a large effect size was found for the combined Memory and Learning variables: $F(3, 18) = 1.93$, $p = .161$; Wilks' Lambda = .76; partial eta squared = .24. An inspection of the individual variables revealed that CVLT Long-Delay had a large effect size: partial eta squared = .19. A moderate effect size was found for Rey Figure Delay: partial eta squared = .06. An inspection of the mean scores indicated that the hydrocephalus group performed more poorly on these measures (See Figure 4.1).

No significant differences were found between hydrocephalus groups for CVLT Trial 5 ($U = 34.50$, $p = .101$) and CVLT Short-Delay ($t(20) = -1.14$, $p = .268$).

4.5.3 Visuo-Motor Skills: Hydrocephalus Compared With No Hydrocephalus

The Visuo-Motor Skills domain was not significant and had a small effect size: $F(3, 18) = .32$, $p = .813$; Wilks' Lambda = .95; partial eta squared = .05.

4.5.4 Functional Outcome: Hydrocephalus Compared With No Hydrocephalus

There were no significant differences and a large effect size for the Functional Outcome domain: $F(6, 15) = .57$, $p = .750$; Wilks' Lambda = .82; partial eta squared = .19. However, an examination of the individual variables revealed only small effect sizes for CBCL Competence (partial eta squared = .04) and WIAT Reading (partial eta squared = .03).

The difference between hydrocephalus groups on CBCL Internalising was evaluated using a Mann-Whitney U Test. No significant differences were found between the groups ($U = 44.50$, $p = .348$).

4.6 Hypothesis Three: Relationship Between Tumour Location and Neuropsychological Outcome at One-Year

Extreme values or outliers requiring recoding were found for the following 5 variables: CVLT Trial 1, CVLT Trial 5, CVLT Short-Delay, Coding, and VMI. After recoding outliers CVLT Trial 1 did not meet the criteria for normality. In addition CPT Omissions and CBCL Internalising did not meet criteria for normality and all three variables were excluded from the MANOVAs.

Four one-way between-groups MANOVAs were planned, one for each neuropsychological domain, to examine differences between children with posterior fossa tumours and supratentorial tumours at one-year. The assumptions of MANOVA were checked before performing the analyses. The variables within each domain met criteria for linearity and multivariate normality and no multivariate outliers were detected. A problem with multicollinearity was again found between

CVLT Short-Delay and CVLT Long-Delay, thus CVLT Short-Delay was excluded from the MANOVA.

The four MANOVAs were conducted excluding CPT Omissions from the Attention and Executive Domain, CVLT Trial 1 and CVLT Short-Delay from the Memory and Learning Domain, and CBCL Internalising from the Functional Outcome Domain. As part of the MANOVAs Levene's Test of Equality of Error Variances and Box's Test of Equality of Covariance Matrices were performed. The assumption of homogeneity of variance-covariance matrices was met for all domains. The VMI and WIAT Mathematics variables were significant on Levene's Test and hence results from the MANOVA were interpreted with caution for these variables.

Mann-Whitney U Tests were used to evaluate the differences between groups on the three variables excluded from the MANOVAs due to violation of the assumption of normality (CPT Omissions, CVLT Trial 1, and CBCL Internalising). CVLT Short-Delay was excluded for violating the assumption of multicollinearity, thus an independent samples t-test was used to examine group differences on this measure.

There was a statistically significant difference between the PF children and ST children on the combined neuropsychological variables for the Memory and Learning domain. There were no statistically significant differences between groups for the remaining three domains, thus effect sizes were used to examine trends in the data. A large effect size was found for each domain.

4.6.1 Attention and Executive: PF Group Compared With ST Group

No statistically significant difference was found for the attention and executive domain but there was a large effect size for the combined dependent variables: $\underline{F}(5, 16) = 1.10$, $\underline{p} = .401$; Wilks' Lambda = .75; partial eta squared = .26. An examination of the individual variables showed that Verbal Fluency had a large effect size: partial eta squared = .17. A moderate effect size was found for FDI (partial eta squared = .09) and Rey Figure Copy (partial eta squared = .08). An inspection of the

mean scores indicated that the PF group performed more poorly than the ST group on all of these measures (See Figure 4.2).

No significant difference was found between the tumour location groups for CPT Omissions evaluated using a Mann-Whitney U Test (U = 41.50, p = .222).

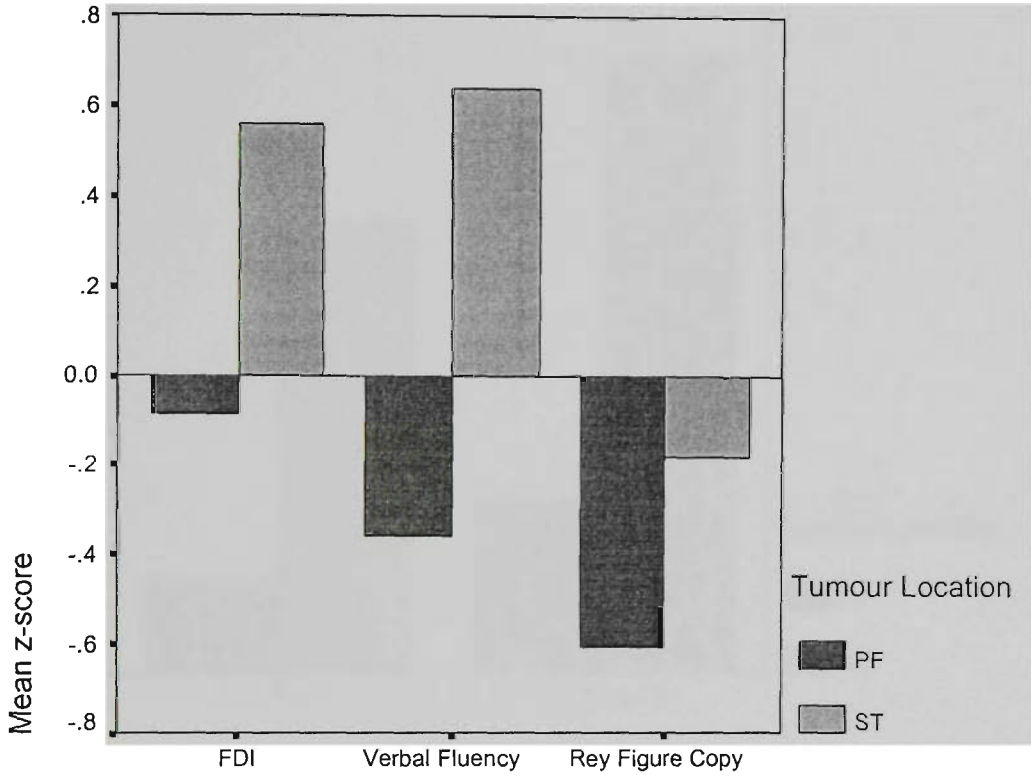

Figure 4.2 Means for PF and ST groups on attention and executive variables with moderate or large effect sizes

4.6.2 Memory and Learning: PF Group Compared With ST Group

There was a statistically significant difference between the PF group and ST group on the combined Memory and Learning variables: F(3, 18) = 3.20, p = .048; Wilks' Lambda = .53; partial eta squared = .35. When the individual variables were inspected, the only difference to reach statistical significant was the CVLT Trial 5: F(1, 20) = 5.97, p = .024, partial eta squared = .23. An examination of the mean scores indicated that the PF group performed more poorly than the ST group on this measure (See Figure 4.3).

No difference was found for CVLT Short-Delay: t (20) = -1.77, p = .093. A statistically significant difference was found between the groups for CVLT Trial 1: U = 21.00, p = .009. The PF group performed more poorly than the ST group (See Figure 4.3).

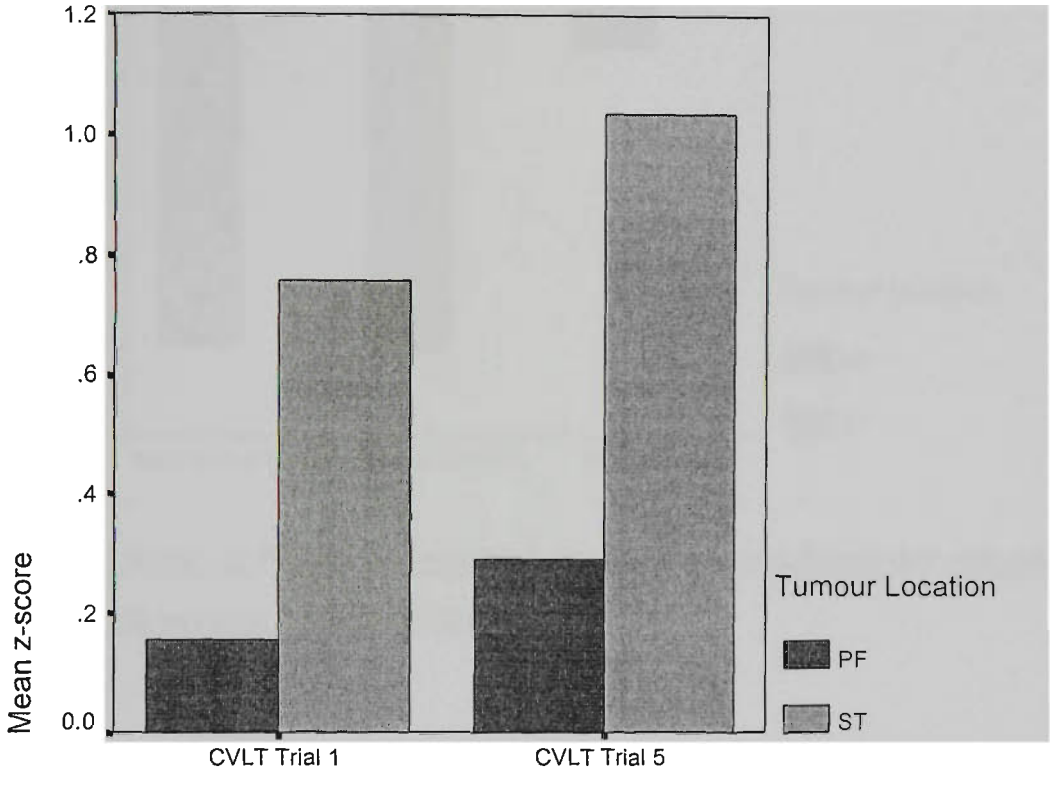

Figure 4.3 Means for PF and ST groups on memory and learning variables with moderate or large effect sizes

4.6.3 Visuo-Motor Skills: PF Group Compared With ST Group

The Visuo-Motor Skills domain was non-significant and had a large effect size: F(3, 18) = 1.81, p = .182; Wilks' Lambda = .77; partial eta squared = .23. An examination of the individual variables showed that Handwriting Speed had a large effect size: partial eta squared = .17. VMI was found to have a moderate effect size (partial eta squared = .13), but as this variable violated the assumption of equality of error variances this result was considered to be inflated. Examination of the mean scores revealed the PF group performed more poorly on Handwriting Speed than the ST group (See Figure 4.4).

Figure 4.4 Means for PF and ST groups on visuo-motor and functional outcome variables with moderate or large effect sizes

4.6.4 Functional Outcome: PF Group Compared With ST Group

There were no statistically significant differences for the Functional Outcome domain but a large effect size was found: $F(6, 15) = 1.44$, $p = .264$; Wilks' Lambda = .63; partial eta squared = .37. When the variables were considered individually, Vineland ABC had a large effect size: partial eta squared = .33. A moderate effect size was found for WIAT Spelling: partial eta squared = .07. The moderate effect size found for WIAT Maths (partial eta squared = .09) was considered an overestimate given this variable violated the assumption of equality of error variances. An examination of the means showed that the PF group performed more poorly than the ST group on these measures (See Figure 4.4).

No significant difference was found between the tumour location groups for CBCL Internalising on a Mann-Whitney U Test ($U = 59.00$, $p = .947$).

4.7 Hypothesis Four: Tumour Location Groups Compared with Normal Population at One-Year

One-sample t-tests were used to compare children in each tumour location group to the normal population at one-year. These comparisons were made for all variables including those not meeting criteria for normality, namely: CPT Omissions (posterior fossa), CVLT Trial 1 (supratentorial), and CBCL Internalising (posterior fossa). Non-normal variables were included for illustrative purposes and it is noted that the results for these variables should be interpreted with caution. Further, it is recognised that the results of multiple one-sample t-tests should be interpreted with some caution as no correction for Type 1 error rate was made. However, a simple correction such as a Bonferroni adjustment is not strictly justified as the normative data to which scores are compared were obtained from different samples. See Appendix Six for a complete list of the mean z-scores for each group at one-year.

4.7.5 PF Group Compared With Normal Population at One-Year

The PF group differed significantly from the normal population on six of the variables. These were: the Rey Figure Copy ($t(11) = -2.47$, $p = .031$) from the Attention and Executive domain, the Rey Figure Delay ($t(11) = -2.74$, $p = .019$) from the Memory and Learning domain, Coding ($t(11) = -2.44$, $p = .033$) and Handwriting Speed ($t(11) = -3.48$, $p = .005$) from the Visuo-Motor Skills domain, and CBCL Competence ($t(11) = -4.32$, $p = .001$) and Vineland ABC ($t(11) = -6.30$, $p < .0005$) from the Functional Outcome domain. The groups also differed on the two variables that did not meet criteria for normality. These were CPT Omissions ($t(11) = 3.07$, $p = .011$) and CBCL Internalising ($t(11) = 2.36$, $p = .038$). It is again noted that these results are exploratory and should be interpreted with caution. The PF group performed more poorly than the normal population on all of these variables (See Figure 4.5).

