**UNIVERSITY OF SOUTHAMPTON**

FACULTY OF MEDICINE

Clinical and Experimental Sciences

# A longitudinal study of health related quality of life in children treated for cerebellar tumours compared with a non-tumour group

by

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ABSTRACT

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# A LONGITUDINAL STUDY OF HEALTH RELATED QUALITY OF LIFE IN CHILDREN TREATED FOR CEREBELLAR TUMOURS COMPARED WITH A NON-TUMOUR GROUP

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This thesis investigated health related quality of life (HRQoL) measured annually at three time points (T1, T2, T3) in children treated for medulloblastoma (SRM) or low grade cerebellar astrocytoma (LGCA) compared with a typically developing group of children. Four research questions were addressed. These were, first, whether HRQoL and other aspects of quality of survival differ between children treated for cerebellar tumours and a representative sample of children in the general population. Second, whether there are differences between HRQoL in children treated for SRM and LGCA. Third, whether HRQoL and the factors that impacted on it changed over time. Fourth whether there were any early modifiable predictors of subsequent HRQoL.

Children treated for cerebellar tumours had a significantly poorer HRQoL and IQ than the Comparison group. In addition, those in the SRM group had significantly poorer health status, and behavioural and executive functioning, the latter by teacher-report only.

Children in the SRM group had a significantly poorer HRQoL, health status (by parent-report only), and behavioural functioning (by teacher-report only) than children in the LGCA group. IQ and executive functioning were similar.

Longitudinally, in the SRM group, HRQoL and health status improved but remained very poor. Behaviour and IQ did not improve, and executive functioning declined (by teacher-report only). In the LGCA group HRQoL and IQ did not improve and remained poor. Specific help at school increased in the SRM group from 40% at T1 to 57% at T3. In the LGCA group the percentages were 11 and 24 compared with a consistent 3% in the Comparison group, indicating increasing need for educational support in both tumour groups.

Motor and sensory functioning, emotional functioning (except by parent-report at T3), and cognitive functioning (by child-report at T3 only) were consistent predictors of HRQoL over time. At T1, emotion and cognition (by child- and parent-report), child's age (by child-report), and motor and sensory functioning (by parent-report) predicted subsequent HRQoL two years later.

These findings show that impairment is evident early on in children treated for cerebellar tumours and persists over time. HRQoL remains poor particularly in the LGCA group where no improvement was observed. These children need to be assessed regularly and monitored as early intervention to mitigate cognitive and emotional difficulties especially in older children, may help to improve subsequent HRQoL. Future research should focus on early interventions.

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# Declaration of Authorship

I, **Kim Sharon Bull**

declare that the thesis entitled

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and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- parts of this work have been published before submission (Bull & Kennedy, 2008; K. Bull & C. Kennedy, 2010; K. S. Bull & C. R. Kennedy, 2010)

**Signed:**……..

**Date:**…….

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## Abbreviations and Glossary

| | |
|---|---|
| ADHD | Attention Deficit Hyperactivity Disorder |
| ANOVA | Analysis of Variance |
| BRI | Behavioral Regulation Index |
| BRIEF | Behavior Rating Inventory of Executive Function |
| CBCL | Child Behaviour Checklist |
| CCLG | Children's Cancer and Leukaemia Group |
| CCNU | lomustine |
| CCSS-NCQ | Childhood Cancer Survivor Study Neurocognitive Questionnaire |
| CHQ | Child Health Questionnaire |
| CI | confidence interval |
| CNS | Central Nervous System |
| CSI | craniospinal irradiation |
| CT | chemotherapy |
| EORTC | European Organization for the Research and Treatment of Cancer |
| FSIQ | Full Scale IQ |
| GEC | Global Executive Functioning Composite score |
| GHQ | General Health Questionnaire |
| GP | General Practitioner |
| HIT-PNET4 | European treatment trial (PNET4) for medulloblastoma |
| HRQoL | health related quality of life |
| HUI | Health Utilities Index |
| IBM | International Business Machines |
| IQ | Intelligence Quotient |
| JAQQ | Juvenile Arthritis Quality of Life Questionnaire |
| LGCA | low grade cerebellar astrocytoma |
| MANOVA | multivariate analysis of variances |
| *Mdn* | Median |
| MI | Metacognition Index |
| NRCT | National Registry of Childhood Tumours |
| NS-SEC | The National Statistics Socio-economic Classification |
| OHRQoL | Oral health related quality of life |
| ONS | Office for National Statistics |
| *p* | probability |
| PedsQL | Pediatric Quality of Life Inventory |

| | |
|---|---|
| PIQ | Performance IQ |
| PRI | Perceptual Reasoning Index |
| PSI | Processing Speed Index |
| QLQ-C30 | Quality of Life Questionnaire-Cancer 30 item |
| QoL | Quality of Life |
| SD | standard deviation |
| SDQ | Strengths and Difficulties Questionnaire |
| SES | socio-economic status |
| SF-36 | Short Form 36 Questionnaire |
| SIOP | International Society of Paediatric Oncology |
| SPSS | Statistical Package for the Social Sciences |
| SRM | standard risk medulloblastoma |
| SRQ-20 | Self Reporting Questionnaire 20 item |
| T1 | Time 1 (first assessment) |
| T2 | Time 2 (second assessment 12 months after the first) |
| T3 | Time 3 (third assessment 24 months after the first and 12 months after the second) |
| TOL | Tower of London |
| UK | United Kingdom |
| vs | versus |
| VCI | Verbal Comprehension Index |
| VIQ | Verbal IQ |
| WHO | World Health Organization |
| WISC | Wechsler Intelligence Scale for Children |
| WMI | Working Memory Index |

‘The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being…’

(World Health Organization, 1946)

# CHAPTER 1 INTRODUCTION

## 1.1. GENERAL INTRODUCTION

This thesis is about health related quality of life (HRQoL) and other aspects of quality of survival (QoS) in children treated for brain tumours. In Europe and North America, after leukaemia, brain tumours are the second most common type of cancer in childhood, representing 23% of all cancers that develop before the age of 15 (Kaatsch, 2010). They are the most common type of solid tumour and each year about 338 children in the UK are diagnosed with a brain tumour (Peris-Bonet et al., 2006). They are also the most common cause of death from cancer in childhood (Reimers, Mortensen, & Schmiegelow, 2007) but fortunately overall five year survival of children diagnosed in Europe is 63% (Gatta et al., 2009), and 74% in the USA (Armstrong, 2010) .

Overall the physical, cognitive and social detriments of treatment for central nervous system (CNS) tumours in childhood are greater than those of treatments for non-CNS malignancies (Armstrong et al., 2009; Bhat et al., 2005; Boman, Hoven, Andclair, Lannering, & Gustafsson, 2009; Eilertsen, Jozefiak, Rannestad, Indredavik, & Vik, 2012; Fluchel et al., 2008; Fuemmeler, Elkin, & Mullins, 2002; Kuehni et al., 2012; Ribi et al., 2005; Robison et al., 2005; Zeltzer et al., 2009). Post treatment disability is common among survivors (Boman et al., 2009; Boman, Lindblad, & Hjern, 2010; Hjern, Lindblad, & Boman, 2007; Korinthenberg et al., 2011; Macedoni-Luksic, Jereb, & Todorovski, 2003) as is an increased risk of chronic medical conditions and significant neurocognitive impairment (Armstrong et al., 2009; Maddrey et al., 2005; Ribi et al., 2005). Survivors experience significantly lower educational attainment than those in the general population (Lancashire et al., 2010), experience psychosocial difficulties (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Frobisher, Lancashire, Winter, Jenkinson, & Hawkins, 2007; Gurney et al., 2009; Koch et al., 2011; Koch et al., 2006; Langeveld et al., 2003; Pang et al., 2008; Reimers, Mortensen, Nysom, & Schmiegelow, 2009), and suffer long term socioeconomic disadvantage (Boman et al., 2010) including discrimination in the work place (Olson, Hung, Bobinski, & Goddard, 2011). In spite of this elevated risk of adverse effects, there is evidence that children with brain tumours attend fewer follow-up visits off-treatment than do children with other types of cancer (Barakat, Schwartz, Szabo, Hussey, & Bunin, 2012). As survival rates increase many more children treated for brain tumours are living with the effects of their disease and treatment long term. Therefore, HRQoL and

early identification of those at risk of poor outcome in these survivors have become important issues.

In the UK the Children Act 2004, which was developed in consultation with children and young people themselves, states that society has a duty to minimise problems a child may face. Five key factors were identified as important to well-being during childhood and also in later life: (i) being healthy, (ii) staying safe, (iii) enjoying and achieving, (iv) making a positive contribution, and (v) achieving economic well-being. Identification of the difficulties that survivors experience and the particular factors that have an impact on their HRQoL are important. This information can be used to inform not only future clinical trials but also intervention strategies so that these children have the same chance of a full-filled life as any other child. Currently, the literature shows poor long-term outcome in childhood cancer survivors, particularly those with central nervous system (CNS) tumours falling well short of the five goals described above.

The following extract (used with permission) was written for a local newspaper by one of the children who participated in the research. It describes a child's experience of the year-long treatment that follows diagnosis for a medulloblastoma.

"Having Cancer is not just Chemotherapy and radiotherapy. It is blood tests, kidney tests, platelets and blood transfusions. It's also needle after needle. Chemotherapy every six weeks. When you have a kidney test it also means a injection in your hand/arm. Radiotherapy is bad but lying on your tummy with your head pinned down is worse and hurts. Also I could hardly walk, eat, drink and felt tired most of the time. I used to be up for treatment at 9am and 5pm. Hardly got much rest time and the hours flew by. I stayed at [….] house near the [….] which is a charity home. Schooling was with the ward 24's teachers for a hour. I get treatment up at [….] hospital, ward 24. That's about 30 miles, one hour away. When I need a blood transfusion It can take at least 3 hours or longer. Chemotherapy can take up to a few days but I only have the one hour version now. My doctor is a nice, joke loving man. Every time I get needled I get a sticker/stamp on my chart and save up for a surprise. All before this started I had to get a portacath, which is connected to a big vain leading to my neck and is mostly for big drugs like chemo. I never watched much telly when I had radiotherapy but I do now. Because I lost a lot of weight I have to have a yellow tube down my nose that goes into my tummy and feeds me with a milky mixture over night. I also have about 4 different drugs a day. All this started when I

was nine and now I'm nearly eleven, that's over a year long. I haven't had much of a life. Even my 10th birthday had to be celebrated in [….] house."

This account illustrates the very large demands on a child imposed by the treatment for a medulloblastoma over a prolonged period.

This study specifically focused on medulloblastoma and low grade cerebellar astrocytoma (LGCA), two of the most common types of brain tumour that affect children, both of which arise in the cerebellum. The cerebellum has been estimated to contain over half of all the neurons in the brain (Zagon, Mclaughlin, & Smith, 1977) and plays an essential role in the coordination of muscle movement and balance, cognitive abilities (e.g. perceptual reasoning, linguistic processing, working memory, processing speed), executive function (planning, organising), behaviour and emotion (Schmahmann & Sherman, 1998). Both of these tumours cause similar clinical features including uncoordinated muscle movements of walking, speech and eye movements, and impairments of cognition, mood, and behaviour. Both of these types of tumour is surgically removed but the treatments differ thereafter: While those with an LGCA typically receive no further treatment, those children with a medulloblastoma typically receive six weeks of radiotherapy and eight cycles of chemotherapy. In all, the treatment continues for about a year. The difference between these two tumours is that a medulloblastoma is malignant while an LGCA is benign.

### 1.2. THESIS AIMS

Because of the rarity of these tumours and the limited age range of the children being studied, it was necessary to include children from eleven specialist childhood cancer units in hospitals throughout England and Wales.

The aims of the present research were to find out how much of an impact each of these two types of brain tumour has on children's HRQoL over time and how their lives compare with those of children who have never had a brain tumour. I also wanted to know whether any of the factors that predict HRQoL potentially could be amenable to intervention. All the children in this study were aged between eight and 14 years at recruitment and initial assessment, and then followed up on two more occasions at yearly intervals. None of them were more than three years post diagnosis when they were recruited and some of them were within their first year following diagnosis and still on treatment. The assessments

included child, parent and teacher questionnaires; child and parent interviews (which are not included in this thesis due to space limitations) and neuropsychological testing of the child.

### 1.3. OVERVIEW OF THE THESIS

This thesis is organised into seven chapters. The remainder of Chapter 1 constitutes the literature review. This was a narrative rather than a systematic review. The electronic data bases that I searched were: The Web of Science; MEDLINE; Embase; PubMed; and PsycARTICLES. I used numerous search terms and in combination including: quality of life; definition; (mental) health/healthy; illness; concept; development; brain/cerebellar/cerebellum/CNS; posterior fossa; executive function/cognition/cognitive/IQ/neurocognitive/neurocognition; affective; syndrome; symptoms; tumour/tumor/cancer/medulloblastoma/astrocytoma/low grade; child/childhood/children/paediatric/pediatric; longitudinal/prospective; Bonferroni; multiple testing; outcome; survivors/survival; rate/incidence; control; proxy/parents/parental; assessment/questionnaires/measures; PedsQL/GHQ/HUI/SDQ/BRIEF; predictors; behaviour/behavior/behavioural/behavioural; and Childhood Cancer Survivor Study (CCSS).

The review begins with an examination of the concept of HRQoL and then more specifically, children's concepts of health and illness, and HRQoL. This is followed by an explanation of how HRQoL in children and adolescents differs from that in adults, including the issue of proxy report and its relation to child self-report. It proceeds to a review of the measures of HRQoL in childhood and factors that influence HRQoL. Next, the impact of adverse events in the child's life as predictors of HRQoL is considered. Following this, the literature regarding HRQoL in children treated for cancer is reviewed and then more specifically the literature on children treated for brain tumours and that on medulloblastoma and LGCA, the two most common brain tumours in childhood. The review concludes by drawing together issues arising from previous research that will be addressed in the present study.

Chapter 2 begins with a statement of the aims and hypotheses and describes the design of the research, patients, and methods. For nearly five years many miles were travelled from Southampton to Penrith, Plymouth and elsewhere to collect data from families in their own homes to encourage continued participation from them over time. Analysing the results

has also been an enormous task and these are presented in four chapters (3 – 6) each of which concludes with a chapter summary addressing the four research questions. The main findings are discussed in chapter 7.

## 1.4. THE CONCEPT OF QUALITY OF LIFE

There is no universal definition of quality of life (QoL). However, among QoL researchers there is a consensus regarding the characteristics that constitute the construct of QoL (World Health Organisation, 1995).

The first of these characteristics, multidimensionality (Gotay, Korn, McCabe, Moore, & Cheson, 1992) arose from the definition of health described by the World Health Organisation (WHO) over sixty years ago. This definition states that,

> "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."
>
> (World Health Organization, 1946)

A definition of QoL found in the Glossary of Pharmacoeconomics (1998) is very closely based on this definition of health where QoL is defined as,

> "physical, social and emotional aspects of a patient's well-being that are relevant and important to the individual."

This definition includes the idea of the importance of the individual's perspective (O'Boyle, 1994) which is a second characteristic of QoL. Each individual has a unique perspective on his or her own QoL as expressed in the following definition provided by the WHO which gives priority to the 'individual's' perception'.

> "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."
>
> (World Health Organisation, 1995)

It also expresses the multidimensionality of QoL and the fact that QoL has both positive and negative dimensions which both need to be considered. These can include,

contentment, mobility, and the ability to function well in the social environment as well as pain and fatigue, negative feelings and dependency.

In spite of the apparent similarities between health status and QoL, there is a clear difference. As Testa and Simonson (1996) explain, the physical, psychological and social aspects of health are influenced by a person's beliefs, expectations and perceptions. They say that these different domains can be measured in two dimensions: the objective and the subjective. The objective focuses on the functioning capacity of an individual. For example, the extent to which the individual can see, hear, speak or walk and thus this defines a person's degree of health. The person's subjective experiences and perceptions translate the objective into the QoL that is experienced. This distinction between the objective and the subjective should be reflected in measures of functional health status and QoL in that the former reflects objectively how a person functions emotionally, physically and socially whereas the latter reflects a person's subjective view of their functional health status (Boruk, Lee, Faynzilbert, & Rosenfeld, 2007). Thus, two people with the same health status may experience a very different QoL due to their differing expectations regarding their health and the way they manage the limitations of disability.

Thus, unlike health, an individual's QoL may not be directly observed as it relates to a person's feelings or thoughts or perceptions about their own personal situation. These perceptions are influenced by psychological factors such as a person's mental health. QoL may also be influenced by a person's physical health, and in relation to the effects of disease and its treatment, QoL may be more accurately described by the term 'health related quality of life' (HRQoL).

### 1.5. CHILDREN'S CONCEPTS OF HEALTH, ILLNESS AND HRQOL

Traditionally, it was believed that children's understanding of illness was limited and developed in stages consistent with Piaget's theory of cognitive development in which he proposed that a child's causal reasoning is guided by logic that is different from adults' and develops in a series of sequentially ordered stages (Bibace & Walsh, 1980). The first two stages were described as phenomenism and contagion, which characterise Piaget's preoperational child (ages two to seven years); the second two stages, contamination and internalization characterise the concrete operational child (seven to eleven years); and the last two stages, physiologic and psychophysiologic characterise the formal operational child (12 years and over). Burbach and Peterson (1986) provide a useful description of

these stages. Phenomenism refers to young children's conceptualisation of illness as being caused by concrete phenomena that are remote such as the sun e.g. "people get colds from the sun". Contagion refers to the belief that illnesses are magically caused by people or objects that are close to the child but not actually touching them e.g. "people get colds when someone else gets near them". Contamination refers to the conceptualisation of illness as being caused by something harmful to the body which is contracted from a person, object or action that is external to the child e.g. "people get colds when outside without a hat". The child at this stage can distinguish between the cause of an illness and how the cause has its effect. Internalisation refers to the conceptualisation of an illness as being caused by an external phenomenon that has an internal effect on the body e.g. "people get colds by breathing in bacteria". The physiologic stage refers to the belief that illness can be triggered by an external source but the nature and source of the illness lies within specific internal structures and functions e.g. "people get colds from viruses". Finally, the psychophysiologic stage refers to that at which children understand the physiological processes of illnesses and that illnesses can have psychological causes e.g. "people get heart attacks by being nerve wracked".

Investigations of healthy and hospitalised children that used standardized Piagetian tasks, to assess cognitive development (e.g. conservation), and to study children's concepts of health and illness, provided evidence for these stages (e.g. Brewster, 1982; Potter & Roberts, 1984; Redpath & Rogers, 1984; Simeonsson, Buckley, & Monson, 1979). That is, children in the pre-operational stage appeared to be confused about the causes of health and illness and based their reasoning on magical beliefs; then as children moved towards the concrete operational stage their beliefs about illness became more sophisticated and they were able to understand the concepts of contagion and infection and the impact on the body that these have; and as children reached the formal operational stage their understanding of illness became more complex (Drahota & Malcarne, 2008).

This traditional view of children's cognitive development has been challenged, however. It ascribes little importance to the cultural and social context in which children develop (Williams & Binnie, 2002) and the evidence for this view was based on poor research methodologies such as inadequate descriptions of samples, instruments and procedures; observer bias and expectancy effects; little effort to control confounding variables; and reliability and validity issues (Burbach & Peterson, 1986). Also, the Piagetian perspective focused on children's cognitive immaturity and their limitations in understanding concepts

such as health and illness whereas evidence has shown that children possess an early competency than was previously thought (Rushforth, 1999). They are able to understand such concepts as physics, biology and psychology, including emotions and desires well before they start formal education (Wellman & Gelman, 1992). In contrast to the Piagetian structuralist theoretical approach to the development of children's schemata about health and illness, the functionalist approach emphasizes that children's concepts develop in relation to their experiences (Carey, 1985; Eiser, 1989) and are not dependent on general changes in cognitive capacity.

Children's understanding of health and illness becomes more sophisticated and precise with age (Myant & Williams, 2005). Children from eight years are able to report on all aspects of their health including abstract terms such as 'irritability', 'energy', and 'healthy', and to recall events from four weeks previously (Rebok et al., 2001). Their knowledge of health and illness and risks of disease is similar to that of adults in that they are able to perceive health as a complex biological, psychological, social, environmental and spiritual concept (Piko & Bak, 2006). They are able to provide complex multifaceted definitions of health such as the absence of disease, the ability to do things, mental and emotional health, and health as determined by growth and strength (Reeve & Bell, 2009). Children as young as eight also have considerable knowledge of cancer, including its causes and prevention, and can provide detailed information about their perceptions and beliefs (Oakley, Bendelow, Barnes, Buchanan, & Husain, 1995). They also understand the need for treatment and hospitalisation, and its impact on the individual and the family (Knighting, Rowa-Dewar, Malcolm, Kearney, & Gibson, 2011).

Mares and Neusar (2010) studied concepts of QoL in 581 children aged eight to 15 years in the general population using a simple open ended questionnaire. They found that children aged eight to eleven years had difficulties in explaining the concept of 'QoL' that were not observed in the older children whose answers became increasingly sophisticated and elaborate with age. However, all the children wished for the same things: to have good family support, to have good relationships, to be looked after, to have a home, to have something to eat, to have friends, to have good behaviour, and to have good grades at school. Usually health was not mentioned. Girls seemed to be more motivated to answer the questionnaire and completed the task more extensively than boys. In explaining the differences between a normal life, a poor life, and an outstanding life, older girls mentioned alcohol and smoking more frequently than boys and moralized more i.e. they

said what was right and wrong and how one should and should not behave. In fact they appeared to respond to the questionnaire in ways more similar to adults which according to Mares and Neusar (2010) reflected their more advanced developmental level.

Shiloh and Waiser (1991), using questionnaires, studied conceptualisations of health and illness in 61 healthy adolescents aged 14 and 15 years in relation to their experiences with health care, level of intelligence, and health locus of control, i.e. their beliefs about the extent to which they have control over their health. They found that the adolescents were able to explain much more about illness than health and that there was no difference in this respect between the sexes. The most frequent themes that emerged explaining both health and illness were roles or behaviours followed by somatic feelings, psychological aspects, and prevention or health promotion. The adolescents did not view health and illness as extremes on a single dimension but rather as different but overlapping constructs. They found no relationship between intelligence and conceptualisations. Those with more experience of medical care were less expressive about health and illness and those with an internal locus of control had a more preventative orientation towards illness. Shiloh and Waiser said that the order of these concepts reflected the salience of the social domain and also the level of cognitive maturity in this age group.

### 1.6. QoL IN CHILDHOOD AND ADOLESCENCE

The concepts, definitions and dimensions of QoL described in section 1.4 are based on adult health outcomes, which cannot automatically be extrapolated to children and adolescents (Mares & Neusar, 2010) as just discussed in section 1.5. The specific aspects of a child's life that comprise the dimensions of physical, psychological and social functioning are different from adults' (Matza, Swensen, Flood, Secnik, & Leidy, 2004). Mares and Neusar (2010) explain that QoL of life in children is qualitatively different from adults in four respects: i) growth and development, i.e. children have their own concepts of health and illness that change during development and which are influenced by their experiences; ii) state of health, i.e. few children have health problems; iii) personality, i.e. children's personalities are relatively unstable as they develop; and iv) social, i.e. the impact on their opinions and views from family, peer and community is much more powerful in children than in adults.

Thus, when assessing a child's social and psychological functioning it is important to take account of the many social contexts in which the child functions (Cox & Paley, 1997). For

example, asthma has been shown to negatively affect QoL in both adults and children (Juniper, 1999) but the specific effects of this disease for children are likely to impact differently because of their context. Asthma may limit a child's participation in play and sports with peers which may lead to social and emotional consequences not experienced by adults. According to Matza et al. (2004), there are two reasons why context is qualitatively different for children. Firstly, contextual factors have a long term effect on a child's social and psychological development e.g. peer rejection is associated with many long-term negative outcomes such as delinquency and school dropout (Kupersmidt, Coie, & Dodge, 1990). Secondly, children have significantly less power than adults to make changes to their environment. Adults who have the finances and social support can leave a dysfunctional relationship or problematic workplace, for example, whereas children do not normally have the option to change a difficult environment. In fact, children are often dependent on adults making decisions on their behalf (Mares & Neusar, 2010).

As discussed above, the individual's perspective is central to the assessment of QoL and taking into account a child's developmental level, also discussed above, raises the question regarding the youngest age at which children can reliably report their health status and QoL. Valid measures of child QoL need to take account of the child's understanding of the concepts being measured as well as the child's competency in language comprehension (Rebok et al., 2001) and reading ability (e.g. Landgraf & Abetz, 1996). Thus, for the child to be able to respond to items on a QoL questionnaire he or she must have a concept of self, a basic understanding of concepts such as emotions and health, be able to make social comparisons and recall personal experiences, and be able to discriminate between responses on a scale (Riley, 2004).

Landgraf and Abetz (1996) suggested that children as young as five can reliably report on concrete health concepts such as pain (McGrath et al., 1996) and nausea (Zeltzer et al., 1988) whereas more subjective domains such as the emotional impact of illness is more likely to be appropriate for older children. It is generally agreed that children can begin reporting their own QoL between the ages of four and six (Connolly & Johnson, 1999; Juniper, 1999) and self-report QoL instruments have accordingly been designed and psychometrically validated for young children, for example, the Pediatric Quality of Life Inventory (PedsQL) (Varni, Seid, & Rode, 1999) and the Child Health Questionnaire (CHQ) (Landgraf, Abetz, & Ware, 2000). However, young children's self-report responses may be less reliable over time (Cremeens, Eiser, & Blades, 2006). This is

because their self-perception is more embedded in their behaviour and short term concrete experiences and events that may affect their responses which have been found to fluctuate more than older children's responses (De Civita et al., 2005). Older children may have a greater developed awareness of their psychological self, and their self in relation to their peers, and also their own emotional functioning and thus can respond to items on a questionnaire as a function of more stable events and self attributes (Cremeens et al., 2006; Cremeens, Eiser, & Blades, 2007; De Civita et al., 2005).

### 1.7. PROXY- VERSUS SELF-REPORT

As discussed above, children vary according to their individual differences in cognitive skills and in their understanding of health concepts including the more abstract aspects of the impact of disease on their QoL. This raises the question of the reliability of child self-report especially in relation to diseases that may have a direct impact on cognitive functioning due to the disease itself or its treatment such as a brain tumour. One solution to this problem is to ask proxies to complete questionnaires on the child's behalf. However, the subjective nature of QoL begs the question as to whether it is possible to accurately measure an individual's QoL from proxy ratings. Proxies and children may indeed differ in their perspectives regarding the child's QoL. Gathering the 'same' data from both children and proxies may involve cross-informant variance. For example, Morrow, Hayen, Quine, Scheinberg, and Craig (2012), in their comparison of child, and parent and doctor proxy ratings of QoL in chronically ill children, found that overall QoL did not differ significantly between types of rater but that there was poor agreement in some subjective domains especially between child and doctor ratings. Children with cerebral palsy and neurological conditions had the lowest agreement with both parents and doctors not only for subjective but also objective domains.

There appear to be two main related issues regarding cross-informant variance. One relates to whether the patient is well or ill and the other relates to whether the domains of QoL under consideration are concrete and more observable, as in physical functioning, or whether they are abstract and less observable by proxies, such as emotional and social functioning. The research of Morrow et al. (2012), above, illustrates this point. These issues were also highlighted by Sprangers and Aaronson in their (1992) review where they found that, in general, proxies tend to underestimate the patients' QoL but that accuracy of ratings increased when the information sought was more concrete and observable. Eiser and Morse (2001a) in their review of parent and child ratings of QoL, also found that the

accuracy of ratings increased when the information was more concrete, but found inconclusive evidence that parent proxies underestimate their sick child's QoL. They did find however that there was higher agreement between parents and sick children than between parents and healthy children.

Thus there is some evidence to suggest that there can be good agreement between parents' and children's ratings of QoL when the child has health problems but this may depend partly on the child's age. For example, Jokovic, Locker, and Guyatt (2004) found that although QoL ratings were similar to their parents, in children, aged between eleven and 14 years, treated for oral, dental and orofacial problems, the parents lacked knowledge about aspects of their child's QoL as evidenced by the endorsement of 'don't know' responses, in particular in relation to their child's social and emotional well-being. This gap in knowledge about their children was more apparent for older children. Parents rated their children's QoL as being poorer, but not significantly so, than their children did. In a Canadian study involving children with asthma, Guyatt, Juniper, Griffith, Feeny, and Ferrie (1997) concluded that complementary information can be obtained from children under eleven years old and their parents when being questioned about changes in the child's symptoms and QoL, whereas parents could provide little additional information to that obtained from adolescents.

In another Canadian study into QoL in children diagnosed with Juvenile Idiopathic Arthritis, April, Feldman et al. (2006) reported that although there was good agreement between child and parental reports of the child's QoL, such agreement was better for psychosocial functioning in younger children than it was in older children. In addition they also found that the longer the child had had the disease, the better the agreement between parent and child. Similar results were reported by Verrips, Vogels, den Ouden et al. (2000) in their study of parent-adolescent agreement about QoL in very low birth weight children. They found that parent-child agreement was very good regarding motor functioning, good regarding autonomy, and cognition but only moderate regarding social, body, and mood scales. They concluded that it seemed difficult for parents to gain an insight into their adolescent child's social and emotional functioning. Parents, especially as their children get older, may lack insight or have limited knowledge, for example, about their children regarding peer relationships outside the home or their emotions due to a lesser need for involvement in their child's life (Jokovic et al., 2004).

Achenbach, McConaughy, and Howell (1987) pointed out that, in relation to child and adolescent behavioural and emotional problems, cross-informant variance should not be equated with informant unreliability but on the contrary, may indicate that different informants contribute different but valid information. According to Achenbach et al. (1987) different informants differ in their opportunities to observe the child, in the effect they have on the child, and in their standards of judgement. It is therefore hardly surprising that their ratings may differ.

The question is therefore raised as to the best way to use the information from multiple informants. If there is a high level of consistency between different informants then one could be substituted for another, whereas a low correlation between informant observations would mean that different view-points would be important to build a complete picture of the child. It is thus important to bear in mind that there is no informant 'gold standard' by which to measure the reliability of informant ratings.