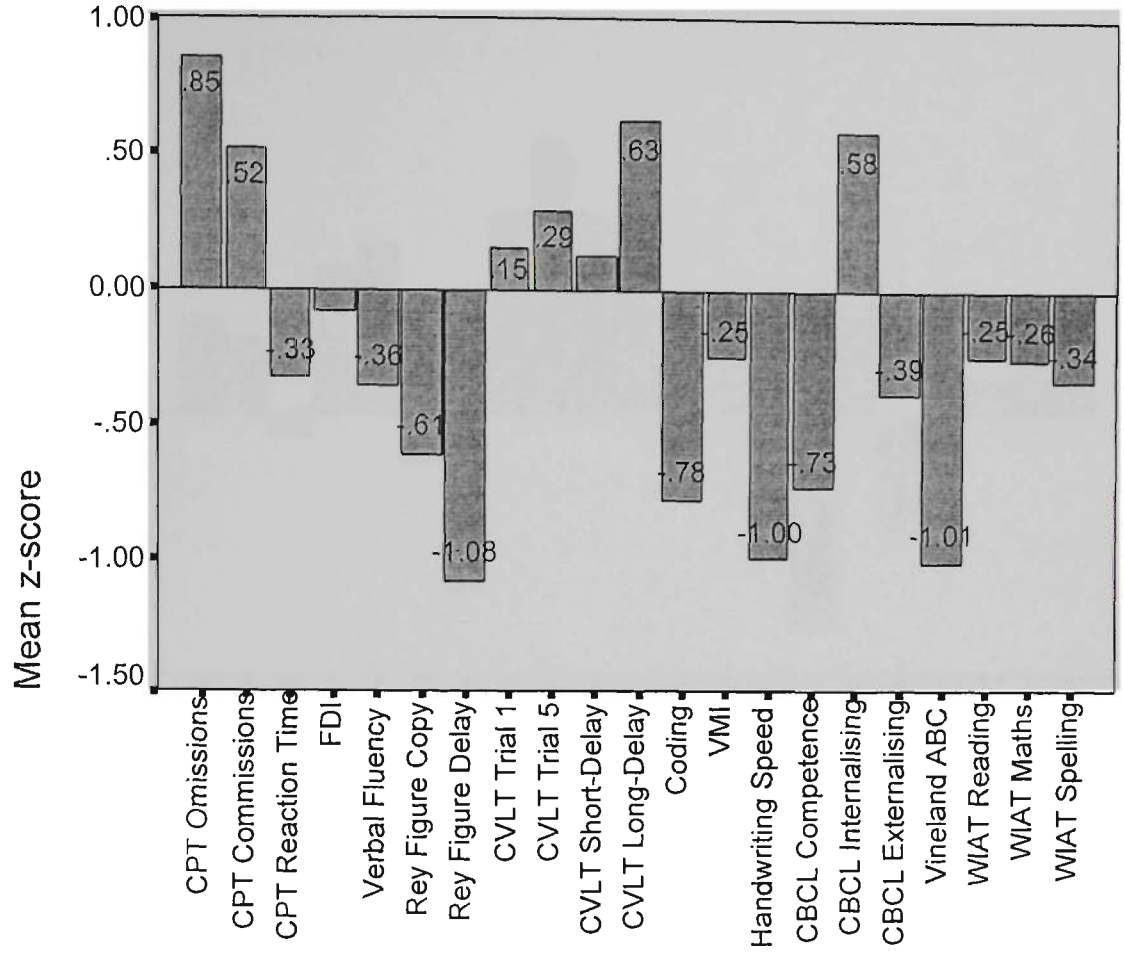

Figure 4.5 Mean difference of the PF group from the normal population at one-year

4.7.6 ST Group Compared With Normal Population at One-Year

The ST group differed from the normal population on four of the variables. These were: CVLT Trial 5 ($t(9) = 7.08$, $p < .0005$), CVLT Short-Delay ($t(9) = 3.07$, $p = .013$), and CVLT Long-Delay ($t(9) = 2.33$, $p = .045$) from the Memory and Learning domain as well as CBCL Competence ($t(9) = -5.19$, $p = .001$) from the Functional Outcome domain. The groups also differed on CVLT Trial 1 which did not meet criteria for normality, although this result is exploratory and should be interpreted with caution. The ST group performed better than the normal population on all of these variables except CBCL Competence (See Figure 4.6).

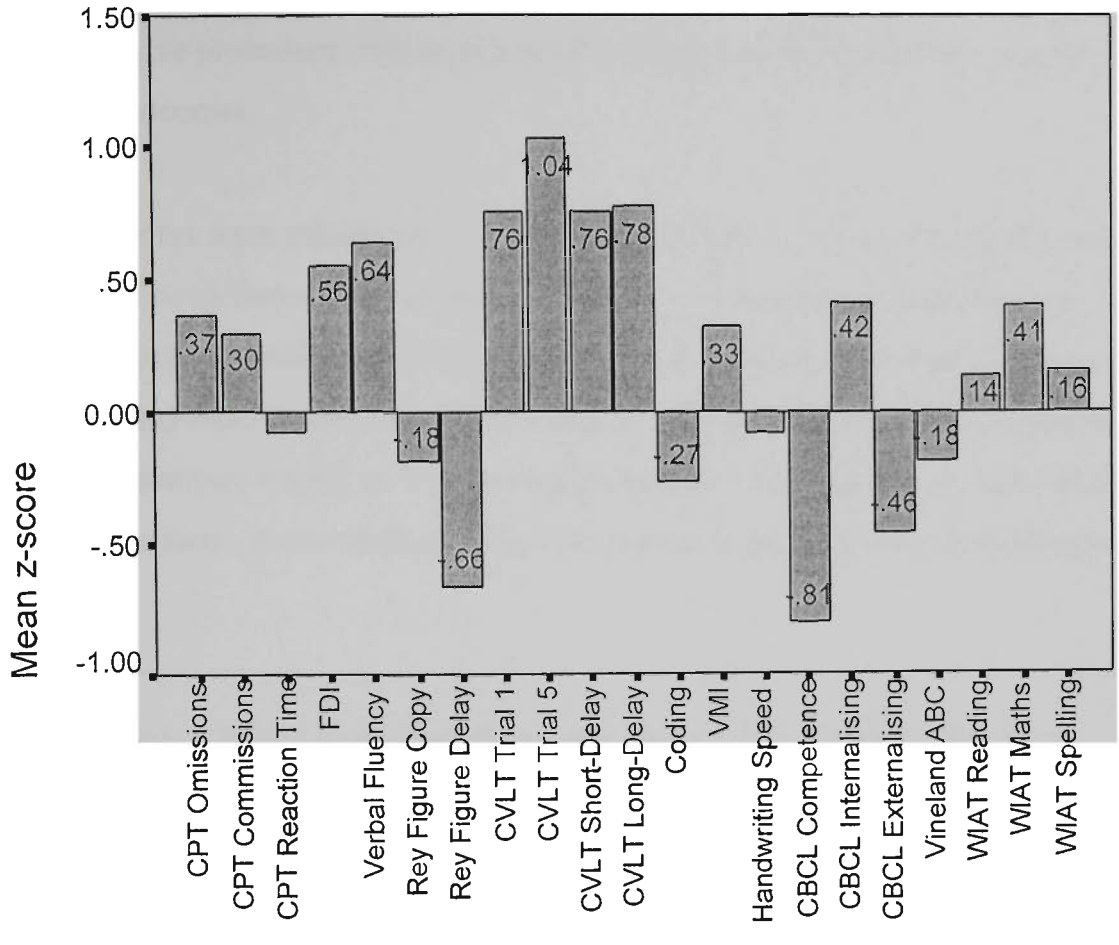

Figure 4.6 Mean difference of the ST group from the normal population at one-year

4.8 Aim Four: Relationship Between Tumour Location and Change Over Time

Of the subset of children seen at both time points extreme values and outliers requiring recoding were found for the following variables at one-year: CVLT Trial 1, CVLT Trial 5, CVLT Short-Delay, and CVLT Long-Delay. At two-years extreme values and outliers requiring recoding were found for: CPT Omissions, Rey Figure Copy, CVLT Trial 1, CVLT Short-Delay, VMI, and WIAT Maths. After recoding outliers the assumption of normality was violated for CVLT Trial 1 at one-year (supratentorial) and for the following 3 variables at two-years: Rey Figure Delay (supratentorial), CVLT Trial 1 (posterior fossa), and CVLT Trial 5 (posterior fossa).

Due to the small sample size (PF N = 10, ST N = 6) and the large number of dependent variables it was not feasible to conduct analyses for every variable.

Bonferroni adjustment to Type I error rate was not conducted as it was felt that using this conservative procedure with such a small number of participants may result in misleading outcomes.

Difference scores were calculated for each variable (Time 2 – Time 1) and converted to z-scores. The difference scores were graphed for each tumour location group. For each group the five variables that showed the greatest amount of change over time (in either direction) were chosen for further analysis. These variables were examined using paired-samples t-tests, or Wilcoxon Signed Ranks Tests for the variables that did not meet criteria for normality. Effect size was calculated for all paired-samples t-tests.

4.8.1 PF Group: Change Over Time From One-Year to Two-Years Post-Surgery

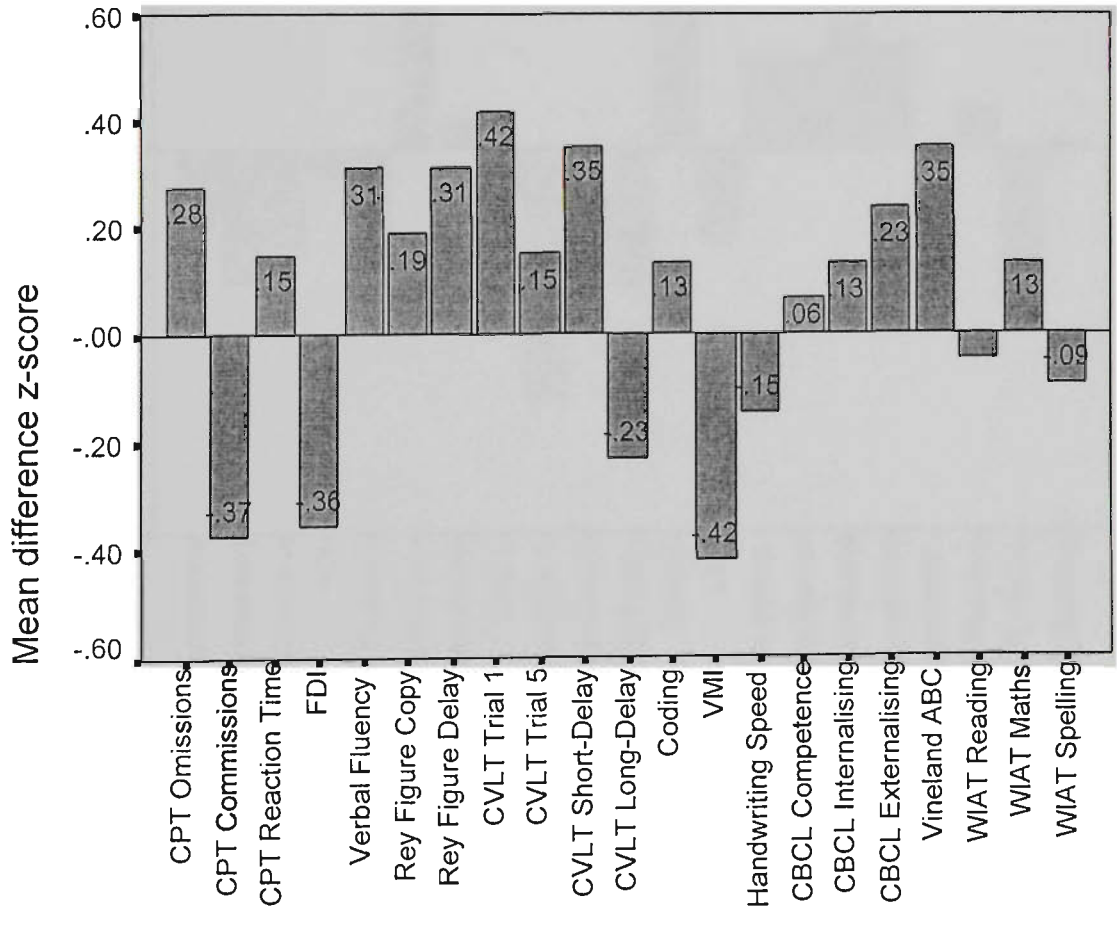

Figure 4.7 Change over time: Difference from one-year to two-years in the PF group

The five variables to show the most change over a one-year period for the PF group were: CPT Commissions, FDI, CVLT Trial 1, CVLT Short-Delay, and VMI (See Figure 4.7). A statistically significant improvement in scores from the one-year assessment to the two-year assessment was found for CVLT Trial 1 ($\underline{Z} = -2.41$, $\underline{p} = .016$) while a significant decline was found for VMI ($\underline{t}(9) = 2.28$, $\underline{p} = .049$, eta squared = .37). The change in scores over time was not significant for CPT Commissions ($\underline{t}(9) = 1.23$, $\underline{p} = .248$, eta squared = .14), FDI ($\underline{t}(9) = 1.50$, $\underline{p} = .168$, eta squared = .20), or CVLT Short-Delay ($\underline{t}(9) = -1.41$, $\underline{p} = .191$, eta squared = .18). All the normal variables had a large effect size.