Levi and Drotar (1999) found a significantly greater discrepancy between reports of QoL from children with cancer and from their parents compared to that for healthy controls. In contrast, Russell et al. (2006) found that parent-child ratings of the child's QoL were highly significantly correlated in children with cancer and also healthy controls but discrepancy in scores between children and parents were greater in the healthy group. De Bolle et al. (2008) found that child and maternal ratings of QoL were highly significantly correlated in children with cancer whereas for healthy controls, there was only high agreement regarding school functioning. These studies all reported that the parents of children with cancer, compared with the parents of the controls, perceived them as having a poorer QoL than did the children themselves, and that parents of healthy children tended to overestimate their child's QoL. De Bolle et al. explained this in terms of parents of children with cancer being more aware of their child's condition and the negative implications of the illness. In addition, the increased responsibilities and attention to their ill child's needs leading to more involvement and communication may account for greater agreement between parents and their child.

In contrast to the above studies, Chang and Yeh (2005) (plus Fluchel et al., 2008; Yeh, Chang, & Chang, 2005) reported a consistent bias for parents to underestimate the impact of cancer and its treatment on their children. They contended that parental proxy-reports of QoL are only appropriate as a substitute for children younger than 12 years of age and

that parental reports of their adolescent offspring were significantly different from the adolescents themselves, especially those who were experiencing a greater impact of the disease and treatment. Thus, they argued that assessment of QoL of adolescents should be based on self-report rather than parental proxy-report and that the latter should be viewed as supplemental information only. This overestimation of adolescents' QoL by their parents may, however, have been influenced by this research's Taiwanese context and culture in which there is little discussion between parents and children about the child's illness. However, similar results have been found in other countries, Canada, for example (see above).

From the above it is clear that children and parents do not necessarily share the same views on the impact of the cancer experience (Carpentieri et al., 2003). Such differences between children and parents may impact on the child's QoL. Parental distress could negatively affect parental perceptions of the child's emotions and behaviours (Mulhern, Fairclough, Smith, & Douglas, 1992) which in turn could affect the child's psychological well-being. For example, maternal depression has been found to affect child QoL (Ferro, Avison, Campbell, & Speechley, 2011; Vance, Morse, Jenney, & Eiser, 2001). Boruk et al. (2007) reported that caregiver ratings of their child's functional health status and QoL were largely influenced by their perceptions of their own functional health status and QoL. Thus, they advised considering caregiver health status when interpreting proxy ratings of children's QoL.

Sprangers and Aaronson in their review (1992) also observed that proxy ratings are more accurate when made by those who live in close proximity to the patient but that the caregiver function of the proxy may be a source of bias in their ratings. In order to overcome these problems they advocate employing well validated QoL instruments longitudinally in order to examine the effects of changes in patient health status on the ability of the proxy to provide valid QoL ratings. Varni, Katz, Colegrove, and Dolgin (1995) (also Varni et al., 1998) recommended including multi-informants in order to assess adequately the QoL of children treated for cancer.

### 1.8. APPROACHES TO THE ASSESSMENT OF QOL

QoL may be measured using generic or disease-targeted instruments. A generic instrument is one which is applicable across a wide range of populations and diseases whereas a disease-targeted instrument is designed to be relevant to a particular disease such as

diabetes (Hays, 2005). According to Hays, generic measures have two basic forms, profile and preference-based. Profile measures are designed to yield scores on multiple aspects of QoL whereas preference-based measures produce a single summary score.

Generic profile QoL measures are used to compare the relative burden of disease on different groups of patients. The SF-36 is the most widely used adult measure of this kind in the world(Hays, 2005). It assesses eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions. It has an additional single item that assesses change in perceived health over the previous 12 months. Meaningful and valid comparisons between different groups assume that the measure is equivalent in the different groups in terms of its acceptability, reliability and validity.

Disease-targeted measures are designed to fill the gaps in generic instruments by tapping aspects of QoL that are particularly relevant to those patients with the disease of interest. An example of an adult disease targeted measure is the European Organization for the Research and Treatment of Cancer-C30 Questionnaire (EORTC QLQ-C30) (Aaronson et al., 1993). This tool assesses QoL in five functional areas: physical, role, cognitive, emotional and social, as well as global HRQoL and financial impact scores. It also provides scales of symptoms commonly reported by cancer patients receiving treatment.

One problem with measuring QoL, and in particular HRQoL is response shift (Fayers & Hays, 2005). This phenomenon relates to the fact that patients adapt in various ways over time due to an alteration in their views of HRQoL caused by an adjustment of their internal standards or by changing their priorities as they learn to adapt to their illness. Response shift may make HRQoL data difficult to interpret particularly in a cross-sectional design. In contrast, a longitudinal design may be used to document these changes in a meaningful way.

### 1.9. MEASURES OF QOL IN CHILDHOOD

As mentioned above in section 1.8, measures of QoL can be divided into generic and specific and a number of generic measures have been devised to assess QoL in children. According to Varni, Burwinkle, and Lane (2005), paediatric QoL questionnaires need to show their usefulness in a clinical context by addressing three important issues: (i) they

must be brief, yet reliable and valid, and provide new and valuable information; (ii) they should be designed to be user-friendly for children and their parents and also be quick and easy to score and interpret; and (iii) they must be responsive to change.

Eiser and Morse (2001b) reviewed measures of QoL in children and concluded that all measures available at that time had limitations regarding limited psychometric data, lack of parallel child/proxy questionnaires, and insufficient attention to children's ability to complete paper and pencil measures. These limitations along with an absence of a universal definition of QoL put at risk the importance of the whole concept due to its apparent vague or unscientific nature. However, they argued that the value of QoL as a concept is still high particularly with regard to disease and treatment outcomes. This is because, even though these outcomes may be measured in more concrete physiological terms, it is the social and psychological aspects of survival that will become ever more important to the survivor as they grow and develop, and will eventually mediate the success of that survival. Based on their review Eiser and Morse recommended the use of the PedsQL as one of the more thoroughly developed generic measures available.

Many specific measures have been developed to measure QoL in various childhood diseases such as juvenile idiopathic arthritis (JAQQ) (Duffy, Arsenault, Duffy, Paquin, & Strawczynski, 1997) or children with various oral, dental and orofacial conditions (OHRQoL) (Jokovic, Stephens, Locker, & Tompson, 2002). Childhood cancer has been a particular object for the development of QoL questionnaires. In their review of such measures, Klassen, Strohm, Maurice-Stam, and Grootenhuis (2010) identified 13 questionnaires which met development and validation standards of health outcomes instruments laid out in guidelines published by the Scientific Advisory Committee of the Medical Outcomes Trust (Aaronson et al., 2002). Of the 13 questionnaires reviewed, just six were suitable for both self- and proxy-report. Of these six, they recommended three based on their good development and psychometric properties but one of these questionnaires showed superiority in these aspects, the PedsQL Cancer module (Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002). Banks, Barrowman, and Klaassen (2008) compared the responsiveness over a four week period of three paediatric QoL measures in a heterogeneous sample of 29 children with an average age of nine years who were undergoing chemotherapy. They used the PedsQL, CHQ and the Health Utilities Index (HUI) (Feeny et al., 1992) and found that the measure that was most responsive to change when administered at weekly intervals was the PedsQL.

## 1.10. ADVERSE EVENTS AND QOL IN CHILDHOOD

Interest in QoL research in childhood populations is often in relation to adverse life events and the impact of these on QoL. There is a clear link, for example, between stressful life events and behavioural and emotional functioning in children and adolescents but there is also a great variability in the way young people respond to the same stressful life event (Rutter, 2007). Protective factors such as individual and family characteristics, as well as environmental factors have been implicated (Greenberg, 2006; Maddi, 2005). Cognitive functioning as a protective factor is one such individual characteristic that has been studied in relation to the cognitive reserve hypothesis (Stern, 2009) which postulates that higher levels of cognitive functioning protect against brain pathology. There is evidence that non-verbal cognitive ability affects emotional and behavioural functioning (Koenen et al., 2009; Pine & Freedman, 2009), and can reduce the impact on a person's emotional and behavioural functioning in the face of a stressful life event that requires problem solving skills (Flouri & Panourgia, 2011).

The unexpected onset of a serious illness or disease is a stressful life event that may impact negatively on QoL due to a sudden change in circumstances and health status. QoL and health status are intricately linked. This is because the concept of QoL arose from the definition of health status. It is not surprising therefore that many studies have shown that poor health status leads to poor QoL (e.g. Meeske, Patel, Palmer, Nelson, & Parow, 2007) but is nevertheless distinct from it (Matza et al., 2004) as was mentioned above. When considering HRQoL, disease status and treatment effects are given and the person has little or no control over them. Disease status and treatment affect health status (Feeny et al., 1992) which again a person has little or no control over. This leads to the question as to whether there are other factors that potentially could be manipulated and that may affect the impact of health status on QoL.

An unexpected serious accident may also impact negatively on a child's QoL. Research involving children with neurological disorders such as resulting from head injury has found that executive dysfunction contributes significantly to the risk of poor QoL (e.g. McCarthy et al., 2006) as does epilepsy (e.g. Sherman, Slick, & Eyrl, 2006). Executive functioning is an individual's ability to carry out goal-directed behaviour and involves planning and sequencing multi-step actions, inhibiting inappropriate behaviour, and maintaining effort over extended periods of time. It is often assessed using a battery of performance based measures, for example, The Tower of London (TOL) (Anderson, Anderson, & Lajoie,

1996), which primarily assesses planning ability. The Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, & Kenworthy, 2000) is a measure that is more ecologically valid than performance based measures which may disguise impairments (Gioia & Isquith, 2004). Gioia and Isquith argue that performance based measures are administered in a distraction-free environment, the tests are highly structured, and they provide clues as to how the child should respond. This is in direct contrast to the demands placed on the child in the real world which is less structured and filled with distractions, and in which the child is expected to concentrate on tasks, remember what to do next, and inhibit the impulse to switch to a more interesting activity. This difference between the artificial and real world environment may account for the poor correlation between performance based measures and ratings of executive functioning (Barkley & Murphy, 2011). The BRIEF allows the rater to respond on the basis of a much broader sample of the child's behaviour over time than is available through direct observation at a particular moment in time. Gioia and Isquith advocate that an ecologically valid model of neuropsychological assessment should comprise three levels of information: specific cognitive functions measured by clinical tests; real world behavioural expressions of these cognitive functions; and environmental factors that impact on the child's function.

A subset of items from the BRIEF has been incorporated into a questionnaire to identify neurocognitive problems in adult survivors of the Childhood Cancer Survival Study (CCSS) in the United States (Armstrong, 2010; Armstrong et al., 2009; Brackett et al., 2012; Brinkman et al., 2012; Clanton et al., 2011; Ellenberg et al., 2009; Kirchhoff et al., 2011; Krull et al., 2011; Krull, Gioia, et al., 2008; Kunin-Batson et al., 2011) in which they also used the adult self-report BRIEF itself (Krull et al., 2012). There have also been recent recommendations in Australia and the United States to incorporate the BRIEF itself into behavioural (Pejnovic et al., 2012) and cognitive (Embry et al., 2012) assessments following treatment to the CNS for childhood cancer. However, to date there are no studies reporting executive function using the BRIEF for children treated for brain tumours.

A child's QoL may also be influenced by their parents. Parental subjective physical and mental health has been found to be a predictor of QoL in children in a general population sample in Greece (Giannakopoulos et al., 2009). In this large cross-sectional study, 1,194 children aged eleven to 18 years and their parents completed a QoL questionnaire as well as a child health care needs questionnaire, a parent physical and mental health

questionnaire, and a family affluence scale. Ninety seven per cent of the children had no specific special health care needs. The common significant predictors of the children's physical and mental well-being were found to be good parental mental health, younger child age, male gender, and higher social support. The strength of this study was its large randomly selected representative sample from the general population and one of the limitations was its inability to establish causal relationships due to its cross-sectional design.

Parental well-being has also been found to be a predictor of QoL in children with intellectual disabilities (Cramm & Nieboer, 2012). In this study, parents of 108 infants, children, and young adults aged less than one year to 24 years with IQs of less than 85 completed a QoL questionnaire on two occasions six months apart. Parents were asked to report on their own educational and income level (SES), their child's daily activities, their child's health status, and their own and their child's social and emotional well-being. They found that the children's health status improved significantly over the six months but their QoL did not. Children's social well-being was significantly poorer at the second assessment and both parents' and children's emotional well-being was also poorer. The best predictor of QoL at the second assessment was QoL six months earlier. Child and parent social and emotional well-being also predicted QoL. SES, health status or the child's daily activities did not predict QoL. An important problem with this research is that only data on parent-report of child QoL were collected and so the results may have been biased by parental perceptions that may have been influenced by how they themselves were feeling. Child-report QoL data should have been collected where possible. Also, although an attempt was made to collect data longitudinally, the six month time frame was rather short. Also there was a wide age range of the children on whom the parents were reporting.

Furthermore, higher levels of parental stress have been found to be related to parent-report of QoL in children with cerebral palsy (Arnaud et al., 2008). In this cross-sectional study the parents of 818 children aged eight to 12 years completed a QoL questionnaire about their child. Parents were also asked to report on their child's physical and intellectual impairments, and level of pain. In addition, they reported their own educational and income level (SES), family structure, and their own stress. They found that parent-report of their child's QoL was related to the domains examined. That is, motor and intellectual impairment was strongly related to poorer physical well-being, autonomy and social

support but better moods and emotions, self-perception, functioning in the school environment and acceptance by peers. Pain was associated with poor QoL in most domains and parental stress in all domains. Similar to the research mentioned above, an important problem with this study is that only data on parent-report of child QoL were collected and so the results may have been biased by parental perceptions that may have been influenced by how stressed they were feeling. Child-report QoL data should have been collected where possible. Also, 47% of the children in this study were at a special school which may have accounted for parents reporting that those with more severe impairments were functioning well in the school environment and were well accepted by their peers and had good emotional functioning. In spite of the limitations in such studies, they all show the importance of adjusting for parental well-being when measuring parent-report of child QoL.

### 1.11. QoL AFTER CHILDHOOD CANCER

One serious life-threatening illness which has particularly become the subject of QoL research over relatively recent years is childhood cancer. This is because the diagnosis of cancer is no longer the 'death sentence' that it once was. Almost 75% of European children up to the age of 14 diagnosed during the 1990's could expect to still be alive five years later whereas only 44% of children diagnosed during the 1970's could have the same hope of survival (Steliarova-Foucher et al., 2004). In spite of increasing survival rates, the impact of such a diagnosis on the child and family should not be underestimated. The progressive nature and continuing threat of the disease makes it qualitatively different as a stressor from other childhood diseases, from adverse life events such as acute trauma caused by a serious injury, or from a bereavement where the time frames are more clearly defined (Ho, Chan, Yau, & Yeung, 2011).

There is conflicting evidence regarding the effect on QoL of children treated for cancer with some studies showing few adverse effects while others show poorer outcomes than healthy children or normative data, and others report conflicting evidence within the same study. This is due to cross-informant and cross-diagnostic group variance as well as different studies focussing on different measures. Some examples of these studies are provided below.

QoL was measured at six time points over a two year period in a longitudinal study of 44 patients aged between eight and 25 years who had undergone surgery for a malignant bone

tumour around the knee joint (Bekkering et al., 2012). The results showed that functional and physical ability improved over the two years, especially during the first year. However, the improvement of self-report perceived physical ability did not match objective observations of walking ability, showing that perceptions differed from actual performance. Emotional functioning was commensurate with normative data over the two year period. One problem with this study due to its longitudinal design was the drop off of participants from 44 at the outset to 24 at the end due to disease progression which is a common problem when studying children with cancer over time. The researchers did not perform a complete case analysis and used data from participants who had relapsed and then were not subsequently included at the next time point. This may have artificially inflated the physical functioning scores over time as those with poorer functioning gradually dropped out. It is also difficult to interpret the emotional functioning data for the same reason.

QoL in 103 adolescents and young adult survivors aged 15 to 29 years was studied in one centre in Greece (Servitzoglou, Papadatou, Tsiantis, & Vasilatou-Kosmidis, 2009). They had all been treated for a variety of childhood malignancies, four to 20 years previously. They were compared with healthy controls from schools and universities using a QoL questionnaire that had been specifically designed for the study as well as the SF-36. The results showed good adjustment and overall good QoL in survivors compared with controls and in spite of severe chronic side effects being reported in their medical notes in 15% of cases, none of the survivors rated their health problems as serious. Social functioning was also rated similar as that of controls.

Some studies have reported poorer QoL in survivors. For example, using the HUI, Fluchel et al. (2008) studied HRQoL cross-sectionally in a heterogeneous sample of children in Uruguay who had been treated for a variety of childhood malignancies including brain tumours. They found that the comparison group of healthy children had a significantly higher (better) mean HRQoL score than survivors of acute lymphoblastic leukaemia (0.80 vs. 0.72) and the children with brain tumours had a mean HRQoL score of 0.60, which represents severe disability. They also found that inter-rater agreement between self and proxy assessment was related to the familiarity between the raters. Inter-rater agreement was also higher for attributes that were easily observable, such as ambulation, but was less than moderate for attributes that were not directly observable such as cognition, emotion and pain, as discussed above in section 1.7. On average, children reported themselves as

having a poorer HRQoL and poorer emotional and cognitive functioning than did their parents. The authors concluded that self and proxy reports should not be considered as interchangeable (as suggested above in section 1.7). The main limitations of this study were the heterogeneous sample of cancer survivors and the large age range which included both children and adults.

A cross-sectional study assessed mental health, psychosocial adjustment, and parental functioning in 40 children, aged nine to 15 years, who had been diagnosed four to 13 years previously with Leukaemia in two hospitals in Norway, compared with 42 healthy controls randomly selected from four schools (Reinfjell, Lofstad, Nordahl, Vikan, & Diseth, 2009). They found that the leukaemia group had significantly poorer behaviour and emotional functioning by parent report but not by self-report, and that mothers' mental health was similar between the two groups. The strengths of this study are the relative homogeneity of the study group in terms of diagnosis and age and also the appropriately selected control group. It was limited by its cross-sectional design and only two measures were used to assess functioning including the CBCL which is problematic in children with health problems (see section 1.12 below).

In some research there are conflicting findings within the same study. For example, Eilertsen, Jozefiak, Rannestad, Indredavik, and Vik (2012) conducted a cross-sectional study of 50 survivors of different types of childhood cancer aged six to 20 years who had been diagnosed four to 16 years previously. They compared survivors with a control group of 29 survivor selected friends. The results showed that survivors and their friends rated themselves as having a similar QoL but survivors of brain tumours rated their QoL (and also late effects) as being poorer. In contrast, parents rated the survivors as having a poorer QoL than did the parents of the friends. This study also highlights the importance of considering parent and child reports separately where possible.

Zeltzer et al. (2009) reviewed the previously published psychological outcome studies of 7,147 survivors from the large cohort of 13,581 survivors, who had been enrolled below the age of 21 in the North American Childhood Cancer Survivor Study between 1970 and 1986. They reported that when compared with siblings and normative data, although the majority of survivors overall were satisfied with their lives and had good psychological health, there were some groups who were at high risk of poor HRQoL with regard to psychological distress, poor physical functioning, and poor neurocognitive abilities.

Leukaemia survivors experienced more psychological distress and social skills deficits than their siblings; brain tumour survivors had higher rates of physical health issues compared with siblings and also leukaemia survivors, and in particular, astrocytoma survivors had more mental health issues than their siblings; neuroblastoma survivors experienced more psychological distress than siblings; bone tumour and sarcoma survivors had more physical problems including pain than siblings, norms and leukaemia survivors, and more psychological distress than siblings or norms; Wilms tumour survivors experienced higher levels of general health issues than their siblings; and lymphoma survivors had higher levels of psychological distress compared with their siblings and norms. This large study explains the conflicting results of smaller scale studies in which different diagnostic groups had been amalgamated and compared with different comparison groups.

Thus, there have been many studies into the possible effects of a number of types of childhood cancer and treatment on the child at different stages of the cancer experience. The majority of such studies have reported that most of the children adapt to the cancer experience and show few adverse effects (Langeveld, Stam, Grootenhuis, & Last, 2002; Shankar et al., 2005; Zeltzer et al., 2009) while others have shown poorer outcome in these children (Reinfjell et al., 2009; Speechley, Barrera, Shaw, Morrison, & Maunsell, 2006). However, children treated for brain tumours are more vulnerable than children with other types of cancer (Barrera et al., 2005; Eilertsen et al., 2012; Kuehni et al., 2012; Zeltzer et al., 2009). In fact, many children diagnosed with a brain tumour have not only received a diagnosis of cancer but also an insult to the brain. The impact on QoL of the sum of these two events can be devastating.

The rest of this literature review will focus specifically on children treated for brain tumours.

### 1.12. QoL AFTER CHILDHOOD BRAIN TUMOURS

As was mentioned at the very beginning of this thesis, brain tumours are the most common type of solid tumour in childhood and every year in the UK approximately 338 children below the age of 15 are diagnosed, and overall 63% of children treated in Europe survive a brain tumour. Sixty per cent of all paediatric brain tumours arise in the posterior fossa (Cantelmi, Schweizer, & Cusimano, 2008) and the two most common types are (malignant) medulloblastomas and (benign) cerebellar astrocytomas which both arise in the

cerebellum. Six and seven year event free survival for standard risk medulloblastoma in Europe has been reported to be 75% (Carrie et al., 2009) and 79% (Lannering et al., 2012) and in the United States eight and ten year event free survival for cerebellar astrocytoma has been reported to be 84% (Wisoff et al., 2011) and 71% (Ogiwara, Bowman, & Tomita, 2012). With the incidence of survivors increasing there is a large potential impact not only on the survivors themselves but also on society, adding to the importance of studying outcome in these children. Survivors of childhood brain tumours have been reported to have poorer QoL than survivors of any other type of childhood cancer (Zeltzer et al., 2009).

Many studies have focused on the neurocognitive aspect of QoL following treatment for a brain tumour in childhood and a decline in IQ has been observed in these children (e.g. Duffner, Cohen, & Thomas, 1983; Kieffer-Renaux et al., 2005; Mabbott et al., 2011; Palmer et al., 2001). This has largely been attributed to the damaging effects of cranial radiotherapy to the developing brain (in particular in very young children) but also to chemotherapy, hydrocephalus, and tumour location (Duffner, 2010; Ellenberg et al., 2009; George et al., 2003; Mulhern et al., 1998; Palmer et al., 2001). Thus, the main focus of studies over recent years has been to refine or eliminate radiotherapy, especially in younger children, with the aim of minimising damage to healthy tissue in the brain, even though reduced-dose protocols have failed to eliminate cognitive decline or reduce it greatly (Cantelmi et al., 2008).

The addition of chemotherapy to radiotherapy (Duffner et al., 1983), especially methotrexate (Duffner, Cohen, Heffner, & Freeman, 1981; Riva et al., 2002), may also have important effects on cognitive functioning. Chemotherapy without methotrexate has also been found to have a detrimental effect on health status, behaviour and QoL in survivors of medulloblastoma when added to craniospinal irradiation (Bull, Spoudeas, Yadegarfar, & Kennedy, 2007).

Similar impairments have also been observed in children who have received no adjuvant therapy at all (Cantelmi et al., 2008; Roncadin, Dennis, Greenberg, & Spiegler, 2008; Steinlin et al., 2003). For example, Reimers et al. (2007) studied 126 patients who had been diagnosed between 1970 and 1997 with various types of brain tumours before the age of 15 years. Sixty-nine of them had received radiotherapy. They assessed working memory, long-term memory, and general intelligence using a battery of tests including the

WISC. When compared with normative data, they found that the mean scores were lower than expected and treatment with radiotherapy, tumour location, hydrocephalus, and inserting a shunt at the time of diagnosis, were all significant risk factors for memory deficits. When they included IQ as a covariate, radiotherapy no longer predicted memory ability but shunt and tumour location remained significant. They concluded that in patients treated with radiotherapy, memory deficits reflected general cognitive dysfunction, whereas memory deficits in non-irradiated patients reflected specific cognitive dysfunction which was most evident in patients with a shunt and those with hemispheric tumours. The findings of this study were limited by its heterogeneous sample diagnosed over a long period of time (27 years) and its comparison with normative data, rather than a control group. The study did highlight, however, the importance of considering tumour location when assessing outcome in childhood brain tumour survivors.

In a long-term follow up study of cognition in a heterogeneous sample of 18 children treated for brain tumours, Briere, Scott, McNall-Knapp, and Adams (2008) reported that there was an overall decline in cognitive functioning, as measured by the WISC, at a mean interval of 38 months post diagnosis. When the children were assessed again at a mean interval of 60 months post diagnosis, they found that the Performance IQ, Perceptual Organization and Processing Speed indices remained stable but that the Freedom from Distractibility index (auditory attention/concentration and working memory) had declined further. However, the generalisability of these results are questionable given the small sample size and selection bias, i.e. all the participants had been referred for neuropsychological evaluation and follow-up and therefore no information was available for those children who had not been referred or only received one assessment. In spite of the limitations of this study it found evidence of neurocognitive sequelae in children treated for posterior fossa tumours (see below).

A decline in IQ has not been reported in all studies, however. For example, Reimers et al. (2003) in their cross-sectional study of a heterogeneous sample of survivors treated for brain tumours, aged between eight and 40 years, found that IQ scores were significantly lower than norms and that younger age at diagnosis and in particular treatment with cranial radiotherapy significantly increased the risk of compromised cognitive functioning. However, time since diagnosis, which spanned 27 years, was not significantly associated with IQ scores. This study found no cognitive impairments in the non-irradiated children but this has been attributed by others (e.g. Cantelmi et al., 2008) to the use of tests of low

sensitivity. Reimers et al. measured cognition using the WISC and the WAIS only, whereas others who reported cognitive impairment in such children used a more comprehensive neuropsychological battery of tests. For example, Riva and Giorgi (2000), in addition to the WISC and the WAIS, included tests of language, executive functioning, attention, and an assessment of behaviour; Steinlin et al. (2003), in addition to the WISC, included tests of executive function, memory, learning, attention and processing speed; and Levisohn, Cronin-Golomb, and Schmahmann (2000), in addition to the WISC, included measures of language, verbal memory, visuospatial functions, executive functions, and behavioural and affect regulation. Levisohn et al. remarked that performance on standardized intelligence scale subtests did not necessarily reflect the clinical and neuropsychological deficits observed in these children.

As mentioned above in section 1.10, in the CCSS (Ellenberg et al., 2009) neurocognitive status was measured using a self-report instrument, the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ), which was derived from the BRIEF. They assessed 802 CNS survivors and compared them with 5,937 non-CNS survivors and 382 sibling controls. All the survivors had been diagnosed between 1970 and 1985 (i.e. 16 to 34 years previously) in 26 centres in the USA and Canada. They found that the CNS survivors reported significantly more neurocognitive dysfunction on all the domains (Task efficiency, Emotional Regulation, Organization and Memory) than non-CNS survivors and siblings. Higher doses of cranial radiotherapy and also medical complications, including visual and hearing impairments, were associated with poorer CCSS-NCQ score. However, diagnosis before the age of two was associated with better memory. When they explored this age effect further, they found that it was confounded by diagnosis, and was only apparent in the astrocytoma survivors, not the medulloblastoma group or other CNS survivors. They also found that CCSS-NCQ scores were highly correlated with variables that indicated success and achievement in adulthood in that poor neurocognitive function was associated with lower income, less marriage, lower education and less employment. This study showed how neurocognitive impairment acquired in childhood can have far reaching effects in adulthood.

One of the main contexts in which children function and in which compromised cognitive functioning may have a direct immediate effect on the child as well as long lasting consequences, is the school environment. Upton and Eiser (2006) studied school experiences in a heterogeneous sample of 40 children aged between six and 16 who had

been diagnosed with a brain tumour between the ages of three months to 13 years. The follow-up interval from end of treatment varied between two years to 12 years five months. They used parent and teacher ratings of the SDQ as well as semi-structured interviews. Seventy eight per cent of the children had special educational needs. School absence ranged from two weeks to two years. Forty three per cent of mothers reported social isolation in their children. The mothers also reported significantly more SDQ Total difficulties than norms as well as more emotional symptoms, hyperactivity and inattention, peer relationships problems, and poorer pro-social behaviour. Teachers reported more Total difficulties, emotional symptoms, and peer relationship problems. However, teacher ratings were lower than parent ratings indicating that they viewed the problems as being less serious than the parents did.

Barrera, Schulte, and Spiegler (2008) studied depression in 54 children with various types of brain tumours aged between eight and 18 years. On the whole they found that the children did not report more symptoms of depression than norms and did not have more difficulties with social skills or have lower self-worth. However, they did find relationships between depressive symptoms, self-worth, social skills and intelligence. For example, females had higher depression scores than males and children with low self-worth had higher depression scores than those with high self-worth. They also found gender differences. Males with greater self-worth had less depression than males with low self-worth but if social skills were high, self-worth made no difference. Females with average self-worth had average depression if their social skills were high. If their social skills were low the females showed depression at a clinical level. There are some limitations to this study including its cross-sectional design and inability to clearly demonstrate the direction of effect. Also the comparison with normative data is less convincing than would be comparison with a control group. Nevertheless, this research highlighted the importance of measuring social skills in survivors of childhood brain tumours.

Fuemmeler et al. (2002) reviewed 31 studies of behavioural, emotional and social adjustment difficulties in survivors of childhood brain tumours. They found that overall rates of distress and maladjustment varied between 25% and 93%. One of the methodological limitations of these studies was the use of the CBCL to measure behaviour. This tool was developed to detect psychopathology (i.e. significant emotional and behavioural disorders) in healthy children and has strong reliability and validity for this

use. However, it has been highly criticised by Perrin, Stein, and Drotar (1991) who argued that there are three key problems with using this as a measure of behaviour in children with health problems. Firstly, some of the items directly relate to physical difficulties (e.g. 'child has asthma', 'stomach-aches', 'constipated' and 'wets self') which may serve to artificially inflate scores in children with health problems compared to their healthy peers thereby spuriously indicating that they have more difficulties. Secondly, this measure may not be sensitive enough to detect less intense difficulties than it was designed to detect, which may nevertheless be of concern to a child with a health problem and their family. Thirdly, the CBCL provides a score for social competence as well as emotional and behavioural difficulties. However, this score is misleading because it focuses on a child's participation in activities and accomplishments but a child with a health problem may not be able to participate in activities due to hospital visits or simply because he or she is not physically able, but this does not mean that he or she is less socially competent. For these reasons the CBCL is not really an appropriate measure to use with children who have been treated for cancer, including brain tumours.