4.8.2 ST Group: Change Over Time From One-Year to Two-Years Post-Surgery

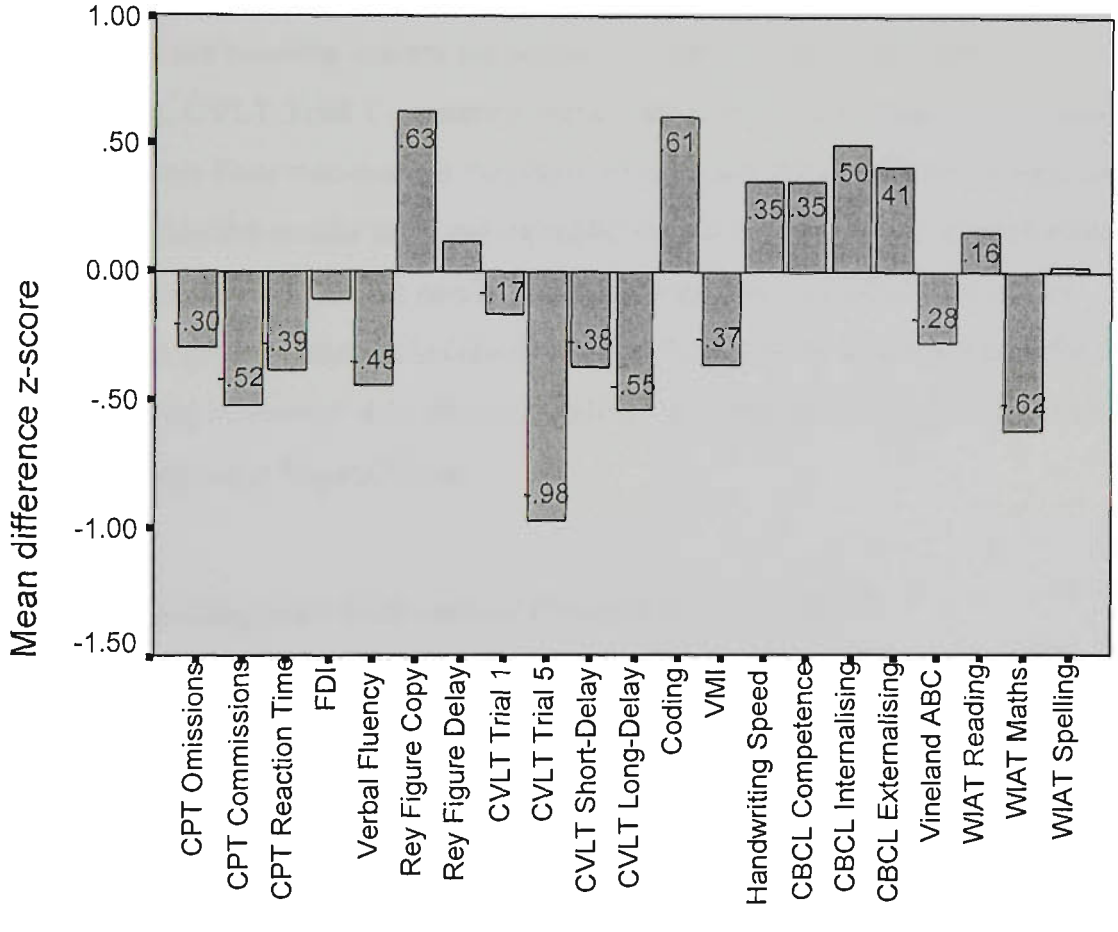

Figure 4.8 Change over time: Difference from one-year to two-years in the ST group

The five variables to show the most change over a one-year period for the ST group were: Rey Figure Copy, CVLT Trial 5, CVLT Long-Delay, Coding, and WIAT

Maths (See Figure 4.8). A statistically significant decline in scores from the one-year assessment to the two-year assessment was found for CVLT Trial 5 ($Z = -2.03$, $p = .042$). The change in scores over time was not significant for Rey Figure Copy ($t(5) = -2.25$, $p = .075$, eta squared = .50), CVLT Long-Delay ($t(5) = 1.51$, $p = .192$, eta squared = .31), Coding ($t(5) = -1.66$, $p = .159$, eta squared = .35), or WIAT Maths ($t(5) = 1.57$, $p = .178$, eta squared = .33). All the normal variables had a large effect size.

4.9 Hypothesis Five: Tumour Location Groups Compared with Normal Population at Two-Years

One-sample t-tests were used to compare children in each tumour location group to the normal population at two-years. These comparisons were made for all variables including those not meeting criteria for normality, namely: Rey Figure Delay (supratentorial), CVLT Trial 1 (posterior fossa), and CVLT Trial 5 (posterior fossa). As for Hypothesis Four non-normal variables were included for illustrative purposes and it is noted that the results for these variables should be interpreted with caution. Further, it is again noted that the results of multiple one-sample t-tests should be interpreted with some caution as no correction for Type 1 error rate was made for the reasons described in Section 4.7. For a complete list of the mean z-scores for each group at two-years see Appendix Six.

4.9.1 PF Group Compared With Normal Population at Two-Years

The PF group differed significantly from the normal population on six of the variables at two-years. These were: CPT Omissions ($t(9) = 7.67$, $p < .0005$) from the Attention and Executive domain, VMI ($t(9) = -2.62$, $p = .028$) and Handwriting Speed ($t(9) = -3.06$, $p = .014$) from the Visuo-Motor Skills domain, and CBCL Competence ($t(9) = -2.55$, $p = .031$), CBCL Internalising ($t(9) = 2.79$, $p = .021$), and Vineland ABC ($t(9) = -2.81$, $p = .020$) from the Functional Outcome domain. The PF group performed worse than the normal population on all of these variables (See Figure 4.9).

The PF group also performed significantly better than the normal population on one of the two variables that did not meet criteria for normality, CVLT Trial 1 ($t(9) = 3.51$, $p = .007$), although this significant result should be interpreted with caution (See Figure 4.9).

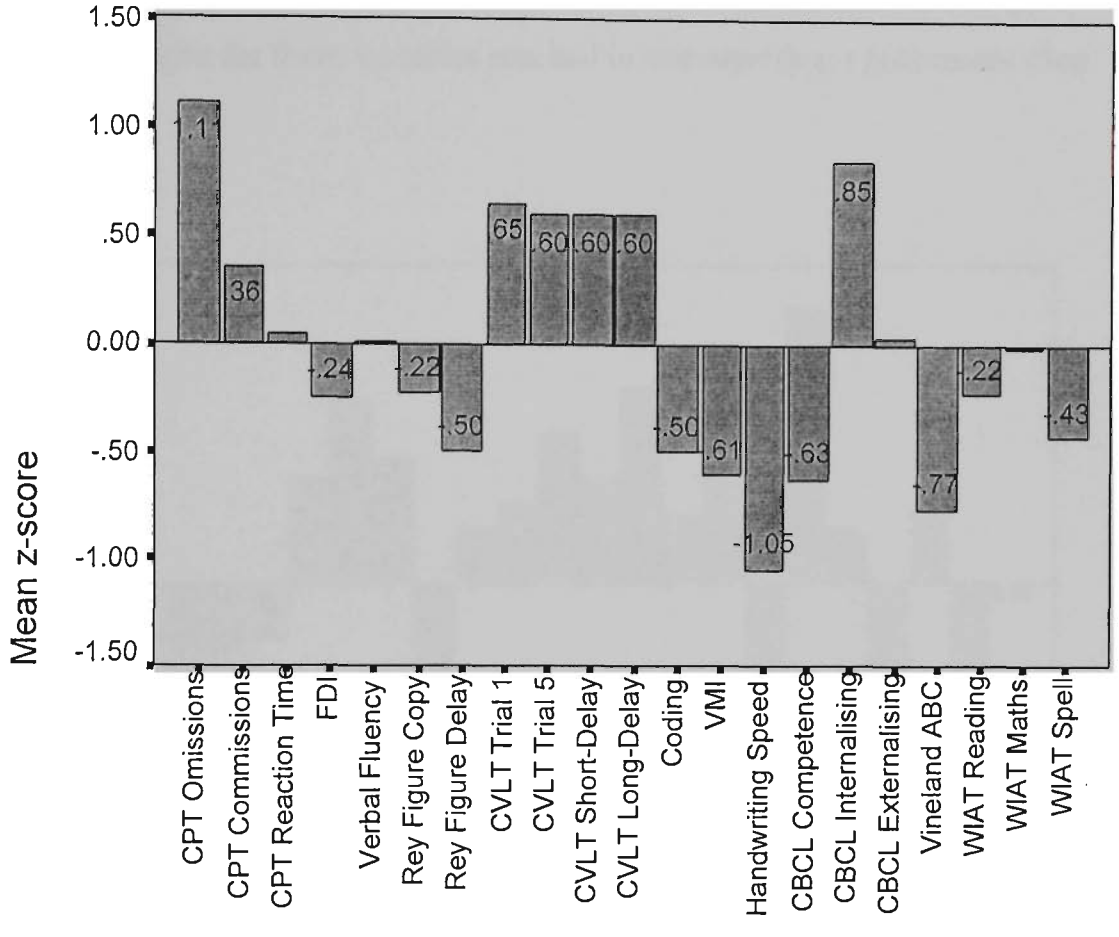

Figure 4.9 Mean difference of the PF group from the normal population at two-years

4.9.2 ST Group Compared With Normal Population at Two-Years

The ST group differed from the normal population on three of the variables at two-years. These were: Rey Figure Copy ($t(5) = 6.70$, $p = .001$) from the Attention and Executive domain, Handwriting Speed ($t(5) = 2.74$, $p = .041$) from the Visuo-Motor Skills domain, and CBCL Competence ($t(5) = -4.55$, $p = .006$) from the Functional Outcome domain. The ST group performed better than the normal population on the Rey Figure Copy and Handwriting Speed but more poorly on CBCL Competence (See Figure 4.10).

The ST group also performed significantly better on the Rey Figure Delay ($t(5) = -2.77$, $p = .039$) than the normal population although this result should be interpreted with caution because this variable did not meet criteria for normality (See Figure 4.10). Figure 4.10 indicates large mean z-scores were obtained for Verbal Fluency, Coding, CBCL Internalising, and Vineland ABC. It should be noted that large standard deviations for these variables resulted in non-significant differences (See Appendix Six).

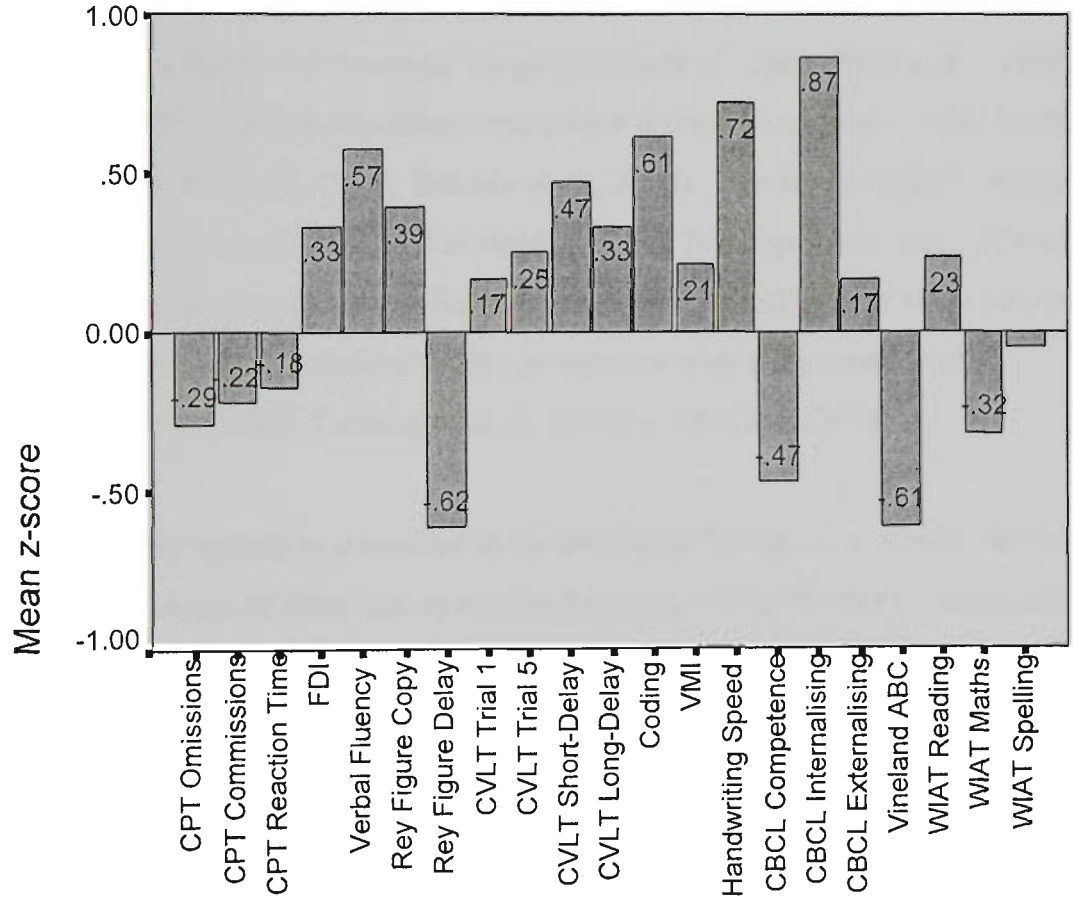

Figure 4.10 Mean difference of the ST group from the normal population at two-years

Chapter Five – Discussion

5.1 Intellectual Ability

The posterior fossa (PF) and supratentorial (ST) groups were equivalent on all IQ measures at the one-year and two-year assessments. Further, these groups did not differ from the normal population on these measures at either assessment. This is consistent with the surgery-only literature for PF tumours, which have found that mean IQ scores fall in the 'average' range (Beebe et al., 2001; Riva et al., 1989) and tend not to differ significantly from comparison groups (Ater et al., 1996; Mulhern et al., 1999; Riva & Giorgi, 2000; Steinlin et al., 2003). Previous research comparing IQ according to tumour location has yielded mixed findings irrespective of treatment protocol, but a number of studies have found the PF and ST groups to be equivalent in terms of intellectual functioning, in concurrence with the present study (Carpentieri et al., 2003; Lannering et al., 1990; Yule et al., 2001).