Outcome in eleven children treated for brain tumours in a single institution in the first year of life between 1980 and 2005 was studied by Gerber et al. (2008). The impact of treatment and neurological, endocrine and cognitive complications on emotional and behavioural functioning and QoL was assessed. They found that nine patients had persistent neurological problems, four had endocrine and growth problems, and cognitive difficulties led to significant school problems in eight (out of ten) of them. Behavioural and psychological problems were reported by four (out of six) patients and seven (out of ten) of their parents. QoL, using the PedsQL was rated considerably lower than controls in both children and their parents, and the QoL dimensions most affected were psychosocial health, social functioning, and school functioning. They concluded that long-term survivors of brain tumours diagnosed in the first year of life were at considerable risk of neurological and cognitive complications and also social isolation thereby decreasing their QoL. However, the findings of this study are limited by its small sample size, and heterogeneity relating to tumour type, location and treatment. Nevertheless it did highlight the variety of problems that these children have to endure which impact on their QoL.

Cardarelli et al. (2006) using the HUI studied health status and HRQoL in 50 survivors of brain tumours aged between eight and 30 years old compared with 74 survivors of extra-cerebral solid tumours and 89 leukaemia survivors. They found that the mean HUI global

utility scores for self- and proxy-report were 0.87 and 0.84 respectively compared with 0.94 and 0.91 in the solid tumour survivors and 0.96 and 0.92 in the leukaemia survivors. They found no significant differences between self- and proxy-reports in any of the groups. The attributes most affected were emotion, pain, sensation and cognition as reported by both self- and proxy-assessment. They concluded that the HUI questionnaire was a user-friendly tool to assess health status and HRQoL in survivors of brain tumours. Limitations of this study included the heterogeneous sample of brain tumour patients and the wide age range.

The studies reviewed so far have all been cross-sectional. Just four studies, now to be summarised below, have considered HRQoL longitudinally in children specifically treated for brain tumours. In a multicentre study 102 survivors of craniopharyngioma, aged four to 40 years, were assessed 4.5 years following diagnosis and again 3.4 years later. They found that hypothalamic involvement, tumour relapse, and tumour progression were associated with poor HRQoL which improved over time but only in patients without hypothalamic involvement (Muller et al., 2005). These findings relate solely to tumour and treatment related information which is important but on its own cannot provide directions for improving QoL. It is important to try to reduce tumour and treatment related confounds in order to focus on other more useful indices of QoL and in children of a similar age. This is not possible to achieve in samples where age ranges include both children and adults, as in Muller et al.'s study, because the QoL in both groups is qualitatively different, as mentioned above (Mares & Neusar, 2010; Matza et al., 2004).

In another multicentre study by Sands et al. (2011) 25 survivors of various brain tumours, aged four to 13 years, were assessed 5.7 years and then 11.6 years post diagnosis. They found that HRQoL and social, emotional and behavioural functioning at both time points were within the normal range with no change over time apart from general health which decreased significantly. It is possible that children experience worsening health status over a longer period of time as evidenced by the findings of Boman et al. (2009) and Korinthenberg et al. (2011) but Sands et al.'s results showing that the other outcomes were in the normal range are surprising. Particularly in view of the fact that they used parent-report QoL only and evidence suggests that parents report poorer QoL in children with cancer than do their children (De Bolle et al., 2008; Levi & Drotar, 1999; Russell et al., 2006). As mentioned above, as children grow older and spend more time outside the home parents may lack knowledge or insight into less observable functioning (e.g. emotional and

social) and therefore it is important to obtain self-report where possible (Jokovic et al., 2004).

In a single centre study (Kuhlthau et al., 2012) 43 children with various brain tumours, treated with proton beam therapy, aged two to 18 years, were assessed at the start of treatment and annually up to three years later. They found that HRQoL scores improved over time and were significantly associated with IQ, behavioural functioning, tumour type and treatment. Mean parent-reported PedsQL Total scores improved from 67.0 within the first two weeks of treatment to 76.5 three years after treatment. At the start of treatment, scores in their medulloblastoma group were lower (57.8) compared with the low grade glioma group (71.5). This may be partly due to the one month time frame in which parents respond to items on the PedsQL which in their sample included time before treatment began when some of the children may have still been relatively well.

In another single centre study (Penn et al., 2008; Penn et al., 2009; Penn et al., 2010) 26 survivors, aged two to 17 years, of various brain tumours (17 with low grade astrocytoma) were assessed one, six and 12 months post diagnosis. They found that HRQoL improved over time compared with their best friend's, whose QoL did not change. This finding is hardly surprising given the short follow-up period in which the children will have still been recovering and gradually getting back to school. Tumour location, HRQoL, and selective attention predicted subsequent HRQoL in the tumour group. In both these single centre studies, the sample sizes per type and location of tumour were small.

A major problem with the studies reviewed above is that brain tumours are relatively uncommon and so in order to achieve a good sample size all tumours are often included. It is difficult to make sense of these findings when tumours differ in type, location and treatment especially given the evidence that QoL scores have been found to differ significantly with regards to tumour type, location, and treatment (e.g. Bhat et al., 2005; Boman et al., 2009; Calaminus, Weinspach, Teske, & Gobel, 2000). To overcome these problems some studies have focused on specific tumour types, the most common, as already mentioned, being medulloblastoma and low grade cerebellar astrocytoma which both arise in the cerebellum. The next section will review research into the outcome of children treated for these two types of tumour.

### 1.13. QoL AFTER MEDULLOBLASTOMA AND LOW GRADE CEREBELLAR ASTROCYTOMA

The cerebellum had long been recognised as being involved in the co-ordination of muscle movement. Then, in 1986 Leiner, Leiner, and Dow (1986) first proposed that the cerebellum may also contribute to 'mental skills'. This hypothesis was generated from their observations of neuroanatomical, neurophysiological, and clinical evidence. They postulated that the huge increase in size of the cerebellum during human evolution arose from an increase in neurons and also neuronal loops between the cerebellum and the cerebral cortex via the dentate nucleus and the thalamus (Figure 1). This led to the considerable evolutionary advantage for humans of being able to manipulate ideas and process information rapidly and then quickly act appropriately. They pointed out that the slow maturation of the cerebellum over the first 15 to 20 years of life is a sequential one in which cerebellar connections are initially made with the sensorimotor cortex and then eventually with the association cortex. This neuroanatomical development correlates with and explains the development of children that Jean Piaget observed where babies first learn to manipulate objects and then much later during adolescence learn to manipulate symbolic concepts.

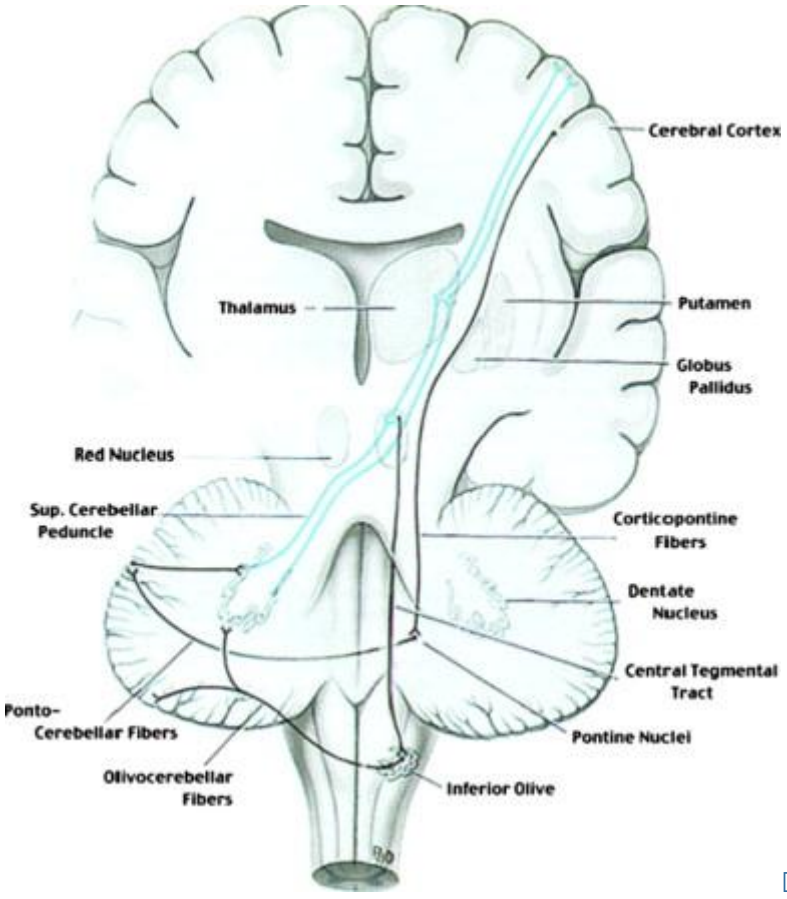


Figure 1. Diagram showing the cortico-cerebellar-thalamic-cortical circuit (Andreasen & Pierson, 2008)

However, it was not until 1998 when Schmahmann and Sherman first described cognitive and behavioural symptoms relating to lesions in the cerebellum in adults that the

cerebellum began to be more widely recognised as also having an essential role not only for movement and balance, but also for working memory, executive function, visual-spatial function, linguistic processing, attention, emotion and mood. Schmahmann and Sherman found that these patients experienced (i) impairments of executive functioning, (ii) visual-spatial deficits, (iii) personality changes characterised by blunted affect and disinhibited and inappropriate behaviour, and (iv) difficulties with language production. They coined the phrase, 'the cerebellar cognitive affective syndrome' to describe these symptoms. The overall effect of this syndrome was to lower intellectual functioning.

In 2000, Levisohn, Cronin-Golomb, and Schmahmann published the first systematic study of 19 children who had had a cerebellar tumour resected (medulloblastoma n=11, astrocytoma n=7, ependymoma n=1) but who had received neither cranial radiotherapy nor methotrexate with the aim of discovering whether the cognitive affective syndrome observed in adults was also evident in children. They found evidence for impairments in executive and visual-spatial functioning, as well as expressive language and verbal memory deficits, and impairments in modulation of affect. They found that behavioural problems were more apparent in older than in younger children as were neuropsychological deficits, although they were quick to point out that these age effects were confounded by tumour type as 75% of the younger children were not those diagnosed with a medulloblastoma. This study was limited by the small sample size and eight of the patients had received chemotherapy (other than methotrexate) that may have affected outcome, as was mentioned earlier in this review. It did, however, provide an initial description of the cognitive affective syndrome in children.

The symptoms of both medulloblastoma and LGCA at presentation reflect the underlying function of the cerebellum, as described above, and therefore are similar and may include physical symptoms such as uncoordinated muscle movements which may cause the child to sway and stagger whilst walking, speech and eye movement impairment, nausea and vomiting, and headaches (Wilne et al., 2012; Wilne, Ferris, Nathwani, & Kennedy, 2006). In addition to these physical symptoms, cognitive, emotional, and behavioural problems may also be present.

The initial treatment for both of these types of tumours involves surgical resection. Those children diagnosed with a malignant standard risk medulloblastoma (SRM) currently typically also receive daily radiotherapy for six weeks and also eight cycles of

chemotherapy according to the Packer regime (Packer et al., 1999). All this treatment lasts about a year before the child can begin to recover. The demands of the treatment for a medulloblastoma are huge and protracted in comparison to the LGCA which is surgically removed and normally requires no further treatment.

As mentioned in the previous section, many studies have focused on cognitive impairments in children treated for a variety of brain tumours within the same study. When studied separately, decline in cognitive functioning has frequently been observed in children treated for medulloblastoma, also largely attributed to cranial radiotherapy (George et al., 2003; Grill et al., 1999; Kieffer-Renaux et al., 2000; Mulhern et al., 1998; Palmer et al., 2001; Saury & Emanuelson, 2011).

Cognitive impairments have also been observed in non-irradiated patients. Cantelmi et al. (2008), in their review of anatomical, clinical and neuroimaging studies, reported that non-irradiated patients with tumours in the posterior fossa exhibited similar cognitive impairments to those who had received cranial irradiation, indicating that radiotherapy alone cannot account for the effects on cognitive functioning.
Beebe et al. (2005) in their study of 103 children aged three to 18 who had received surgery alone for low grade cerebellar astrocytomas reported that these non-irradiated children were found to have substantial cognitive and adaptive impairments on average nine months after surgery that were not associated with medical complications nor tumour location within the cerebellum, and of course they had not received radiotherapy. Their findings called into question the widely held belief that children treated surgically for low-grade cerebellar astrocytomas are at little or no risk of long-term deficits, which means that these children typically are not referred for psychological or neuropsychological follow-up. One of the strengths of this study is the homogeneity of the sample in terms of tumour type and treatment but the age range was wide and there was no concurrent clinical or healthy group for comparison (only published normative data), also the assessments were conducted early on with no follow-up and therefore there was no indication if there had been recovery of function over time.

Steinlin et al. (2003) conducted a follow-up study of 24 patients aged between 7.6 and 26.7 years at follow-up and diagnosed between 3.6 and 15.5 years with a benign cerebellar tumour which was treated with surgery alone. Time since diagnosis ranged between 2.1 and 18.3 years. The main aims were to determine the patterns of neuropsychological

functioning and the relationship between this and age at diagnosis. They found that overall the sample had normal intelligence with a mean IQ of 99.1 but more extensive neuropsychological testing revealed significant problems in attention, memory, processing speed, interference and visuo-constructive problems, and executive function. They also found behavioural difficulties in 33% of the patients. Age at diagnosis and size of tumour had no influence on outcome. This study, similarly to Beebe et al.'s, confirmed the importance of the cerebellum for cognitive development and similarly a strength of the study was the homogeneity of the sample in terms of tumour type and treatment, but the age range was wide and included both children and adults, the time interval since diagnosis was wide, and there was no comparison group.

Riva and Giorgi (2000) described the effect that lesions of the cerebellar had on higher cognitive functions and behaviour in their study of 26 children surgically treated for posterior fossa tumours. Fifteen of the children, aged between seven and 12.6 years, had undergone surgery for cerebellar astrocytoma, and eleven, aged between six and 12.1 years, for medulloblastoma. They found that children with tumours in the right hand side of the cerebellum had auditory sequential memory and language processing difficulties, whereas those children with tumours in the left part of the cerebellum showed deficits in spatial and visual sequential memory. In addition, lesions of the vermis led to either post-surgical mutism with speech and language problems similar to agrammatism, or behavioural difficulties which ranged from irritability to autistic like behaviours. They concluded that the cerebellum modulates cognitive and social functions in children which supported Schmahmann's (1991) proposal that the cerebellum contributes to higher functions. Similar to Steinlin and also Beebe, a major strength of this study was the homogeneity of the sample in terms of tumour location and also type. In addition, the age range of the children was small and similar in each tumour group, and all the evaluations were conducted between five and six weeks in the post-operative period. The sample was small but the results provided evidence for the importance of the cerebellum for cognition and behaviour.

There has been a paucity of studies specifically focusing on QoL in these patients but one of the earliest attempts was presented by Bloom, Wallace, and Henk (1969). They described children below the age of 15 who had been diagnosed with a medulloblastoma between 1950 and 1964 at the Royal Marsden Hospital in the UK. At this time such a diagnosis incurred a high mortality rate but they reported a five year survival rate of 32%

in their sample of 68. They classified survivors according to four categories: I) no disability, active life; II) mild disability, active life; III) partial disability; and IV) total disability – and reported 82% as having no serious disability and leading active lives five years post diagnosis.

Nearly 20 years later, when the five year survival expectancy for medulloblastoma was 50% Packer et al. (1987) conducted a cross-sectional study of QoL with patients diagnosed between 1975 and 1984. Similar to Bloom et al., they found that 19 of the 24 patients they studied (79%) were functioning well in every-day activities, the median full scale IQ was 97, with all, apart from three (12%), functioning within the normal range. However, specific learning, memory, and fine motor disabilities were present in over half of the patients. The factors associated with poorer performance and lower IQ were reduced alertness preoperatively, the need for a permanent shunt, younger age at diagnosis, and post-operative complications. They concluded that the majority of long term survivors had normal cognitive functioning, but that specific intellectual/academic disabilities and preoperative/postoperative factors had strongly impacted on the QoL of some survivors. There were many limitations to this second attempt at studying QoL in this relatively homogenous sample. There were just two main measures of QoL, IQ (n = 17) and a performance score (n = 24) which was given at a neuro-oncology clinic. It is difficult to draw any conclusions from such a small sample. No attempt was made to seek the patients' subjective views of their QoL but at that time there were no measures available to assess this in children.

LeBaron, Zeltzer, Scott, and Marlin (1988) studied quality of survival in 15 children aged seven to 18 years who had been diagnosed 20 months (range four to 104) previously with either medulloblastoma (n=9), astrocytoma (n=5), or ependymoma (n=1) and who had all received radiotherapy, apart from four of the children with astrocytoma. Using a battery of neuropsychological tests, information from school records and parent report of the CBCL they found that 50% of the children were experiencing serious motor, sensory, academic, cognitive and emotional problems whether they had been irradiated or not. Thirteen of the children were reported to be 'slow workers' by their teachers, and only four of the 15 were able to take part in normal lessons. Doctors rated 80% of the children to have good or excellent functional status according to Bloom's (1969) four categories of disability, three of whom had received no radiotherapy. There was no relationship between patient

outcomes and doctor ratings of functional status which showed that some deficits may not necessarily be evident to trained professionals without proper evaluation.

Bhat et al. (2005) studied QoL using the PedsQL in 134 children at a mean age of 12 years who had been treated four years previously for a variety of brain tumours including 32 with medulloblastoma and 55 with low grade glioma. Compared with a sample of 717 healthy children, they found significant differences in overall QoL and in all subscales in the overall sample of tumour survivors. In the group of children with medulloblastoma, parent-report PedsQL Total mean scores were 65.1 and parents of children with low grade glioma reported higher PedsQL Total mean scores (75.4) and better physical and emotional functioning than in children with other types of tumour. They also divided their whole sample into those treated with surgery alone and those treated with radiotherapy and chemotherapy +/- surgery. Parent-report PedsQL Total mean (sd) scores in the surgery only group (n=36) were 75.2 (19.9) and in the radiotherapy plus chemotherapy group (n=45) 70.3 (17.6). Thus, they reported that tumour type and treatment led to differences in QoL. However within each of these divisions treatment modality and tumour type were not tightly controlled and varied, possibly confounding the results. Tumour location, sex, age and time from diagnosis were not associated with overall QoL. Although the findings were not clear, the study did show that tumour pathology and treatment may affect QoL.

Ribi et al. (2005) studied QoL in 18 long-term survivors (age range 8.5 to 31.9 years) of childhood medulloblastoma diagnosed (age range 1.1 to 14.7 years) over a 20 year period in one institution. They had been treated with radiotherapy and/or chemotherapy. The follow-up time ranged between three to 24 years. They assessed the impact of treatment, neurological, endocrine, and cognitive complications on behavioural (CBCL) and psychological adjustment, and QoL (PedsQL), using qualitative and quantitative measures. Seventy two per cent had suffered significant school problems and all had significant deficits in cognitive functioning including executive functioning. Behavioural and emotional problems were reported by parents in 42% of the survivors. In terms of QoL, the authors did not report the PedsQL Total score but reported that according to self-report, the dimension most affected in comparison with norms was social functioning. Parent ratings were significantly lower than those of their children and Ribi et al. postulated that an optimistic bias in self-report ratings of QoL might fulfil a protective function. They found no significant relationships between clinical factors and QoL.

Bull et al. (2007) studied QoL in 108 patients (age range 6.6 to 24.3 years) treated for medulloblastoma diagnosed (age range 2.8 to 14.9 years) over an eight year period with either craniospinal irradiation alone (CSI) or CSI plus chemotherapy (CSI+CT). We found that Health status (HUI) was poorer in those treated for CSI+CT and they needed greater therapeutic and educational support. There were also trends to poorer behavioural and emotional functioning and QoL. We concluded that there was a significant difference between the two treatment regimens in the impact that they had had on the QoL of survivors.

Not all studies of QoL in children treated for medulloblastoma have shown compromised QoL. Maddrey et al. (2005) studied cognition, psychosocial functioning and QoL in 16 ten-year survivors of childhood medulloblastoma aged between 13.6 and 27.9 years, diagnosed between the ages of one and 15 years of age. All had received CSI but just nine had received CT in addition. The mean IQ for all participating survivors was 75 with a range of between 54 and 110 and 50% of them had significant impairments in cognitive functioning including executive functioning which was related to age at diagnosis, post-operative complications, and time since diagnosis. Psychosocial functioning such as employment, the ability to drive and participation in normal education was also compromised. However, they found that both self- and proxy-report QoL scores were in the normal range. Maddrey et al. postulated that the lack of reduction in QoL may be due to lack of self-awareness of deficits due to insult to the brain but caregivers in their study also reported QoL to be similar to that of norms so this is probably not a feasible explanation. It is also possible that the survivors and their care givers had adapted to the deficits, but if this is the case then this was not observed in Ribi et al.'s (2005) sample.

Pompili et al. (2002) studied QoL in 20 adult survivors (age range 18 to 40 years) who had received surgery for cerebellar astrocytoma in childhood (age range two to 16 years) between 15 and 30 years previously compared with a control group of healthy volunteers. Using a non-standardized QoL questionnaire that included the dimensions: energy, leisure, cognition, socializing, work, symptoms, sex life, depression, well-being, memory, family and adolescence, compared with controls, the cerebellar astrocytoma group reported a significantly poorer QoL and for all dimensions excepting sex life, with adolescence and socializing being the most striking. They found no relationship between QoL and age at surgery. As well as the QoL questionnaire, they used some basic questionnaires regarding functioning in every day life. They found that 95% were able to use public transport and to

execute postal and banking transactions, all had completed their education, one with help, and four at university level, 65% had a driving licence, 35% had their own family and 25% had children, and 58% of the over 25's were working. Unfortunately Pompili et al. provided none of these every day life data for the controls but conceded that the survivors had a normal life compared with perceptions of their own QoL. The study highlighted the importance of measuring self-reported QoL rather than relying on simple objective indices of functioning, and also the importance of including a comparison group to obtain a full picture of potential difficulties. They also showed how difficulties in this population could easily go unnoticed by health professionals if a proper appraisal of QoL is not undertaken. In addition, their study refutes the notion of response shift (Fayers & Hays, 2005) whereby people adapt to their circumstances and show improved ratings on QoL scales over time.

Similarly, Daszkiewicz, Maryniak, Roszkowski, and Barszcz (2009) developed their own questionnaire to gather data on long-term psychosocial functioning from 104 survivors (age range not reported) who had received surgery between 1980 and 2005 for low grade cerebellar astrocytoma between the ages of one and 25 years, three to 22 years previously. They found that 58% had various types of neurological deficits particularly disequilibrium and more than 50% had significant emotional and behavioural problems particularly irritability. Ninety eight per cent of parents rated their child's outcome as 'good' or 'very good' compared to 87% of the patients themselves. Most of the children were following the normal academic curriculum at school and most of the adults were either employed or at university, some were able to drive, and a few had established families of their own. Thus, there was no evidence for cognitive dysfunction and in contrast to Pompili et al. (2002), the effects of the disease and treatment did not appear to have long term consequences for their QoL and day to day functioning even in the face of permanent neurological deficits. However, the rating of outcome was in response to just one global question on their custom-designed questionnaire with just seven items. These high positive response ratings may have been due to feelings of gratitude to the treatment received in relation to simply being alive but it is difficult to know what prompted this positive response. Their study suggests, however, that QoL cannot be measured in such a simplistic fashion and that different dimensions must be taken into consideration (Gotay et al., 1992).

Aarsen et al. (2006) studied functional outcome and QoL, using a standardized questionnaire developed in the Netherlands, four to eleven years post diagnosis in 38

children treated for low grade astrocytoma in different areas of the brain at one to 15 years old. In their sample, treatments varied and they also included children who had had a recurrence of the tumour. They found that 61% had impairments and 10% severe disability. They found differences in outcome between those treated for supratentorial tumours, who had received more educational support, and those whose tumours were infratentorial, who had more behavioural and social problems. They also found a reduction in QoL in all domains except for emotions, and those diagnosed during adolescence had poorer social functioning than those diagnosed prior to adolescence. Cognitive, social and behavioural deficits did not become apparent in some cases until years after diagnosis due to the phenomenon of 'growing into deficits'(Aarsen et al., 2006). By both child- and parent-report, motor, cognitive, and social problems were poorer than published norms. QoL did not differ between tumour location (infratentorial vs supratentorial) but those children who had experienced recurrence of their tumour had a poorer QoL than those who had not.

Zuzak et al. (2008) studied long-term outcome in 21 survivors, aged eight to 41 years, treated with surgery alone for LGCA six to 27 years previously between the ages of two and 14 years. They found neurological problems in 43% of the survivors but the ability to perform daily activities was normal. They found cognitive deficits leading to significant school problems in 19% of the survivors and 27% experienced behavioural and emotional difficulties. However, using the PedsQL for adults and children alike, HRQoL including physical functioning was reported by survivors to be similar to or even higher than published norms.

Musial-Bright, Panteli, and Driever (2011) reported similar findings to those of Zuzak et al. (2008) in their study of 49 survivors of low grade glioma, aged between four and 17 years who had been diagnosed between the ages of one and 16 years old and followed up between four months and 14 years later. Using the KINDL questionnaire that was designed for German speaking children, children rated their QoL to be higher than published norms but there was a significant difference between child- and parent-report and parents rated their children's emotional well-being to be lower than norms. Girls rated their QoL to be lower than did the boys. Older age at diagnosis was associated with better physical and emotional functioning. In this study, the tumours were heterogeneous in terms of type, location and treatment, and five of the patients had progressive disease. Due to the small sample sizes, the authors were unable to perform sub-groups analyses.

However, those with supratentorial tumours had higher disability scores than those with infratentorial tumours but extent of disability was not associated with reduced QoL.

Few studies have compared outcome in those children diagnosed with a medulloblastoma with those diagnosed with a cerebellar astrocytoma. One of the earliest was conducted by Hirsch, Renier, Czernichow, Benveniste, and Pierrekahn (1979). They described outcome in 57 children diagnosed with medulloblastoma compared with 31 children having received surgery alone for LGCA between 1964 and 1976 and found significant deficits in QoL in these children. They used Bloom et al.'s (1969) classification system (mentioned above) to describe QoL in these children and found that 73% of children in the medulloblastoma group had led an active life in comparison to Bloom et al.'s 82% (there were no figures for the cerebellar astrocytoma group). However, psychological tests revealed a more detailed picture of deficit with 58% of the children having an IQ score of between 70 and 90, compared with 19% in the astrocytoma group. Thirty one per cent had an IQ of less than 70, compared with 19% in the astrocytoma group. In addition behavioural problems were found in 93% of the medulloblastoma children compared with 59% in the astrocytoma group, compared with 30% in the normal population at that time. Also, 82% compared with 37% in the astrocytoma group, had deficits in spatial orientation, dysphasia or dysgraphia. They stressed that in their sample every child in the medulloblastoma group had either behavioural problems and/or specific difficulties. They also reported that only 25% of children in the medulloblastoma group had experienced normal schooling compared with 73% in the astrocytoma group and 80% in the general population at that time.

Ronning, Sundet, Due-Tonnessen, Lundar, and Helseth (2005) studied cognitive functioning in 12 young adults who had received surgery for LGCA as children and eleven who had received treatment for medulloblastoma 12 to 21 years earlier at an age range of 1.8 to 14.9 years. They found that the medulloblastoma group had poorer neurological and neuropsychological functioning than the LGCA group and that both groups performed below standard norms with the LGCA group performing particularly poorly on measures of motor speed, attention, and executive functioning compared to norms. In the LGCA group there was a non-significant tendency for those children who were diagnosed at a younger age to have a higher IQ whereas in the medulloblastoma group younger age at diagnosis was associated with a poorer outcome (see also Ellenberg et al., 2009). This study provided evidence that cerebellar damage led to persistent cognitive dysfunction in

the absence of adjuvant therapies and that the additional treatment in the medulloblastoma group led to greater deficits years after treatment. Although this study compared two homogenous groups in terms of tumour type, the numbers were small and the group was heterogeneous in terms of age at and time since diagnosis. Also, the participants had all been treated in one centre over a ten year period and neuropsychological outcome was compared with normative data rather than a concurrent comparison group. Nevertheless, this study did show the presence of neuropsychological deficits in the LGCA group which had a different pattern from those in the medulloblastoma group. They ascribed the benefit of younger age at surgery in the LGCA group to neuronal plasticity in the immature brain and mechanical trauma that may gradually improve over time compared to the deleterious effects of radiotherapy in addition to mechanical trauma seen in the medulloblastoma group.

Benesch et al. (2009) studied late effects in 17 patients who had been treated between 1990 and 2005 with various treatments for medulloblastoma and six for ependymoma compared with eight who had been treated with surgery alone for LGCA. All the patients varied in age at assessment between nine and 49 years and had finished treatment between one and 207 months previously. They compiled a late effects severity score from variables relating to neurology, endocrine, auditory/visual, and other physical problems. They reported more physical problems in the medulloblastoma and ependymoma groups than in the cerebellar astrocytoma group and a lower IQ (mean score 86.09 vs 101.5), reporting a decline in IQ in time from end of treatment in the malignant tumour group. QoL was similar in the two groups and they found no relationship between neurocognitive functioning and QoL, but they did find that younger patients with more physical problems had a poorer QoL. They concluded that QoL was probably less compromised in patients treated for malignant cerebellar tumours than was neurocognitive functioning. The findings of this study were limited, however, by group heterogeneity and small sample sizes making reliable group comparisons difficult to achieve.

Roncadin et al. (2008) documented the incidence of medical events in 29 survivors of childhood medulloblastomas treated between 1965 and 1991 with various doses of radiotherapy, and chemotherapy in seven cases. The 29 survivors of cerebellar astrocytomas had received surgery alone. Their medical notes were reviewed for medical events at four different time periods (diagnosis, perioperative, short-term, and long-term survival) to investigate whether medical events would predict neuro-behavioural outcome

(IQ, memory, functional independence, and HRQoL). They reported that the two groups of children presented similarly at diagnosis and experienced similar perioperative events. They found that medical and behavioural outcome was significantly poorer in the medulloblastoma group and that poorer long term outcome in the astrocytoma group was associated with more adverse events in the peri-operative and short term survival periods. One of the main strengths of this study was that they were able to condense many medical variables associated with the presence and treatment of these tumours to an overall estimate of medical adversity and to document the long term effect on behavioural functioning. However, there were limitations to the study. Their study was retrospective and included participants who had been diagnosed over a 26 year period and had survived event free. The medical events were categorised into very broad time frames. For example, the short term survival period spanned the five years after the initial hospital stay which included the time period when the medulloblastoma patients were still receiving treatment and some children in both groups were still recovering from events that had occurred in the peri-operative period, for example, posterior fossa syndrome. This is a condition that occurs within days after surgery to the cerebellum and includes symptoms such as mutism or speech disturbances, difficulties swallowing, decreased motor movement, facial palsies, and emotional lability that may take months to resolve and the child may never fully recover (Kirk, Howard, & Scott, 1995). Also, the long term survival period (beyond the first five years after the initial hospitalisation period) ranged widely between five and 31 years. In addition, age at diagnosis was very variable (range one to 16 years), as was age at testing (eight to 36 years).