IQ was strongly related to a number of the neuropsychological outcome variables including measures of attention, executive function, verbal memory, visuo-motor skills, behavioural outcome, and academic achievement. This suggests that to a certain extent neuropsychological outcome can be anticipated from intellectual assessment. However, intellectual ability could not itself be predicted from the three prediction variables (NSS, tumour volume, and hydrocephalus). It is likely that intellectual decline was not observed in this sample because the severity of neurological insult was relatively mild when compared to children with malignant tumours requiring radiotherapy.

5.2 Neurological Severity Score

The hypothesis that a higher NSS would predict poor cognitive and behavioural functioning was only partially supported. No strong correlations were found between the NSS and any of the neuropsychological variables. The NSS correlated

moderately and negatively with two variables: CBCL Externalising and CVLT Trial 1. This indicated that as the NSS increases children exhibit less externalising problem behaviours but more difficulties with the initial registration of information. The remaining correlations between the NSS and neuropsychological variables were either small or non-existent relationships, but the results for the small correlations were also paradoxical. While higher NSSs were associated with greater deficits in CPT Commissions and Reaction Time, Rey Figure Copy and Delay, CVLT Trial 5, Handwriting, and Vineland ABC, high NSSs were also associated with better outcome in terms of FDI, CBCL Competence, CBCL Internalising, and WIAT Maths and Spelling.

Thus, taking into account the small and moderate correlations in the present study the NSS could be used to predict some aspects of attention (sustained attention), executive function (visuo-spatial organisation), memory (verbal and visual), visuo-motor skill (handwriting speed), and adaptive behaviour. However, it was not useful for predicting attentional control, verbal fluency, delayed verbal memory, more novel visuo-motor tasks (Coding and VMI), social competence, problem behaviours, or academic ability.

Consistent with the present study Ater et al. (1996) found a relationship between the NSS and aspects of attention, executive function, and memory (verbal and visual). Further, they also found that the NSS did not predict verbal fluency or academic skills. However, in contrast to this study they discovered a relationship between the NSS and FSIQ, PIQ, and the VMI.

This study replicated most of the findings of Ater et al. (1996) even though the strength of the relationships was generally small. The present finding of small relationships and the failure to detect some relationships found by Ater et al. (1996) may be due to a number of reasons including the small range of NSS values obtained in this study. The NSS ranged from 2 – 6 in the present study, but ranged from 0 – 12 in the Ater et al. (1996) study. Their study included both a larger sample size and malignant tumours, which may account for the heterogeneity and severity of neurological symptoms in their sample. Another implication of the restricted range of NSSs in the present study is that the results can not be generalised to the

prediction of outcome in children with an NSS greater than 6 (or less than 2). However, the likelihood of obtaining greater scores does not seem high since the average NSS in the Ater et al. (1996) study ranged from 1.27 to 4.23 according to tumour location. The median NSS in the present study was 4.

The discrepancy in findings may also be a result of the timing of assessment. In the Ater et al. (1996) study neuropsychological assessments were conducted within three months of diagnosis (including pre-surgical assessments) while the child was potentially experiencing acute symptoms. Given that neuropsychological assessments in the present study were conducted one-year after diagnosis the participants had presumably experienced some recovery in terms of both neurological and neuropsychological symptoms which would result in a lesser degree of relationship between current neuropsychological functioning and initial neurological symptoms. Hence, the NSS may be more appropriate for predicting short-term outcome.

Further, different results might be obtained if the sample was large enough to divide according to tumour location. Although PF and ST did not differ on the NSS, the different neuropsychological profiles of these groups might mean more significant relationships would be found if the groups were examined separately.

There were some difficulties implementing the NSS in the present study because the descriptions of the symptom categories were not comprehensive enough. In this study a priori decisions were made regarding the scoring of certain neurological signs and symptoms common in the brain tumour population.

Although the overall pattern of results in this study is very similar to the findings of Ater et al. (1996) the results do not demonstrate the usefulness of NSS as a method for predicting outcome. The failure to find large relationships in a sample size of twenty-two suggests the NSS is not a useful clinical tool for predicting outcome in individual children. Previous research utilising cumulative scores to quantify medical events has been variable, but a number of studies have also failed to find a significant relationship between medical factors and neuropsychological functioning, memory, or disability (Beebe et al., 2001; Dennis et al., 1991; Lannering et al.,

1990). The studies that have found a relationship between these factors and neuropsychological outcome have only examined selective medical factors in children treated with adjuvant therapy (Chapman et al., 1995; Hoppe-Hirsch et al., 1995; Kao et al., 1994). Beebe et al. (2001) were the only other group to study pre-, peri-, and post-operative complications in a surgery-only sample. They found no significant relationships with neuropsychological outcome within one-year of surgery.

5.3 Tumour Volume

Overall tumour volume correlated with the neuropsychological variables better than the NSS. One strong, positive relationship was found between tumour volume and CBCL Competence. Three moderate, positive correlations were also found between tumour volume and Rey Figure Copy, CVLT Short-Delay, and CVLT Long-Delay. Thus, contrary to the second hypothesis greater tumour volume was associated with better outcome in terms of social competence, verbal memory, and visuo-spatial skill/organisation. This unexpected direction of correlations was also found in eight of the thirteen variables with a small relationship to tumour volume (FDI, Verbal Fluency, Rey Figure Delay, CVLT Trial 1 and Trial 5, Vineland ABC, and WIAT Maths and Spelling). Therefore, only five variables correlated with tumour volume in the direction that might be expected from a neuropsychological perspective, namely that the greater the extent of damage, the greater the neuropsychological sequelae. However, the degree of relationship between tumour volume and these five variables (CPT Omissions, CPT Commissions, CPT Reaction Time, CBCL Externalising, and WIAT Reading) was only small. The only variables with no relationship to tumour volume were CBCL Internalising and the Visuo-Motor skills domain.

An extensive search of the literature yielded one study that has examined tumour size (Steinlin et al., 2003). Steinlin et al. (2003) found that PF tumour size had no influence on outcome, although it was unclear how they defined tumour size (they primarily had two-dimensional measurements and no three-dimensional

measurements) or how these relationships were assessed as there was a lack of any description of the method or results in their paper.

Given the paradoxical finding that large tumour volume tended to predict higher functioning on many of the neuropsychological variables it would be imprudent and premature to draw conclusions regarding the relationship of tumour volume and neuropsychological outcome, particularly as there is little other literature on the subject and the present sample size was small. It is possible that tumour size is not an important factor in predicting outcome severity, but this does not explain why this study found four large and moderate correlations. There was potentially some other factor moderating these results.

Another explanation for the present findings is that the size of a lesion within the cerebellum is not as relevant to the severity of outcome as lesion size within the supratentorium is thought to be. The failure of Steinlin et al. (2003) to find a relationship between tumour size and outcome following PF tumour lends support to this explanation. It is also possible that rate of tumour growth is a better predictor of outcome than tumour size. Benign tumours have a slow rate of growth that allows the brain to accommodate by redirecting neural pathways around the periphery of the tumour, hence slow growing tumours are detected later (and can grow quite large). Rapidly growing tumours do not allow for this accommodation and neural pathways are damaged. Although this study only included benign (slow growing) tumours, the tumours were only detected once they began to impact on brain functioning. Thus the larger tumours in this study were able to reach their size without detection because they were not causing disruption to neural pathways until later in their course. Therefore it is likely that outcome in this sample could not be predicted from lesion size because the slow rate of tumour growth allowed the brain to accommodate. Nevertheless, given the present findings are unusual and there is a lack of research into tumour volume, this would be an interesting issue for further examination in a larger study.

5.4 Hydrocephalus

Due to the small sample size in this study there was insufficient power to detect statistically significant differences between children who had hydrocephalus and those that did not. However, in support of the second hypothesis when effect sizes were examined there were four moderate to large trends amongst the neuropsychological variables in the Attention and Executive domain and the Memory and Learning domain. Large effect sizes were found for Verbal Fluency and CVLT Long-Delay and moderate effect sizes were found for CPT Reaction Time and Rey Figure Delay. The children who experienced hydrocephalus performed more poorly on all these measures. It is interesting to note that no moderate or large effect sizes were found for the Visuo-Motor Skills domain or the Functional Outcome domain. The present findings suggest that hydrocephalus in children diagnosed with brain tumours is most likely to cause deficits in sustained processing speed, executive function (verbal fluency), and delayed memory (verbal and visual).

The brain tumour literature examining outcome after hydrocephalus has tended to use intellectual ability as the measure of outcome. Decline in intellectual ability has been associated with hydrocephalus requiring shunting or hydrocephalus of long duration (Reimers et al., 2003; Yule et al., 2001). In this study hydrocephalus had no relationship with intellectual ability, however this study only examined presence or absence of hydrocephalus and not the severity or duration. Hydrocephalus symptoms did vary within the present sample ranging from mild to severe and requiring a shunt. With a larger sample the importance of the severity of hydrocephalus or the duration of hydrocephalus symptoms could be examined with respect to a wider range of neuropsychological measures. This is particularly important when considering that Yule et al. (2001) did not find a relationship between IQ and the presence/absence of hydrocephalus or IICP, rather it was the duration of symptoms that was significant. Nevertheless, this is amongst the first study to attempt to prospectively examine the relationship between hydrocephalus and a wider range of cognitive abilities in children diagnosed with brain tumours. The wider literature on hydrocephalus has documented alterations in attention/information processing, executive, and memory

ability in these children (Anderson et al., 2001; Fletcher et al., 1996; Fletcher et al., 2000).

The present study failed to find a relationship between functional outcome and hydrocephalus. Another study to use the CBCL as a measure of behavioural outcome also failed to find a relationship between behaviour and hydrocephalus (Mulhern et al., 1993). In addition, other research has shown that hydrocephalus or IICP symptoms do not predict overall disability level (Lannering et al., 1990).

Despite the fact the brain tumour literature has not fully elucidated the contribution of hydrocephalus to neuropsychological outcome it seems reasonable to conclude that the influence of hydrocephalus would depend upon the severity and duration of the symptoms. Further, it would be expected that severe hydrocephalus in children diagnosed with brain tumour might produce sequelae beyond decline in intellectual ability. The findings of the present study provide preliminary evidence that hydrocephalus contributes to poor neuropsychological outcome. The sequelae identified by this study, namely deficits of speed of information processing, executive function and delayed memory, are consistent with the deficits identified in the broader hydrocephalus literature (Anderson et al., 2001; Fletcher et al., 1996; Fletcher et al., 2000). Despite this correspondence, these results need to be interpreted with caution as hydrocephalus and tumour location were confounded in this study.

5.5 Prediction of Outcome

A surgery-only sample provides the unique opportunity to study predictive factors without the confounding effects of other treatments. This is the first study to replicate the method used by another study to quantify the severity of pre-, peri-, and post-operative neurological events and complications in children with brain tumours. The NSS was chosen over other methods because it was relatively well described and allows for consideration of the cumulative effect of neurological symptoms by quantifying events from the pre-operative to post-operative period (including pre-existing neurological disorders). The results of this study did not prove the NSS to

be the best method of prediction as the original study had found (Ater et al., 1996). Nevertheless, the overall pattern of results was similar to that of Ater et al. (1996) in that the NSS tended to predict similar neuropsychological functions, but the degree of relationship between the NSS and these measures was smaller in this study. The failure to establish clear relationships between the NSS and outcome in a group study suggests that it is of limited value as a method of prediction in the case of individuals.