There are currently no published studies that have looked at QoL in these children over time.

### 1.14. THE PRESENT INVESTIGATION

As this literature review has shown, many studies have focused specifically on cognitive functioning, particularly IQ as a measure of outcome in children treated for brain tumours, especially those treated for cerebellar tumours. Although important, this focus on outcome may well be too narrow, especially in the light of evidence supporting the cognitive affective syndrome which has shown that children with cerebellar tumours suffer not only motor and sensory, and cognitive deficits, but also difficulties with emotional, social and behavioural functioning, as well as dysexecutive functioning. Such ignoring of the wider picture, including subjective perceptions of QoL, only partially tells the story of life after

treatment and may fail to identify potentially important deficits. For example, Aarsen et al. (2009) found specific deficits in selective attention and executive function in children treated for pilocytic astrocytomas with surgery alone who had normal IQ (mean=99, SD=16). More sophisticated, in-depth assessments may shed light on apparent discrepancies such as this.

The majority of reports are cross-sectional studies which cannot assess the developmental trajectory of outcome (Msall, 2010). As mentioned above, a cross-sectional design only reflects what is happening at a given moment in time, while a longitudinal design allows the measurement and description of patterns of change but it is not without its problems. Attempts to track QoL, or other outcomes, over time have been limited, for example, by high rates of attrition of participants (Armstrong et al., 2009; Bekkering et al., 2012; Kuhlthau et al., 2012; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001). This attrition leads to problems for data analysis, due to missing data, and there are more opportunities for this to occur over time. It is also important to keep the measures of variables the same from one period to the next otherwise inference can be difficult. This may be problematic especially when a wide age range in participants is included, necessitating the need for different age appropriate questionnaires as individuals make the transition from childhood to adulthood. Samples that include both children and adults are qualitatively different because their QoL is different (Mares & Neusar, 2010; Matza et al., 2004). This limits complete case analyses and reduces the numbers for statistical analyses due to the need to divide the sample into different age groups dictated by the age-appropriateness of the measures used. In spite of these difficulties a longitudinal design provides much stronger evidence for the direction and magnitude of causal relationships between variables (Menard, 2002).

Baltes and Nesselroade (1979), cited in Menard (2002), listed five reasons for conducting longitudinal research: It is possible to directly identify (i) whether individuals change from one period to another; (i) whether individuals change in the same or different ways; (iii) whether certain changes are correlated with each other; (iv) why individuals change from one period to another; and (v) why different individuals change in different ways from one period to another. All these reasons are concerned with patterns of developmental change which are particularly pertinent to the study of children.

Because childhood cancer and in particular brain tumours are relatively rare, for practical reasons many outcome studies of childhood brain tumours have small samples, are broad in focus and heterogeneous with respect to age (and therefore outcome measures), tumour location and type (and therefore treatment), and/or interval from diagnosis (Tao & Parsons, 2005). As shown above, all these factors have been found to affect outcome in survivors and so to combine children in a way that ignores such variability provides little understanding about the extent and breadth of deficit in particular groups of children. In addition, cohorts, ages, and time periods are all aggregates of individuals' characteristics embedded in a social and temporal context and if these categories are wide they may actually serve as proxies for many unmeasured variables, such as improvements in diagnostic, surgical and treatment techniques, attitudes towards illness and treatment, availability and use of rehabilitation techniques, or the sharing of information with the child, all of which may have a bearing on the child's QoL. Thus, there is potentially a huge methodological problem of confounding in heterogeneous samples. It is therefore important to try to keep samples as homogenous as possible to try to minimise unwanted effects.

As discussed in section 1.7, children and parents do not necessarily share the same point of view and parents of children with cancer tend to underestimate their child's QoL. However, a lack of acknowledgement of difficulties on questionnaires completed by children may not reflect a true picture of their psychological well-being but rather reflect denial, a lack of insight, or an unwillingness to acknowledge difficulties (Carpentieri et al., 2003). It is therefore essential that multi-informants are used to gather information about QoL in children, not only to provide, possibly different, but complementary views about the child's QoL, but also to take account of the multiple social contexts in which the child functions (Cox & Paley, 1997) as each one is likely to impact on the child's QoL.

One of the most important of these contexts is the school environment. Some teachers have reported behavioural difficulties in children with brain tumours (Aarsen et al., 2006), while others have rated them as being similar to norms (Radcliffe, Bennett, Kazak, Foley, & Phillips, 1996). A high percentage of children with brain tumours require special education (Aarsen et al., 2009; Kuehni et al., 2012) due to learning problems (Carpentieri et al., 2003) and teachers may be a valuable source of information regarding difficulties at school (Callu et al., 2008).

Selection of appropriate comparison groups is another limitation since the readily available group of siblings or friends that are often used in research are not representative of children in the general population and may have been affected in some way by their sibling's/friend's diagnosis. Similarly, published norms are not ideal either, as a comparison because normative samples differ for each measure and some published norms may not be appropriate, especially when multiple measures or tests are completed in one sitting. Normative samples are not tailored either to meet specific requirements that may be important in measuring QoL such as the school environment or geographical region or location such as city versus rural. There could be cohort effects that are important too, such as socio-economic climate which may change from one period of time to another, causing higher overall levels of feelings of well-being, or norms of acceptable behaviour may change over time, for example, or children's ability to sustain concentration may change due to new teaching methods or changes in technology. Also, by administering questionnaires and tests in the same way to a comparison group means that order effects and reactions to questionnaires and tests can be controlled (Kendall & Sheldrick, 2000). For these reasons it is essential to have an appropriate comparison group.

The present study was designed to overcome these methodological limitations by drawing on a sufficiently large population of brain tumour survivors to select a sample that had all survived a tumour at a single site within the brain, and treated with either surgery alone or the same adjuvant therapy, had all been diagnosed within the previous three years, were all of sufficient age to provide reliable self-report but young enough to remain of school-age throughout the study and, by studying them in their home environment, to help to maintain high levels of participation over a 24 month period. In studying a homogeneous group of survivors, it is possible to eliminate the many confounders that have limited the findings from previous studies. The study now to be described also looked at multiple issues relating to QoL including those that could possibly be enhanced through interventions. It also drew upon three different perspectives, the child's, the parent's and the teacher's, and recruited an appropriate comparison group. The present study was unique in addressing all these methodological issues.

The common themes that have emerged from previous research, in spite of the methodological limitations described, are that children treated for brain tumours are at increased risk of disability, and psychosocial difficulties. In particular, those treated for cerebellar tumours may be at risk of specific difficulties relating to the role of the

cerebellum in cognition, emotion, and behaviour, as well as movement. In addition, there has been some suggestion that parental mental health may be a factor in relation to a child's QoL.

Thus, by addressing previous methodological limitations, and taking into consideration these common themes this study aimed to investigate:

- whether HRQoL in the first five years after tumour diagnosis differs between children treated for cerebellar tumours, who are old enough to report reliably on their HRQoL, and a comparable representative sample of children in the general population;
- whether there are differences between HRQoL in the children treated for SRM from those treated for LGCA associated with their differing treatments, but common for location in the cerebellum;

The study also aimed to investigate:

- whether QoL in these children changes over time and the factors that impact on QoL and whether these differ over time; and
- whether early predictors that might be amenable to alteration by interventions were predictive of subsequent HRQoL.

This is the first multi-centre study of longitudinal QoL data in children treated for the two most common types of brain tumour, medulloblastoma and cerebellar astrocytoma compared with a contemporaneous typically developing non-tumour comparison group.

# CHAPTER 2 METHODS

Based on the previous literature, and for the purposes of the research described in this thesis, QoL was defined as physical, emotional, behavioural, cognitive, and social functioning.

This longitudinal research project was a study of children with either one of the two most common childhood brain tumours, that both arise in the cerebellum, compared with a typically developing group of children (Comparison). The children with brain tumours had had a diagnosis of either SRM or LGCA. The treatment of both tumour types involves neurosurgery and those with an SRM receive craniospinal irradiation and chemotherapy in addition. The multi-modal, multi-informant assessments were conducted on three occasions at annual intervals.

## 2.1. HYPOTHESES

1. At the first assessment (T1) children with SRM will have a reduced QoL, poorer health status, more behavioural and emotional problems, and poorer cognitive functioning as reported by parents, teachers and the children themselves, than children with LGCA, and both these groups will have poorer scores on these measures than the Comparison group.
2. QoL, health status, and behavioural and emotional functioning will improve over time in the tumour groups as the children's health improves and they adapt to their situation but these factors will not change in the Comparison group. In the LGCA and Comparison groups, cognitive functioning will not change over time and in the SRM group it will decline.
3. In all groups parent ratings of their own mental health will predict their ratings of their child's QoL, and behavioural functioning, and in all groups parent mental health will predict children's ratings of their own QoL.
4. Health status, cognition, emotion, behaviour and peer relationships will predict the child's QoL by both child- and also parent-report.

## 2.2. DESIGN

A prospective multi-centre longitudinal cohort study design was used.

For each group and assuming a 65% recruitment rate, it was calculated that 57 families would need to be approached to reach an overall recruitment target of 37 children in the first year, totalling 111 children. Ten per cent loss of participants per annum was assumed that would provide a total of 100 and 90 children in the second and third years of the study respectively. This power calculation is based on the predicted sample of 90 children at the third follow-up assessment. With a sample size of three x 30 children, it was calculated that it would be possible to detect any existing difference in QoL between each of the three groups of 0.65 SD with an 80% power at $p<0.05$ using a one-directional t-test. There would be a similar power to detect differences between parent, child and teacher ratings within each of the groups of 30.

## 2.3. SAMPLE

The recruitment target, as mentioned above, was 37 children in each of three groups: SRM, LGCA, and Comparison plus all the children's main caregivers and teachers. Thus, total target sample = 111 children + 111 main caregivers + 111 teachers. The children with brain tumours were recruited from Children's Cancer and Leukaemia Group centres across England and Wales whose role was to provide families with information about the study and seek verbal consent to be approached by me for further information and possible enrolment in the study.

### 2.3.1. Inclusion and exclusion criteria

**Inclusion criteria for brain tumour groups**

- Standard risk medulloblastoma at diagnosis with no evidence of metastatic disease.

**OR**

- Low grade cerebellar astrocytoma treated with neurosurgery only.

**AND**

- Diagnosis no more than three years previously.
- Age range eight to 14 years inclusive at point of entry into the study.
- Written informed consent (and patient assent where appropriate).

**Exclusion criteria for brain tumour groups**

- Metastatic medulloblastoma at diagnosis.

- LGCA patients receiving chemotherapy.
- Patient previously treated for any type of malignant disease.
- Current progressive disease.
- Other significant medical condition or developmental disability prior to enrolment that may impact on QoL independently of having a brain tumour.
- Deemed unsuitable by treating clinician for reasons judged by him or her to be important, for example, other significant stressful life events such as a death in the family.
- Participants whose command of English would not be adequate enough to complete questionnaires written in English or to take part in interviews (not part of this thesis) conducted in English (assessed over the phone at first contact).

**Inclusion criteria for Comparison group**

- Age range eight to 14 years inclusive at point of entry into the study.
- Written informed consent (and patient assent where appropriate).
- In the same year group in the same schools as the children with tumours.

**Exclusion criteria for Comparison group**

- Child previously treated for any type of malignant disease.
- Significant medical condition or developmental disability that may impact on QoL.
- Deemed unsuitable by head teacher for reasons judged by him or her to be important, for example, other significant stressful life events such as a death in the family.
- Participants whose command of English would not be adequate enough to complete questionnaires written in English or to take part in interviews conducted in English (assessed over the phone at first contact).

All children referred to the study were suitable for inclusion.

## 2.4. MATERIALS AND METHODS

The following two questionnaires were completed by all children about themselves and by parents about their children.

### 2.4.1. Pediatric Quality of Life Inventory (PedsQL)

The PedsQL (Varni et al., 1999) is a self-administered multi-dimensional measure of HRQoL in healthy children and adolescents and those with acute and chronic health conditions (Varni, Limbers, & Burwinkle, 2007a) with a one month recall period. It is designed for use with children aged between two and 18 years, as reported by their parents and for children themselves aged between five and 18 years. New versions of the PedsQL are in constant development and include those for infants, young adults, and older adults as well as new translations (PedsQL.org). The PedsQL consists of 23 items, takes approximately five minutes to complete, and provides information about functioning in four dimensions: physical (eight items), emotional (five items), social (five items) and school (five items). Each item is scored on a five point response scale ranging from 0 = never a problem to 4 = almost always a problem. Physical items include, "It is hard for me to walk down the road a little bit"; emotional items include, "I feel afraid or scared"; social items include, "I have trouble getting on with other kids"; and school items include, "It is hard to pay attention in class". Items are reverse scored and linearly transformed to a 0 – 100 scale where higher scores indicate better HRQoL. Scale scores are computed as the sum of the items divided by the number of items answered but if more than 50% of the items are missing then the scale score is not computed. Summary scores for physical health (the same eight items as in the physical functioning scale) and psychosocial health (comprising the 15 items in the emotional, social and school functioning scales) can be calculated as well as a total summary score. At-risk status for impaired HRQoL for child self-report total scale score is considered to be 69.7, and 65.4 for parent proxy-report (Varni, Burwinkle, Seid, & Skarr, 2003).

Internal consistency reliability of >.70 has been reported for the majority of parent proxy-report sub scales across all age groups and >.90 for the total summary score (Varni et al., 2003; Varni, Limbers, & Burwinkle, 2007b). Construct validity using 'the known groups approach' was previously demonstrated by comparing healthy children with those with chronic health conditions and finding statistically significant differences between the two groups with most effect sizes being medium or large (Varni et al., 2007a). The PedsQL total scale score has also shown good internal consistency reliability being .88 for child self-report, .93 for parent proxy-report; and to have good construct validity in paediatric cancer (Varni et al., 2002). It is also responsive to clinical change over time (Banks et al., 2008). It has been used in studies of children with brain tumours (e.g. Bhat et al., 2005; Bull et al., 2007) and to compare healthy children with those with cancer, and between

those children on and off treatment (Varni et al., 2002). The above evidence including its applicability to ill as well as healthy populations, and its brevity, suggests that the PedsQL would be an ideal measure of HRQoL for the current study.