The remaining two prediction variables, tumour volume and hydrocephalus, surpassed the NSS as a method of prediction in that they 'predicted' twice as many neuropsychological variables and had larger associations with some of the variables. The quandary with using tumour volume to predict outcome is that the majority of relationships found in this study between tumour volume and neuropsychological outcome were in an unexpected direction. Large tumour volume was predominantly associated with better outcome. Consequently it is difficult to conclude that tumour volume should be used as a predictor given that the basis for the direction of the relationships found is not understood. It is possible that these results were moderated by some other factor and that the rate of tumour growth is more critical to the disruption of neurological and neuropsychological function.

Hydrocephalus was the predictor with the most consistent results. The relationships between hydrocephalus and the neuropsychological variables it predicted were straightforward, that is children with hydrocephalus had poorer outcome on all the variables. Further, hydrocephalus was clearly a better predictor for attention, executive, and memory deficits over poor visuo-motor skills or functional outcome. The relationship of the NSS and tumour volume to the neuropsychological variables was less clear as the relationships were positive for some variables and negative for others. Thus the basis for these relationships was not well understood.

There has been very little previous research on these three methods of prediction and there is a particular lack of research comparing such methods. This is the first study to prospectively explore the relationship of predictive factors to a range of neuropsychological outcome measures. The results of this study did not reveal one of these factors to be an overwhelmingly useful method of prediction. Perhaps one-

year was a sufficient period of time in which to overcome the neuropsychological sequelae of these neurological events, particularly as these surgery-only patients experienced relatively mild neurological complications. However, the results do suggest that the occurrence of hydrocephalus is most likely to signify problems at one-year post-surgery. The NSS was not a useful measure in this study. Tumour size requires further investigation to ascertain its value due to the puzzling results.

5.6 Neuropsychological Outcome at One-Year

5.6.1 PF Group Compared With ST Group

In support of the third hypothesis the PF group had a distinct profile of neuropsychological deficits compared to the ST group. Due to the small sample size this study did not have much power to detect statistically significant differences using MANOVA, although one significant difference was found (CVLT Trial 5). Effect sizes were examined for the remaining variables to detect trends in the data (moderate or large).

In summary, the PF and ST groups differed on a number of neuropsychological measures, with the PF group performing more poorly on all of them. The neuropsychological measures on which they differed were: FDI, Verbal Fluency, Rey Figure Copy, CVLT Trial 1, CVLT Trial 5, Handwriting Speed, Vineland ABC, and WIAT Spelling. These differences suggest that the PF group was more deficient in terms of their attentional control/working memory, executive function, the registration of new verbal information and verbal learning, motor speed, adaptive behaviour, and spelling ability.

The finding that the children with PF tumours were worse than the ST children in terms of cognitive sequelae and functional outcome is in contrast to most of the previous research comparing these tumour locations. Research including children treated with adjuvant therapy generally find cognitive outcome to be worse in children with ST tumours (Duffner et al., 1996; Glauser & Packer, 1991; Mulhern et al., 1992; Ris & Noll, 1994) although a handful of studies have found no differences

(Dennis et al., 1998; Lannering et al., 1990; Yule et al., 2001). Children with ST tumours have also been found to fare worse on measures of psychological-emotional outcome and disability (Lannering et al., 1990). Ris and Noll (1994) made an important point that the inclusion of children with craniopharyngiomas in ST groups may be the reason for group differences, and by excluding children with craniopharyngiomas the children with PF tumours have been shown to have greater deficits. This may account for the present findings because children with craniopharyngiomas were excluded from the ST group.

Of the surgery-only literature two studies made comparisons between tumour location and both obtained different results to this study (Ater et al., 1996; Carpentieri et al., 2003). One of the surgery-only studies found that there were no particular patterns of deficits on cognitive and academic measures between the PF and ST groups when followed up within three-months of surgery (Carpentieri et al., 2003). However, in contrast to the present study Carpentieri et al. (2003) did not make direct statistical comparisons between the groups, rather they compared the groups in terms of their pattern of deficits relative to the normal population. They categorised 'below average' or 'above average' performance as age-appropriate scaled or standardised scores that were one standard deviation or more away from the mean. In the present study this sort of technique would only have identified three variables where the groups differed rather than eight (CVLT Trial 5, Handwriting Speed, and Vineland ABC). Carpentieri et al. (2003) did not have measures equivalent to these three variables in their study. Therefore, their failure to find differences between groups was most likely a result of not making direct statistical comparisons between groups and the fact they examined different measures of outcome.

Ater et al. (1996) conducted the other surgery-only study to compare outcome according to tumour location. They used the same technique as Carpentieri et al. (2003) to compare locations, however, they found differences between their groups. Relative to the normal population children with ST tumours had deficits in PIQ, attention, memory, motor, and academic domains while the children with PF tumours only had deficits on the memory and motor domains. Thus their ST group had deficits in three additional areas (PIQ, attention, and academic) to the PF group. The

findings of the present study were discordant with the above results as there were no differences between the groups on PIQ, and the PF group performed more poorly on attention and academic measures than the ST group. Ater et al. (1996) found that both groups performed poorly on the memory and motor domains and they did not make further comparisons of these measures. The graph of their results suggests that the PF group had greater deficits in the motor domain and fewer in the memory domain compared with the ST group. Again the findings of their study were contrary to the present results in terms of memory deficits, but the one point of agreement between the studies was that the PF group performed more poorly in the motor domain.

It is difficult to explain the discrepancy between this research and Ater et al. (1996), especially given they were able to find group differences without making direct statistical comparisons. The two major methodological differences between the studies were, firstly, the time of assessment. They assessed children within three-months of surgery and that included some pre-surgical assessments. Secondly, their sample comprised children with a diagnosis of astrocytoma, including malignant astrocytomas that required treatment other than surgery. Perhaps the distribution of pre-surgical assessments and/or malignant tumours between the groups led to these very different results.

It must, however, be emphasised that in the present study tumour location was confounded by the complication of hydrocephalus. It is unknown to what degree this relationship between hydrocephalus and tumour location is representative of the surgery-only population, it is possibly a true reflection of the incidence of hydrocephalus in each tumour location group. Nevertheless, it would be a point of interest to explore the relationship of tumour location to outcome without this potential confound to determine whether it does contribute its own effect on the results. To covary for hydrocephalus in the present study would have significantly reduced any chances of detecting differences between the groups, but it is accepted that this may have been a problem influencing the present results. A future study might attempt to recruit a larger sample to accommodate these issues.

5.6.2 PF Group Compared with Normal Population

The fourth hypothesis that children with PF tumours would have a distinct neuropsychological profile that distinguished them from the normal population at the one-year assessment was supported. The PF group had significant deficits on eight of the twenty-one variables, namely: CPT Omissions, Rey Figure Copy and Delay, Coding, Handwriting Speed, CBCL Competence and Internalising, and the Vineland ABC. These results indicate that children with PF tumours demonstrate cognitive and behavioural difficulties one-year after surgery, characterised by increased problems with sustained attention, complex visual copying and memory, visuo-motor speed, and behaviour. The PF children had sparing of their attentional control, verbal fluency, verbal learning and memory, and academic skills relative to the normal population. A number of recent studies have also shown children with PF tumours to have neuropsychological impairment in the absence of radiotherapy or chemotherapy (Beebe et al., 2001; Riva & Giorgi, 2000; Scott et al., 2001; Steinlin et al., 2003).

There have been two studies to examine sustained attention in children treated with surgery-only for PF tumours. Riva et al. (1989) found their surgery-only group was equivalent to both the controls and the children treated with adjuvant therapy on a measure of sustained attention. However, Steinlin et al. (2003) found their sample had multiple attentional difficulties including deficits of sustained attention. Both studies were conducted at least two-years after surgical resection of the tumour but Riva et al. (1989) had a much smaller sample size, which would reduce their power to detect significant differences. The present 'one-year' findings were limited in their capacity to contribute to the present debate regarding sustained attention difficulties. Only one sustained attention variable was significantly different and this variable did not meet criteria for normality hence this significant finding needs to be interpreted carefully. Attentional control and working memory were normal in this sample.

Children with PF tumours had deficits on the Rey Figure Copy and Delay relative to the normal population. Deficits on the Rey Figure Copy reflect difficulties with visuo-spatial skills and/or organisational ability (executive function). The Rey

Figure Copy was used as a measure of executive function in this study. It appears that executive dysfunction is the primary reason for the poor performance of the PF group on this task given that they performed normally on other measures reflecting visuo-spatial (PIQ) and visuo-motor skill (VMI). Steinlin et al. (2003) found the Rey Figure Copy to be the worst affected function in their surgery-only study, even relative to the Delay trial. Executive problems have been found in other surgery-only studies using a more complex executive function measure, the Wisconsin Card Sorting Test (Karatekin et al., 2000; Riva & Giorgi, 2000). The PF group were comparable to the norms on the other executive test used in this study, namely Verbal Fluency, whereas other surgery-only literature has found PF children perform poorly on this task (Riva & Giorgi, 2000; Steinlin et al., 2003). Nevertheless, these results provide partial support for a cerebellar role in executive functioning as proposed by Schmahmann and Sherman (1998).

Contrary to the results of Steinlin et al. (2003) the present study found the Rey Figure Delay to be worse than the Copy trial. In fact, the Rey Figure Delay (visual memory) was the most affected function in the present study. In this case poor memory for complex visual information may reflect difficulty with both encoding (due to poor organisation of the Copy trial) and retrieval. Two recent studies that used the Rey Figure also found delayed recall to be impaired (Levisohn et al., 2000; Steinlin et al., 2003). Packer et al. (1989) found no impairment of Rey Figure recall but their sample size was much smaller than the recent studies. There is also evidence that other forms of visual memory are impaired in these children (Ater et al., 1996; Riva & Giorgi, 2000). Analogous to the executive function results, the PF group was only impaired on the visual measure of memory while verbal memory was spared. In fact, CVLT Long-Delay was better than the normal population and approached significance. This contrasts with the prior literature addressing verbal memory (Ater et al., 1996; Levisohn et al., 2000; Riva & Giorgi, 2000). Two of these studies assessed children within months of surgery (Ater et al., 1996; Riva & Giorgi, 2000) while the other had a 1 – 22 month follow-up period and included children with chemotherapy (Levisohn et al., 2000). Therefore this is the first study to examine verbal memory in the medium-term in a surgery-only sample.

The children with PF tumours in this study clearly experienced difficulty with visuo-motor speed. This is consistent with the surgery-only literature which found PF children to be slow on time based tasks, such as those assessing information processing that involves a motor component (Riva & Giorgi, 2000; Steinlin et al., 2003) or those assessing fine motor speed and dexterity (Ater et al., 1996; Packer et al., 1989). The tasks utilised in this study (Coding and Handwriting Speed) placed different levels of demand on information processing, but both involved a motor speed and motor control component. Difficulty with these tasks was not exclusively due to slow reaction time/motor speed, otherwise impairment in CPT Reaction Time would have been found. Further, visuo-motor integration (VMI), which requires motor control but does not place demands on motor speed, was intact in these children. Thus, it appears these children have difficulty with tests placing demands on both these components (speed and control). Difficulties with motor speed and control are expected on the basis of our knowledge of the function cerebellum in controlling and regulating movement, particularly movements that need to be performed rapidly and precisely.

In this study the deficits experienced by children with PF tumours were primarily of a visuo-spatial rather than verbal nature. The visual and verbal deficits found in Riva and Giorgi's (2000) study were related to left cerebellar and right cerebellar tumours respectively. Scott et al. (2001) also found this pattern of lateralisation within the cerebellum. The present study did not have sufficient participants to examine tumour location within the cerebellum, but most of the children did not have clearly lateralised cerebellar tumours, rather the majority of tumours arose from the midline.

Finally, in terms of functional outcomes the PF group had no academic achievement difficulties, but they did have a number of significant behavioural problems relative to the normal population. As well as an elevated number of Internalising emotional/behavioural symptoms, these children had evidence of social difficulties and poor adaptive behaviour. The only behavioural variable they did not have significant problems on was the Externalising scale. Beebe et al. (2001) found very similar results in their study, with children experiencing significant problems of adaptive behaviour and internalising symptoms, but no problems with externalising behaviours. Mulhern et al. (1993) also found this pattern of CBCL elevations in a

study of children recently diagnosed with brain tumour. They also found that the best two predictors of poor social competence were non-hemispheric tumour (ie. ventricular or PF tumours) and severe functional impairment respectively. Further, their study indicated that the type of tumour treatment was not an important predictor of behavioural outcome (Mulhern et al., 1993).

The range of social, emotional, and behavioural difficulties found here may represent difficulty adjusting to the diagnosis of brain tumour and the various neurological, cognitive, and psychosocial changes that follow diagnosis and treatment. A number of studies also suggest an anatomical basis for psychological and emotional dysfunction in children treated for PF tumour (Levisohn et al., 2000; Riva & Giorgi, 2000; Steinlin et al., 2003). These studies have implicated damage to the vermis as the cause of emotional, behavioural, and psychological sequelae, as vermal lesions were generally associated with such outcomes. However, this may not be the case for all types of behavioural presentations, for instance Beebe et al. (2001) found significantly poorer adaptive behaviour (Vineland ABC) was associated with vermal lesions, but internalising and externalising problem behaviours (CBCL) were not. Further, not all PF children with behavioural problems have been found to have lesions of the vermis (Steinlin et al., 2003). The majority of PF tumours in the present sample arose from the midline but the small sample size did not permit any formal analysis of the association between emotional and behavioural sequelae and tumour location within the cerebellum.

The difficulties experienced by the PF group compared with the normal population at one-year were sustained attention, visuo-spatial organisation and memory, visuo-motor speed, and emotional-behavioural sequelae. When compared with the symptom complex of CCAS (executive, visuo-spatial, language, and personality/affective problems) the pattern of symptoms at one-year was partially consistent with this syndrome (Schmahmann, 2001a; Schmahmann & Sherman, 1998). More specifically some executive, visuo-spatial, and affective problems were evident. However, contrary to Schmahmann's (2001a) findings no verbal fluency impairment was found. Further, this study did not examine expressive language (naming and word finding difficulties), which are the types of language difficulties that comprise CCAS, and have previously been noted in a paediatric population

(Levisohn et al., 2000). Nevertheless, reviews of the adult literature suggest that there is stronger evidence for the impairment of executive functions and visuo-spatial skills than the other symptoms of CCAS (Daum et al., 2001; Justus & Ivry, 2001).

5.6.3 ST Group Compared with Normal Population

The fourth hypothesis that the ST group would have a profile of deficits that distinguish them from the normal population at one-year was not supported. There were four variables on which they were significantly better than the normal population. These were the four CVLT variables, hence verbal learning and memory were in fact a strength for the ST group. These children did have one difficulty relative to the normal population in terms of social competence (CBCL Competence).

These results are quite striking considering that most of the literature, irrespective of treatment type, suggests that children with ST tumours are more impaired than children with PF tumours and/or the normal population (Ater et al., 1996; Carpentieri et al., 2003; Duffner et al., 1996; Glauser & Packer, 1991; Mulhern et al., 1992; Ris & Noll, 1994). Of the two surgery-only studies that have examined a range of cognitive functions in children with ST tumours, one found deficits of PIQ, attention, memory, motor, and academic skills relative to the norms (Ater et al., 1996). The other also found these children have problems with PIQ, memory, and motor functions (Carpentieri et al., 2003), but in contrast to Ater et al. (1996) found no problems with academic skills (they did not examine attention). Therefore, the results of the present study contradict the deficits found by these two studies, particularly in terms of verbal memory, which was a specific strength of the ST group.

There are a number of reasons that account for this discrepancy. Firstly these other studies both assessed children within three-months of surgery and included children with malignant tumours. Therefore the deficits in the present sample might be expected to be less severe given they all had benign tumours and assuming some recovery occurred over the additional nine-months prior to assessment. Secondly, the other studies had larger sample sizes that would allow them to detect statistically

significant differences more easily and might also mean the inclusion of more children with tumours in locations likely to affect verbal memory. The present study included only two children with left (medial) temporal tumours. Thirdly, children with a diagnosis of craniopharyngioma were excluded from this study; this diagnosis is often reported to be associated with memory problems. Finally, higher than normal CVLT scores may be a problem related to the use of standardisation data from the USA. Previous research has shown that demographic differences between the USA and Australia result in differences in mean performances on the Wechsler tests (Shores & Carstairs, 2000). This may also be the case with the CVLT.

The only area of significant difficulty for the ST group was social competence. Social competence difficulties suggest that one-year following tumour removal these children have not returned to a normal routine of involvement in household responsibilities or involvement in social or sporting activities. Although past research has found significant psychological and emotional sequelae in children treated for ST tumours (Lannering et al., 1990) very few studies have examined social outcomes according to tumour location, with one exception (Mulhern et al., 1993). Mulhern et al. (1993) examined the prediction of social competence and behavioural outcomes in detail and found that children with brain tumours had a higher incidence of social competence and behavioural problems than the general population. However, poor social competence was best predicted by non-hemispheric tumour (ventricular or PF tumours; Mulhern et al., 1993). Although the present ST sample included some children with ventricular tumours, there are clearly other factors involved in determining these outcomes. A review of the wider brain tumour literature on behavioural, emotional, and social adjustment revealed poor social competence was the most consistently reported problem across studies (Fuemmeler, Elkin, & Mullins, 2002). For instance, Vannatta et al. (1998) have shown that brain tumour survivors frequently experienced poor social adjustment and difficulty with peer relationships.

5.6.4 Summary of Outcomes at One-Year

From the results examining neuropsychological outcome at one-year it is apparent that the PF children were experiencing a greater number of difficulties than the children with ST tumours. When compared directly with the ST group, the PF group performed more poorly on eight of the variables. However, the PF group only performed more poorly than the normal population on three of these eight measures (Rey Figure Copy, Handwriting Speed, and Vineland ABC). The remaining differences appeared to be due to the ST group performing better than the normal population, particularly on the verbal memory measures, which reached statistical significance.

Relative to the normal population both groups were functioning well in terms of verbal memory and academic skills, even though the PF group was relatively weaker than the ST group on some of these measures. The ST group was also functioning well in the areas of attention, executive functioning, and visuo-motor skills. Compared with previous literature it is unusual to find children with ST tumours functioning so well compared to children with PF tumours and the normal population. However, this is the first study to examine surgery-only outcomes for children with (benign) ST tumours over a period as long as one-year.

The PF group had impairments in sustained attention, visuo-spatial organisation and memory, visuo-motor speed, and behavioural outcome. These findings were not altogether unexpected from the literature, with the exception of sustained attention for which there is very little research. The PF group had a higher incidence of hydrocephalus, which reflects the greater impact of PF tumours on the ventricular system due to their proximity to these structures. However, the Rey Figure Delay was the only measure on which both the hydrocephalus and the PF group had deficits. Nevertheless it is acknowledged that hydrocephalus may have contributed to poorer outcome in this group. The only impairment both tumour location groups had in common was poor social competence relative to the normal population. This finding suggests that these social difficulties result from the process of adjustment that follows the diagnosis and treatment of a significant illness such as brain tumour,

or from a more general neuropathologic process associated with brain tumours and their treatment, rather than being an outcome specific to lesion location or vermal involvement.

5.7 Patterns of Change Over Time

5.7.1 Change Over Time and Outcome at Two-Years: PF Group

Of the subset of PF children assessed at two-years, the five variables that showed the most change from one to two-years post-surgery were: CPT Commissions, FDI, CVLT Trial 1, CVLT Trial 5, and VMI. FDI and VMI showed decline over that period, but only the decline for VMI was significant. CPT Commissions, CVLT Trial 1, and CVLT Trial 5 showed improvement, but only CVLT Trial 1 significantly improved.

In support of the fifth hypothesis the PF group continued to experience difficulties that distinguished them from the normal population at two-years post-surgery. The pattern of deficits at two-years was somewhat different to the pattern of deficits at one-year. To summarise, the results at two-years were:

- CPT Omissions, Handwriting Speed, CBCL Competence, CBCL Internalising, and Vineland ABC remained significant deficits
- Rey Figure Copy, Rey Figure Delay, and Coding improved and were no longer significant deficits
- VMI deteriorated and was the only new deficit to emerge at two-years

Although there was improvement in CPT Commissions and decline in FDI between the assessments, the overall pattern of impairment relative to the norms was the same at both time points. That is, the PF group continued to perform very poorly in terms of CPT Omissions, reflecting difficulty with sustained attention, but the remaining attention variables were comparable to the normal population. The fact that CPT Omissions remained a significant deficit at two-years certainly adds some weight to the argument for sustained attention difficulties in children treated for PF tumours and is consistent with the findings of Steinlin et al. (2003) as previously discussed

(See section 5.6.2). The type of difficulty these children experience is primarily inattentiveness, since they perform normally in terms of their sustained speed of processing and level of impulsivity.

At two-years post-surgery there was virtually no evidence of executive problems in the PF group. Both the executive variables improved over time, with Verbal Fluency remaining comparable to the normal population and the Rey Figure Copy no longer a significant deficit. As explained above the only other study to examine Rey Figure Copy in this type of sample found it to be the worst affected measure on assessment at least two-years post-surgery (Steinlin et al., 2003). The mean z-score for the Rey Figure Copy in their study was –1.9 and in this study was –0.2. The reasons for this discrepancy are not clear, it is possible the small sample size in this study represented a subset of better functioning children.

The Rey Figure Delay also improved over time and was no longer a significant deficit at two-years. This variable was the most impaired measure at one-year, improving just over half a standard deviation between assessments. This improvement is probably somewhat due to the improvement in visuo-spatial and organisational ability witnessed on the Rey Figure Copy. While these results do show improvement the Rey Figure Delay was still half a standard deviation below the normal population and reflects the difficulty some children were still experiencing with this visual memory task. Further, two previous studies with large sample sizes found children were impaired on the Delay trial (Levisohn et al., 2000; Steinlin et al., 2003) while a study with a smaller sample size failed to find such an impairment (Packer et al., 1989).

Most of the verbal memory measures showed improvement over time, particularly CVLT Trial 1. Though CVLT Long-Delay did not show improvement, all of the verbal memory variables were around half a standard deviation better than the normative data at two-years. Verbal memory was the PF group's greatest strength at both of the assessments, with an even better performance at the two-year assessment, although this was not significant. Once again, this contrasts with previous studies that found verbal memory deficits, but these studies all had shorter (and more

variable) follow-up periods (Ater et al., 1996; Levisohn et al., 2000; Riva & Giorgi, 2000).

Within the Visuo-Motor Skills domain Handwriting Speed remained significantly impaired at two-years whereas Coding improved and was no longer significantly different from the normal population. However, VMI showed a significant deterioration over the one-year period and was significantly impaired at two-years. Although Coding was no longer a significant deficit and VMI became one, there was not very much difference between their means. These results show that PF children continued to experience difficulty with visuo-motor skills over time, with some evidence of decline in specific skills. These types of difficulties with motor speed and regulation of movement would be expected following cerebellar lesions. The other surgery-only study to examine visuo-motor integration found, like the present study, no deficits within one-year post-surgery (Beebe et al., 2001). The present study provides very important evidence that recovery of function does not always transpire and in fact significant decline in scores may occur for particular skills. Decline in standardised scores either represents a deterioration of function or an arrest in development, which can only be determined by an analysis of raw scores.

While the behavioural measures showed some change over time the general pattern of difficulties relative to the normal population was much the same at two-years. CBCL Competence, CBCL Internalising, and Vineland ABC remained significantly worse than the norms and CBCL Externalising remained normal. Again, Beebe et al. (2001) also found this pattern of problems in terms of adaptive behaviour and internalising symptoms in children with PF tumours. These results indicate that behavioural difficulties might be enduring over time, a finding that has received some support from previous surgery-only literature (Meyer & Kieran, 2002; Pompili et al., 2002; Steinlin et al., 2003). In fact, one study that explored the quality-of-life in adults treated for benign cerebellar tumours in childhood found that similar behavioural problems to those observed in this study formed the two dimensions that were most significantly affected relative to controls (Pompili et al., 2002). More specifically, out of twelve dimensions studied, the two most significant ones were Socialising and Adolescence. 'Socialising' comprised questions about social activities such as the degree and quality of contact with other people. 'Adolescence'

covered difficulties experienced at school, involvement in activities, and reflections on socialising, emotional state, and sexual development as an adolescent (Pompili et al., 2002). These dimensions are very similar to the competency scales (activities, social, school) that comprise CBCL Competence and some aspects also encompass emotional state as measured by CBCL Internalising.

The academic scores showed very little change over time and they remained similar to the normal population across both the assessments. While problems with academic skills are not typically detected around the time of surgery in PF children (Ater et al., 1996; Packer et al., 1989) they have been found up to one-year later (Beebe et al., 2001). More specifically, Beebe et al. (2001) found mathematics and spelling skills were impaired while reading was not. Although the present study did not find significant deficits, it indicated that mathematics skills were better preserved relative to reading and spelling, and perhaps a sample size as large as Beebe et al. (2001) may have allowed for the detection of impairment in this group.

In summary, the overall amount of decline and improvement over time was minimal and limited to specific measures. The most notable changes to occur from one-year to two-years were improvements in the Rey Figure Copy and Delay and the deterioration of the VMI relative to peers. These improvements resulted in relatively normal performance across the Attention and Executive Domain and the Memory and Learning Domain, with the exception of a significant deficit in CPT Omissions. This represented increased levels of inattentiveness when sustaining attention, although the other two sustained attention measures (impulsivity and processing speed) were normal. Verbal memory was the greatest strength in the PF group at two-years. Visuo-motor skills remained an area of particular difficulty for this group, especially with the decline of visuo-motor integration over time. In terms of the Functional Outcome Domain, these children continued to demonstrate the same pattern of behavioural difficulties over time, while academic skills remained relatively intact. These findings suggest that the poor performance in this group is probably not influenced by hydrocephalus since the pattern of deficits that resulted from hydrocephalus was different from the pattern of deficits at two-years.

Further, the pattern of neuropsychological deficits at two-years provided only very limited support for the total symptom complex of CCAS. There was no evidence of executive or language deficits. Nor was there evidence of visual and verbal memory impairment as Levisohn et al. (2000) found. There was only limited evidence for visuo-spatial deficits, which were limited to impairments of visuo-motor skills. However, there was continued evidence of emotional and behavioural disturbances, which may be associated with the midline location of the majority of tumours in this study.

This study provides important evidence that some skills decline over time. A previous study has also noted decline over time of specific memory and motor skills in children treated with surgery and chemotherapy, even though this did not result in impairment of those skills (Copeland et al., 1999). Nevertheless these findings provide further support for the importance of monitoring these children over time and conducting further research into the longer-term outcome of these children with a view to developing appropriate intervention.

Research into the quality-of-life of adults who had benign cerebellar tumours in childhood has shown how the impact of these problems is significant and lasting (Pompili et al., 2002). The particular dimensions that they found to be most problematic, 'socialising' and 'adolescence' captured similar information to the behavioural measures that were significant in the present study. Further, two of the three next most significantly affected dimensions were cognition and memory (Pompili et al., 2002). This study highlighted the important influence of behavioural and cognitive sequelae on quality-of-life long after surgery for brain tumour, and again emphasises the importance of long-term follow-up and intervention.

5.7.2 Change Over Time and Outcome at Two-Years: ST Group

Of the subset of ST children assessed at two-years, the five variables that showed the most change over time were: Rey Figure Copy, CVLT Trial 5, CVLT Long-Delay, Coding, and WIAT Maths. The Rey Figure Copy and Coding showed improvement

while the remaining variables deteriorated. Only the change in CVLT Trial 5 was significant.

The fifth hypothesis was not supported for the ST group at two-years since they only had one significant deficit relative to the normal population. However, the pattern of strengths and weaknesses at two-years was slightly different to the pattern at one-year. In summary, the results at two-years were:

- CBCL Competence remained a significant deficit
- All the CVLT variables deteriorated and were no longer significant strengths
- Rey Figure Copy and Handwriting Speed were new strengths to emerge at two-years

The attention measures remained fairly stable across time and were similar to the normal population. This is contrary to the findings of Ater et al. (1996) who found attention to be the worst affected function of all the functions they examined. In this study the performance of the ST group on both the executive measures was better than the normal population. There was particular (though non-significant) improvement in the Rey Figure Copy and it was significantly better than the normal population at two-years. Verbal Fluency had a higher mean score than the Rey but a larger standard deviation and thus was not significantly different from the normal population. Nevertheless, these results indicate that the ST group was functioning very well in terms of their attention and executive functioning. Using more comprehensive measures Carpentieri et al. (2003) also found executive functioning to be intact in their sample. In adults, impairments of executive functioning would be expected following frontal lobe lesions, and a growing body of evidence indicates this is also the case in children (for review see Anderson et al., 2001). Clearly the present results depend upon tumour location within the supratentorium and given the lack of children with frontal lobe tumours (at two-years) intact executive functioning might be expected.

There were no measures in the Memory and Learning Domain that were significantly different from the normal population. The mean z-score for visual memory was .62 lower than the normal population, but due to a large standard deviation a significant difference was not found. This was also the case at one-year. There was a decline in

the ST groups performance on verbal memory measures (and this was significant for CVLT Trial 5) that meant the ST group no longer differed from the normal population on these measures. The two surgery-only studies to examine memory in ST children in any detail found both visual and verbal memory impairments (Ater et al., 1996; Carpentieri et al., 2003). These studies had the advantage of a large sample size, but they included children with malignant tumours and were investigating short-term outcomes.

There were no deficits in the Visuo-Motor Skills Domain with general improvement between the assessments. In fact, the ST group had significantly faster Handwriting Speed than the normal population. This suggests that none of these children had tumours in a location that would cause disruption to motor control, regulation, and/or speed. Motor control and speed have been shown to be impaired in other studies of children treated for ST tumours (Ater et al., 1996; Carpentieri et al., 2003).

CBCL Competence remained the only significant deficit of the behavioural measures. However, the means of CBCL Internalising and Vineland ABC both appeared to be impaired but these differences were not significant due to the large standard deviations of these variables. Clearly some of the children were functioning more poorly on these measures. Social competence, internalising problems, and adaptive behaviour were also the three impaired behavioural measures in the PF group. Long-term investigation of surgery-only children has revealed significant mood and behavioural problems up to five-years post-surgery (Meyer & Kieran, 2002). Lannering et al. (1990) examined long-term sequelae an average of ten-years after diagnosis of brain tumour (range 5 – 16.5 years). In contrast to the present study they found that children with ST tumours had a higher frequency of psychological and emotional sequelae than children with PF tumours, although this study included children treated with radiotherapy. However, Mulhern et al. (1993) found that tumour treatment was unimportant in the prediction of behavioural problems. Further, in their mixed tumour location sample they found a similar pattern of CBCL elevations as the present study namely elevated Social Competence and Internalising but normal Externalising scales (Mulhern et al., 1993). Vannatta et al. (1998) also found brain tumour survivors experienced difficulty with peer relationships and social isolation irrespective of treatment type.

Fuemmeler et al. (2002) conducted a review of the literature on social, emotional, and behavioural outcome published over a thirty-year period. They found that children surviving brain tumours are most consistently at risk for poor social competence and poor long-term quality-of-life. While some studies reported internalising problems, very few studies examined, or reported, externalising problems. They attributed this to the 'clinical lore' that children surviving brain tumours do not tend to experience externalising problems. Further, their review indicated that there are a range of factors that moderate adjustment, including family functioning, functional impairment, cognitive deficits, and tumour and treatment variables (Fuemmeler et al., 2002). When examined as a whole, the literature clearly indicates that children with ST or PF tumours are at risk of behavioural problems, even when treated with surgery alone. Perhaps the increase in internalising and adaptive behaviour problems in the present study signifies a trend towards social, emotional, and behavioural adjustment difficulties that will continue in the years to come.

The ST group's academic skills were not significantly different from the normal population despite a significant decline in Maths. Of the surgery-only research examining academic skills (in the short-term) one study found academic skills were impaired in ST children (Ater et al., 1996). Other studies found academic skills were intact (Bordeaux et al., 1988; Carpentieri et al., 2003). Although these studies combined tumour locations one of them found no differences between PF and ST tumour location (Carpentieri et al., 2003). The studies considering long-term academic outcomes did not differentiate between tumour location either. Of these studies, Moore et al. (1992) found academic skills were intact in a surgery and chemotherapy sample. However, long-term follow-up of a surgery-only sample showed that these children experienced significantly greater academic adjustment problems relative to the normal population (Meyer & Kieran, 2002). Clearly the impairment of academic skills is a result of many complex and interacting factors beyond simple distinctions between tumour location and treatment type.

In summary, while there was some decline across time in certain measures, the overall picture at two-years was similar to that at one-year. The ST group continued

to function well in terms of their attention, executive, verbal learning and memory, visuo-motor, and academic skills. Although not significant there was some indication that visual memory was an area of difficulty. Similar to the results at one-year, behavioural functioning was the area of poorest outcome for this group, which is supported by a wealth of literature. The generally good cognitive outcome for this group is likely to have been influenced by the location of tumours within the ST. Given the small sample size tumours in parts of the brain that might affect functions such as executive skills and memory were not well represented in this sample.

5.7.3 Summary of Recovery and Outcome at Two-Years

The variables to distinguish the PF and ST groups in terms of deficits at two years were sustained inattention (CPT Omissions) and visuo-motor skills. Apart from these distinctions the groups were equivalent to the normal population on attention, executive, visual memory, verbal learning and memory, and academic outcomes. More specifically, both groups were functioning slightly better than the normal population on verbal learning and memory and slightly worse on visual memory, although these differences were not significant. An important finding in this study is that both groups experienced poor social, emotional, and behavioural outcomes, with greater severity being associated with PF tumour location.

5.8 Neuropsychological Outcome According to Tumour Location: Conclusions and Clinical Implications

The results of this study show that children treated with surgery-only for PF tumours were functioning more poorly on cognitive and behavioural measures than children treated with surgery-only for ST tumours. When followed up one-year later there was evidence of both improvement and deterioration of specific skills in each group relative to the normal population. The literature generally reports poorer outcomes for children with ST tumours. The ST group in the present study had good cognitive outcomes, but it is acknowledged that this may be a consequence of small sample size and a resultant limited range of tumour location within the ST. The neuropsychological deficits associated with PF tumour location indicate that this

region of the brain is implicated in cognitive functioning beyond motor related cognition, which is consistent with recent literature. Some authors suggest that children treated with surgery-only recover function over time (Bordeaux et al., 1988; DeVos et al., 1995). However, this was not the case in the present study, which found evidence of decline in specific areas. This study has highlighted the importance of ongoing follow-up of this patient population in order to provide appropriate clinical monitoring and intervention. It also identified areas of difficulty that could be addressed by a multidisciplinary team including Psychologists, Occupational Therapists, and Social Workers.

Surgery for brain tumours clearly has an impact on developing functions. The present study found the impairment of some skills remained constant over time, while other skills showed evidence of decline. The fact that some of the differences between the tumour groups and the normal population remained stable over time support the proposition that the processes of recovery and development may continue, even though functioning does not necessarily return to normal levels, a finding supported by Dennis, Hetherington, Spiegler, and Barnes (1999) in their study of PF lesions. However, the present study also showed that some skills deteriorate relative to peers, hence there must be other processes at play. A common hypothesis for deterioration following neurological injury is that children are unable to continue to acquire skills at a normal rate (Anderson et al., 2001). In a study of IQ decline in children treated for medulloblastoma, Palmer et al. (2001) examined this hypothesis and the competing hypothesis that children continue to lose skills over time. They found that decline was due to a slower rate of skill acquisition. It is likely that the decline in functioning found in the present study was due to the same reason, rather than representing deterioration from their previous level of functioning at one-year. Further research using raw scores would confirm this hypothesis. Nevertheless, brain tumours and their subsequent treatment impact on previously acquired skills as well as the acquisition of new skills, even in the absence of radiotherapy or chemotherapy.

Behavioural difficulties were the one common finding between the tumour location groups in this study. The literature regarding functional outcomes generally makes no comparison between PF and ST tumour location. Although direct statistical

comparisons were not made between the groups at two-years, the results suggest a similar pattern of behavioural disturbances occur in these children, but slightly more severely in the PF group. Further, the present study found no impairment of academic skills in either group. These findings suggest that functional outcomes are similar for each group and provides some support for combining the groups in statistical analyses of functional outcome. The studies that have done this have also shown that these children are at risk of social, emotional, and behavioural adjustment problems irrespective of the type of treatment they have undergone (Meyer & Kieran, 2002; Mulhern et al., 1993; Vannatta et al., 1998). Long-term research has shown these sequelae have a very significant impact on quality-of-life as an adult (Fuemmeler et al., 2002; Pompili et al., 2002). Future studies might address the cause of behavioural sequelae to determine whether it results from factors beyond neuropathologic changes, such as psychological trauma and the psychosocial environment.

While this study did not identify academic difficulties at either time point one surgery-only study found evidence of these difficulties over the long-term (Meyer & Kieran, 2002). The results of other short- to long-term studies have corresponded with the present findings, generally failing to find academic impairment (Bordeaux et al., 1988; Carpentieri et al., 2003; Moore et al., 1992). Nevertheless, the research to date has not been convincing in ruling out the occurrence of academic deficits in surgery-only children nor has it elucidated the factors involved in producing poor academic outcomes. Given that children treated with surgery-only may be vulnerable to academic problems in the long-term (Meyer & Kieran, 2002), future research needs to take into account the complex and interacting factors that determine academic outcomes to help understand whether and why these difficulties occur. These factors include fatigue, days off school, family environment, and cognitive impairment.

One of the major problems with the present 'recovery' research is the small sample size. Only a subset of each group was assessed at both time points. This was particularly a problem for the ST group. This is important to take into account when considering the outcomes found in this study, and it is possible a larger sample size

would have allowed for the detection of further and perhaps different impairments in these groups.

5.9 Limitations and Future Directions

The primary limitation of this study was the small sample size, particularly at the two-year time point. This is a difficulty with much of the research in the area of paediatric brain tumours, particularly when attempting to capture a surgery-only sample, and is one of the main reasons retrospective procedures are often employed. This study included all but one of the eligible participants and would have required a much longer period of investigation to improve the numbers significantly. The small sample resulted in limited statistical power to detect group differences. It also placed limitations on the types of relationships that could be explored.

A larger sample size would have allowed this study to address some of the other limitations. For instance, hydrocephalus and PF tumour location were confounded and the separate contribution of these factors to neuropsychological outcome could be examined in a larger study. Further, the present study included children with a variety of (benign) tumour pathologies and a wide age range. This results in greater heterogeneity within the sample and further reduces statistical power.

Future research into the importance of tumour localisation with the PF and ST would be particularly interesting given the literature that indicates that different profiles of deficit might be expected. Given that long-term outcome extends well beyond two-years post-surgery, further longitudinal research to investigate the longer-term outcomes of treatment with surgery-only is imperative in order to bring about appropriate changes to clinical management and reduce the impact of long-term sequelae on these children.

It is acknowledged that practice effects may have occurred on specific tests as a result of repeated assessment (such as tests of memory). However, the results suggest that this is unlikely to have had much effect on the data at the two-year assessment given the evidence of decline in some of these skills over time.

The present study could have been enhanced by including a healthy control group of age and SES matched children drawn from the same community. Controlling for the demographic, country, and time in which the normative data were collected might have resulted in slightly different findings for some skills/tests, such as the CVLT.

This study was limited in terms of the prediction variables it examined and did not take into account a range of other variables that were likely to influence sequelae, such as psychosocial and demographic factors. The results of the present investigation into prediction variables inferred modifications to the way in which these variables are examined in the future. These include the need to investigate the severity or duration of hydrocephalus symptoms and to consider the rate of tumour growth rather than tumour size in order to obtain more meaningful results.

It would be useful for clinicians to be able to give a more accurate indication of an individual's outcome following brain tumour treatment, but this study demonstrated that the NSS is of extremely limited value for single cases. If an instrument like the NSS were further improved definitions should be made clearer and sensitivity within each of the four categories could be improved by creating a more finely graded scoring system. Future investigations would also need to take a more psychometrically rigid approach to the assignment of ordinal scores by removing the open ended system of scoring.

Despite these limitations this is the first study to prospectively examine the relationships of several predictive factors to a wide range of neuropsychological outcomes. It is also one of the only studies to use a longitudinal design to comprehensively explore and compare the relationship of tumour location to outcome in a surgery-only sample.

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APPENDIX ONE

General Questionnaire

The development of cognitive and learning difficulties in children treated for posterior fossa tumours.

General Questionnaire

Child's Name: _____Sex: M/F D.O.B:_____

Address: _____

Post Code: _____

Telephone Number: _____

Presenting Symptoms: Your child may have had a range of symptoms that you now recognise as due to the brain tumour. In your opinion what were they?

_____

Did you notice any recent problems at school or any changes in behaviour. Please circle Yes or No. If yes, please specify

_____

Child's development to date: Apart from these recent changes did your child have any of the following problems prior to this most recent illness?

Medical Condition Yes/No

If yes, please specify

_____

Behavioural Problems Yes/No

If yes, please specify

_____

Language Problems Yes/No

If yes, please specify

_____

Visual Problems Yes/No

If yes, please specify

_____

Hearing Problems Yes/No

If yes, please specify

Physical abnormalities Yes/No

If yes, please specify

Learning Problems Yes/No

If yes, please specify

Co-ordination Problems Yes/No

If yes, please specify

Poor Interaction with peers or siblings Yes/No

If yes, please specify

Developmental Milestones:

Age when your child crawled: _____

Age when your child walked independently _____

Age when your child first put 2 or more words together _____

Child's hand preference: Left/Right/Both/Not yet established

Did you have any concerns regarding your child's developmental progress before the brain tumour was diagnosed? Yes/No

If yes, please specify_____

School Details:

School or Kindergarten: _____

Grade/Year: _____

How many days of school have been missed over the last month? _____

How many days of school have been missed over the last twelve months? _____

Has your child repeated a year at school or kindergarten: Yes/No

If Yes Which year? _____

Has your child received Integration aide in the last twelve months Yes/No

If Yes how many hours per week? _____

Has your child received special tuition in the last twelve months Yes/No

If Yes how many hours per week? _____

If your child is in grade three or beyond did your child have any difficulties learning to read during the early school years? (Prep to Grade 3) Yes/No

Family Information:

Mother's occupation: _____

Mother's education: _____

(Highest level achieved eg. Year 10, VCE or equiv, Trade certificate, degree)

Father's occupation: _____

Fathers education: _____

(Highest level achieved eg. Year 10, VCE or equiv, Trade certificate, degree)

Number of siblings: _____

Language/s spoken at home: _____

Family Tree: (insert details or a diagram)

Has the family unit changed in the last 12 months. Yes/No

If yes, please specify

_____

Thank you for taking the time to complete this questionaire. Todays Date _____

APPENDIX TWO

Semi-Structured Interview

Semi-Structured Interview - Outline

The following is an outline of the topics covered in the semi-structured interview conducted with the parent(s) at each assessment. All aspects of this outline were addressed in a flexible order of questioning.

Medical

- Vision or hearing impairment/changes
- Balance and coordination
- Gross and fine motor skills
- Current therapy (eg. occupational therapy, physiotherapy)
- Other medical problems
- Medical and early developmental history (if not previously obtained)

Cognitive Changes/Difficulties: quality of changes compared with past performance and with peers

- Attention and concentration
- Memory and learning
- Organisation and planning
- Other cognitive changes

Academic Status

- Current school, grade, teacher
- Amount of school missed, grades repeated
- Current academic assistance (tutor, integration aide, visiting teacher)
- Reading, writing, spelling
- Mathematics
- Academic progress in other areas
- Teacher's report or comments

Social, Emotional, and Behavioural Issues

- Friendship group
- Interaction with peers, social skills
- Interaction with siblings
- Behaviour at home and school
- Anger, withdrawal, depression, anxiety
- Extracurricular activities
- Sports
- Interests

APPENDIX THREE

Victoria University Psychology Department Ethics Committee Approval

From: "Keis Ohtsuka" <Keis.Ohtsuka@vu.edu.au> Thu 7:25 PM
Subject: Ethics Approval - Mia Rowe
To: Alan Tucker <alan.tucker@vu.edu.au>
CC: Janine Jarski <janine.jarski@vu.edu.au>

Victoria University Psychology Department Ethics Committee

Approval Form

Name of Student: Mia Rowe
Name of Supervisor: Dr Alan Tucker & Robyn Stargatt
Title of Project: A study of neuropsychological outcomes in children with intracranial tumours.

Recommendations: APPLICATION APPROVED

Comments: Note an typographical error in the availability date of research report to participants.

Name of Chair of Ethics Committee Dr Keis Ohtsuka

Signed Date: 2 August 2001

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Keis Ohtsuka, PhD
Lecturer
Department of Psychology
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Victoria University of Technology
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MELBOURNE CITY MC, VIC 8001
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URL: http://www.staff.vu.edu.au/Keis

Keis.Ohtsuka.vcf	**Name:** Keis.Ohtsuka.vcf **Type:** VCard (text/x-vcard) **Encoding:** 7bit **Description:** Card for Keis.Ohtsuka

APPENDIX FOUR

RCH Ethics in Human Research Committee Approval

ROYAL CHILDREN'S HOSPITAL
ETHICS IN HUMAN RESEARCH COMMITTEE

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9 June, 1999

Ms Robyn Stargatt
Psychology
RCH

Dear Ms Stargatt,

Please find attached the Ethics in Human Research Committee Approval for the project **EHRC 99027A** entitled "Neuropsychological and academic outcomes of children undergoing treatment for posterior fossa tumours - a prospective study", for which you are listed as the contact person.

Please note the conditions on which this approval is granted.

In commencing this project, please complete the enclosed "Notification of Project Commencement" Form and return it to the Research Institute Office.

Thank you

Adam Chapman
Coordinator, Human Ethics
Ethics in Human Research Committee

Melbourne, Victoria

Department ETHICS IN HUMAN RESEARCH COMMITTEE

Flemington Road,
Parkville, Victoria, 3052
Australia.
Telephone: (03) 9345 5522
Facsimile: (03) 9345 5789

APPROVAL

EHRC REF. No: 99027 A

PROJECT TITLE: Neuropsychological and academic outcomes of children undergoing treatment for posterior fossa tumours - a prospective study

INVESTIGATOR(S): R Stargatt, V Anderson, J Rosenfeld

DATE OF NEW APPROVAL: 08 June 1999

DURATION: 48 months

SIGNED: [redacted]
COMMITTEE REPRESENTATIVE

8/6/99
DATE

CONDITIONS

ALL PROJECTS

1. Any proposed change in protocol and the reasons for that change, together with an indication of ethical implications (if any), must be submitted to the Ethics in Human Research Committee for approval.
2. The Principal Investigator must notify the Secretary of the Ethics in Human Research Committee of:
   - Actual starting date of project.
   - Any adverse effects of the study on participants and steps taken to deal with them.
   - Any unforeseen events.
3. A progress report must be submitted annually and at the conclusion of the project, with special emphasis on ethical matters.

DRUG TRIALS

4. The investigators must maintain all records relating to the study for a period of 23 years.
5. The investigator(s) must report to the Sponsor and the Ethics in Human Research Committee within 24 hours of becoming aware of any serious adverse event experienced by any subject during the trial.

Melbourne, Victoria

Department

Flemington Road,
Parkville, Victoria, 3052
Australia.
Telephone: (03) 9345 5522
Facsimile: (03) 9345 5789

ETHICS IN HUMAN RESEARCH COMMITTEE

APPROVAL

EHRC REF. No: **99027 B**

PROJECT TITLE: Neuropsychological and academic outcomes of children undergoing treatment for posterior fossa tumours - a prospective study

INVESTIGATOR(S): R Stargatt, V Anderson, J Rosenfeld

DATE OF MODIFICATION APPROVAL: **14th May, 2001.**

DURATION: 48 months

SIGNED: [redacted] 16/5/01

COMMITTEE REPRESENTATIVE DATE

Approval subject to the title of the Project and Information Statements being altered to include the supra tentorial tumours.

CONDITIONS

ALL PROJECTS

1. Any proposed change in protocol and the reasons for that change, together with an indication of ethical implications (if any), must be submitted to the Ethics in Human Research Committee for approval.
2. The Principal Investigator must notify the Secretary of the Ethics in Human Research Committee of:
   - Actual starting date of project.
   - Any adverse effects of the study on participants and steps taken to deal with them.
   - Any unforeseen events.
3. A progress report must be submitted annually and at the conclusion of the project, with special emphasis on ethical matters.

DRUG TRIALS

4. The investigators must maintain all records relating to the study for a period of 23 years.
5. The investigator(s) must report to the Sponsor and the Ethics in Human Research Committee within 24 hours of becoming aware of any serious adverse event experienced by any subject during the trial.

APPENDIX FIVE

Correlation Tables

Table 1 Small correlations between NSS and neuropsychological variables at one-year

	NSS		NSS
CPT Commissions+	.21	Handwriting Speed	-.19
CPT Reaction Time+	.17	CBCL Competence	.27
FDI	.14	CBCL Internalising+	-.10
Rey Figure Copy	-.16	Vineland ABC	-.20
Rey Figure Delay	-.16	WIAT Maths	.26
CVLT Trial 5	-.13	WIAT Spelling	.23

+ Note: High scores indicate deficits

Table 2 Small correlations between tumour volume and neuropsychological variables at one-year

	Tumour Volume
CPT Omissions+	.14
CPT Commissions+	.28
CPT Reaction Time+	.12
FDI	.18
Verbal Fluency	.18
Rey Figure Delay	.12
CVLT Trial 1	.13
CVLT Trial 5	.19
CBCL Externalising+	.11
Vineland ABC	.22
WIAT Reading	-.12
WIAT Maths	.26
WIAT Spelling	.29

+ Note: High scores indicate deficits

APPENDIX SIX

Table of Mean Z-Scores at One- and Two-Years

Mean z-scores for tumour location groups on neuropsychological variables

POSTERIOR FOSSA	One-Year		Two-Years	
	Mean	SD	Mean	SD
CPT Omissions	.85	1.01	1.11	.64
CPT Commissions	.52	.91	.36	1.13
CPT Reaction Time	-.33	1.28	.05	.93
FDI	-.08	1.12	-.24	.81
Verbal Fluency	-.36	1.01	.02	1.18
Rey Figure Copy	-.61	.86	-.22	.92
Rey Figure Delay	-1.08	1.37	-.50	1.16
CVLT Trial 1	.15	.41	.65	.59
CVLT Trial 5	.29	.86	.60	.94
CVLT Short-Delay	.13	.88	.60	.97
CVLT Long-Delay	.63	1.00	.60	.99
Coding	-.78	1.10	-.50	1.17
VMI	-.26	.38	-.61	.73
Handwriting Speed	-1.00	.99	-1.05	1.08
CBCL Competence	-.73	.59	-.63	.77
CBCL Internalising	.58	.85	.85	.96
CBCL Externalising	-.39	.86	.04	1.06
Vineland ABC	-1.01	.56	-.77	.86
WIAT Reading	-.25	.99	-.22	1.02
WIAT Maths	-.26	.78	-.01	.79
WIAT Spelling	-.34	1.00	-.43	1.47
SUPRA-TENTORIAL	**One-Year**		**Two-Years**	
	Mean	**SD**	**Mean**	**SD**
CPT Omissions	.37	1.12	-.29	.75
CPT Commissions	.30	.98	-.22	1.11
CPT Reaction Time	-.07	1.21	-.18	1.49
FDI	.56	1.03	.33	.81
Verbal Fluency	.64	1.33	.57	1.31
Rey Figure Copy	-.18	.68	.39	.14
Rey Figure Delay	-.66	1.16	-.62	.54
CVLT Trial 1	.76	.51	.17	1.72
CVLT Trial 5	1.04	.46	.25	1.04
CVLT Short-Delay	.76	.78	.47	.66
CVLT Long-Delay	.78	1.06	.33	1.81
Coding	-.27	1.23	.61	1.42
VMI	.33	1.09	.21	.25
Handwriting Speed	-.07	1.17	.72	.65
CBCL Competence	-.81	.49	-.48	.26
CBCL Internalising	.42	.81	.87	1.24
CBCL Externalising	-.46	.92	.17	1.36
Vineland ABC	-.18	.68	-.61	.71
WIAT Reading	.14	.81	.23	.76
WIAT Maths	.41	1.42	-.32	.82
WIAT Spelling	.16	.81	-.04	.96