### 2.4.2. Health Utilities Index (HUI)

The HUI (Feeny et al., 1992) is a self-administered (but other formats are available) measure of health status and HRQoL in healthy children (Raat, Bonsel, Essink-Bot, Landgraf, & Gemke, 2002) and adults, and those with a wide variety of medical conditions (Horsman, Furlong, Feeny, & Torrance, 2003). There are four recall periods available, one-week, two-weeks, four-weeks, or 'usual' health. The one-week recall period was used for this study. It is designed for completion by parents of children aged from six years, and for children themselves aged from eight years (with the assistance of an adult) or from 12 years without assistance. It takes approximately ten minutes to complete. Self-assessment is considered to be the gold standard perspective for describing the health status of participants. This 16 item questionnaire, when formatted as 'HUI3', measures function in eight domains: vision, hearing, speech, ambulation, dexterity, cognition, emotion and pain, with five or six levels of functioning in each domain. Each question is followed by a choice of four to six possible responses. For example, question 16, 'Overall, how would you rate the subject's health during the past week?' is followed by a choice of a) excellent, b) very good, c) good, d) fair or e) poor. The scores on the domains can be combined to give an overall HRQoL score on an interval scale which ranges from 0.00, which is the equivalent of being dead to 1.00, which defines perfect health. It is possible to have a negative score which indicates a health state which is worse than dead. It does not allow for missing responses. A score between 0.70 and 0.88 is considered to represent moderate disability and a score less than 0.70 represents severe disability. A difference in overall HRQoL of 0.03 is considered to be clinically important (Fayers & Hays, 2005) .

The HUI has been shown to be acceptable, reliable, and valid in many childhood populations (Feeny et al., 1992; Feeny et al., 1993; Torrance, Furlong, Feeny, & Boyle, 1995) and it has also shown responsiveness to changes in health status over time (Barr, Petrie, Furlong, Rothney, & Feeny, 1997; Furlong, Feeny, Torrance, & Barr, 2001). It is sensitive to clinical problems (apart from behavioural problems) in children who have been treated for brain tumours (Barr et al., 1994; Billson & Walker, 1994; Bull et al., 2007; Glaser, Abdul Rashid, & Walker, 1997; Kanabar et al., 1995; Kennedy & Leyland, 1999). For these reasons it seems to be an ideal measure of health status for the current study.

### 2.4.3. Strengths and Difficulties Questionnaire (SDQ)

This questionnaire was completed by all children about themselves and by parents and teachers about the child. Developed by Goodman (1997) the SDQ is for parents and teachers of children aged between four and 16 years, and for children themselves aged from eleven to 17 years. The SDQ is a behavioural screening questionnaire suitable for healthy children (e.g. Hawes & Dadds, 2004) and those with chronic illness (e.g. Glazebrook, Hollis, Heussler, Goodman, & Coates, 2003) that takes about five minutes to complete and has a six month recall period. It asks about 25 attributes, some of which are positive and some negative. These 25 items are divided between five scales of five items each: emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationships (with scores ranging between zero and ten) and these items can be summated to generate a total difficulties score ranging between zero and 40. The fifth scale is a measure of pro-social behaviour and higher scores on this scale indicate better social functioning. Sample items include: "I get very angry and often lose my temper", "I fight a lot, I can make other people do what I want", "I am restless, I cannot stay still for long" and "I have one good friend or more". A higher score indicates more difficulties. Total difficulties scores ranging between zero and 13 are considered to be normal, those ranging between 14 and 16 are borderline and those scores between 17 and 40 are abnormal. Scale scores can be prorated if at least three items are completed.

The SDQ has been shown to be reliable and valid. For example, a test-retest reliability coefficient of .85 has been reported for the SDQ total score (Goodman, 1999). It also has been found to correlate highly with the widely used Rutter questionnaires (Goodman, 1997) and the CBCL (Goodman & Scott, 1999) and has been found to discriminate equally well between high and low risk samples (Goodman, 1997; Goodman & Scott, 1999). It is sensitive and specific in the detection of psychiatric problems in children (as validated by comparison with semi-structured psychiatric interview) and has been found to be identify clinical problems in children whose primary problems are neurological such as hemiplegia (Goodman & Graham, 1996). A very high prevalence of such problems have also been found in children with brain tumours (Kennedy & Leyland, 1999). The SDQ was deemed appropriate for this study because of its brevity and because of its suitability for use in both healthy and ill populations. In addition, the availability of a teacher report provides an indication of the child's performance and behaviour in school. Also, this questionnaire focuses on strengths of the child as well as difficulties and captures social

and other behaviours which may not be well assessed by quality of life or health status measures.

### 2.4.4. Behavior Rating Inventory of Executive Function (BRIEF)

This questionnaire was completed by all parents and teachers about the child.
The BRIEF (Gioia et al., 2000) is a self-administered measure of executive function in daily life for completion by parents and teachers of children aged between five and 18 years. It has a six month recall period and takes approximately 15 minutes to complete. It consists of 86 items which constitute eight subdomains of executive function: Working Memory, Inhibit, Plan/organize, Organization of Materials, Monitor, Emotional Control, and Shift. These subdomains each contribute to one of two supra-ordinate scales, the Behavioral Regulation Index, which includes the inhibit, shift and emotional control scales, and the Metacognition Index which comprises the initiate, working memory, plan/organise, organisation of materials, and monitor scales. These two supra-ordinate scales are combined to obtain an overall score of executive function, the Global Executive Composite score. Respondents have to say whether a behaviour is either "never", "sometimes" or "always" a problem and sample items include: "When given three things to do, remembers only the first or last", "Has explosive, angry outbursts", "Forgets to hand in homework, even when completed", and "Cannot find things in room or school desk". A total of two missing responses on each domain are permitted and given a score of one. Raw scores are converted to standardized *T* scores with a mean of 50 and a standard deviation of ten. *T* scores of >65 represent clinically significant impairment. There are also two validity scales, one that measures rater negativity and the other that measures inconsistent responses on similar items.

For both parent and teacher questionnaires, internal consistency reliability has been found to be high, ranging from .80 to .98 for both normative and clinical samples and test-retest correlations for parent report ranged between .76 and .85 (Gioia et al., 2000). There is also evidence of convergent and divergent validity using well established measures of attentional and behavioural functioning (Gioia et al., 2000). In addition, it has ecological validity in that the items on the questionnaire relate to every-day behaviours. The BRIEF has been used in many childhood diagnostic samples in comparison with controls, for example, children with epilepsy (Sherman et al., 2006), traumatic brain injury (e.g. Sesma, Slomine, Ding, & McCarthy, 2008) and brain lesions (Gioia et al., 2000). The above evidence suggests that the BRIEF would be an ideal measure for this study.

### 2.4.5. General Health Questionnaire (GHQ)

The following questionnaire was completed by all parents about themselves. The 60 item GHQ (Goldberg & Williams, 1988) is the most widely used self-administered, self-report measure of adult mental health in the general population. It was designed to be a screening tool to detect psychiatric disorders in community settings such as GP surgeries and non-psychiatric clinical settings such as general medical out-patients. The 12 item version, GHQ-12 (Goldberg & Williams, 1991), takes one or two minutes to complete. Each question consists of a symptom or item of behaviour that the respondent has recently experienced and endorses on a four point scale from "less than usual" to "much more than usual" and sample items include: "Been able to concentrate on whatever you're doing?", "Lost much sleep over worry?", "Felt that you are playing a useful part in things?", and "Felt capable of making decisions about things?". There are three possible scoring methods. It can be scored using the bimodal response scale (0-0-1-1), known as the GHQ scoring method, in which only deviations from normal are scored which provides a total score of 12, or the C-GHQ method, in which items are also scored using a bimodal response scale (0-1-1-1) that reflect health (0) or illness (1), also with a total of 12, or as a 'Likert scale' (0-1-2-3), in which case the items are summated to provide a total score ranging from 0 to 36 with higher scores indicating poorer mental health. Missing items are not permitted. Goldberg et al. (1997) recommended using the GHQ scoring method to identify cases and the Likert scale to assess severity.

For the GHQ-12 the split half reliability has been reported to be .83, test-retest reliability .73, specificity 78.5% and sensitivity 93.5% (Goldberg & Williams, 2006). Convergent validity of .78 between the GHQ-12 and the Self Reporting Questionnaire (SRQ-20) was reported by Mari and Williams (1985). Pevalin (2000) recommended its use for longitudinal studies to indicate minor psychiatric morbidity. For the above reasons it seems to be an ideal measure for the current study.

### 2.4.6. Wechsler Intelligence Scale for Children® (4th UK Edition)

This test was administered to all children. The WISC® IV UK (Wechsler, 2004) is designed for children aged from six years to 16 years eleven months and requires no reading or writing. It is one of the most frequently used measures of neuropsychological functioning and takes about 60 to 90 minutes to administer to individual children. It assesses intellectual functioning in the cognitive domains of verbal comprehension, perceptual reasoning, working memory, and processing speed. It also provides a

composite score that represents a child's general intellectual ability. Since 1939 when Wechsler developed his first measure of intelligence, the Wechsler-Bellevue Intelligence Scale (Wechsler, 1939), in response to a need to measure non-verbal as well as verbal intelligence, the test has been frequently updated to take account of new theories of intellectual functioning. The WISC® IV UK is the most updated version for use in the UK. It takes account of the Cattell Horn Carrol (CHC) theory of cognitive abilities (Carroll, 1997) that emphasises the domains of fluid reasoning, working memory, and processing speed.

### 2.4.7. Measure of socio-economic status

The measure of socio-economic status (SES) that was chosen was The National Statistics Socio-economic Classification (NS-SEC) (ONS, 2004). It is an occupationally based classification system that has been used in all official statistics and surveys since 2001 in England and Wales. It has clear rules for classifying occupations into eight classes, which can be subdivided into five and three classes (see below). The NS-SEC was developed from a sociological classification system developed by Erikson and Goldthorpe (Erikson & Goldthorpe, 1992) which has been widely used in research, is internationally accepted, has been well validated, and is conceptually clear. The NS-SEC improved on the original schema and has been thoroughly validated (ONS, 2004). It is for these reasons that it was chosen as a measure of SES for this research.

The three class version was used for this research. First of all the occupation of the main wage earner in the household was classified according to one of the 17 Operational Categories of the NS-SEC based on the rules in the ONS NS-SEC Manual 2004. This category was then matched to one of eight Analytic Classes which was then matched to the collapsed three class version: (i) managerial and professional occupations, (ii) intermediate occupations, and (iii) routine and manual occupations. SES prior to the child's illness was taken to be the SES of the family rather than current SES at each time point because work status of the main caregiver frequently changes as a result of having to care for a seriously ill child with many parents having to give up work, temporarily at least.

## 2.5. PROCEDURE

The scientific and ethical aspects of the study were reviewed by the Children's Cancer and Leukaemia Group (CCLG) which comprises specialist childhood cancer treatment hospitals across the UK. After approval was granted from the CCLG, the study (CCLG

number: CNS 2005 01) was submitted to Trent Multi-centre Research Ethics Committee for ethical approval. Once ethical approval had been obtained (number: 04/MRE04/47), each CCLG centre who had committed themselves to supporting the research gained Research and Development approval (Southampton number: RHM CH10330) and data protection approval was also granted.

### 2.5.1. Recruitment of children with brain tumours

Overall patients were consecutively recruited from 11 CCLG centres across England and Wales between February 2005 and January 2008. The start date for recruitment varied between hospitals due to differing dates for Trust Management approval of the study. Children and parents were approached by their treating clinician who briefly explained the study at a regular clinic appointment. Seventy four patients and parents were approached by their clinicians about the study and all showed a positive response apart from two.

The children diagnosed with SRM, post-surgery, received treatment according to the Packer regimen i.e. six weeks of daily craniospinal radiotherapy of 23.4 Gy with a 55.8 Gy boost to the posterior fossa plus weekly vincristine for eight weeks followed six weeks later by eight six week cycles of chemotherapy consisting of CCNU and cisplatin plus vincristine, given weekly for three weeks (Packer et al., 1999). There were no major deviations from this standard treatment. Those children diagnosed with an LGCA all had surgery, then no further treatment.

Families' contact details were sent to me and then I contacted the family and explained the study in full over the phone. If the parent agreed to participate, I made an appointment to visit them in their own home to conduct interviews (not part of this thesis) and administer to the child the WISC. This visit took on average three hours (but the participants seemed to enjoy the opportunity to take part and did not mind spending this time with me). I sent information sheets and questionnaires by post prior to the visit, obtained written consent at the first visit and collected the completed questionnaires. I sent the questionnaires prior to the visit to reduce the visit time rather than asking participants to complete questionnaires during the visit. Parents were given instructions by phone prior to the visit regarding how they should provide assistance to their child without influencing their responses to the items. After the visit I contacted the patient's head teacher and made arrangements to recruit a Comparison child (see below) and sent the teacher questionnaires to the patient's teacher for completion.

### 2.5.2. Recruitment of Comparison children

It should be noted that when considering the nature of this group of children, the aim was to recruit a sample which would represent 'average' children of the same age in the general population rather than 'healthy' children. This distinction between 'average' and 'healthy' has been described by Kendall and Sheldrick (2000). The latter reflects the medical model in which pathology is considered to be abnormal and therefore exclusion criteria are used to ensure that a 'healthy' comparison group is selected to ensure 'normality' i.e. free from pathology, and therefore participants are excluded if they reach clinical cut off points on questionnaires, for example. The problem with this approach is the danger of creating a 'supernormal' comparison group, thereby artificially exaggerating group differences. The latter view of normality as being 'average' has dominated psychological research and is more inclusive with participant scores reflecting more of a normal distribution. It was felt that in order to truly assess QoL in children with brain tumours, it was important to assess how their QoL should have been by comparing them with an 'average' sample rather than a 'healthy' one.

Recruitment of the Comparison group followed the following procedure. I contacted the patient's head teacher by letter which was followed up a week later with a telephone call. Only three out of 45 schools approached declined to help with the study. One deputy head teacher said that the staff were under enormous pressure at the time, another head teacher felt that issues with the particular child and his family and the school made it inappropriate for the school to be involved in the study, and the final head teacher declined on the grounds that she was confident that no parents would be willing to help with the research. In those schools where head teachers were willing to help, the usual method of recruitment was that I was told how many children there were in total in the patient's year group. From this total number, one number was randomly selected using SPSS. I then contacted the school to inform them of the random number and they counted down the list of children in alphabetical order from A to Z until they reached the number that they had been given. Thus one family was then contacted by the head teacher using a letter of invitation that had been prepared by me in advance, with a reply slip, which was to be returned directly to me in a stamped addressed envelope. If the reply slip was not returned within two weeks then the head teacher was asked to send out a follow-up letter. If, there was still no reply from the family then another family was randomly selected from the year group.

Five schools gave up after several attempts at sending out letters of invitation unsuccessfully, five families did not want a Comparison child to be selected from the school, one child (patient) attended a special school and therefore it was inappropriate to select a comparison child from this particular school, one child had recently moved to the area and had not yet started school so a Comparison child could not be selected in this case, and in one year group most of the children would have reached 15 years old and were no longer eligible to be selected for the Comparison group. Of all the Comparison families who were randomly selected none were deemed to be ineligible. Seventeen schools were not approached for the purposes of recruiting a Comparison child as the Comparison sample target had already been reached by the time those children with brain tumours entered the study.

An alternative method of recruitment suggested by one lay member of the ethics committee was for the head teacher to write to the parents of all the children in the year group enclosing a letter from me, inviting participation but making it clear that only one volunteer would be selected to take part in the study, and including a reply slip and a stamped addressed envelope to be returned directly to me. Randomisation then took place from the reply slips I received. This method was chosen by only one primary school.

### 2.5.3. Recruitment of sample and related issues

At the time, there were a total of 22 CCLG centres in the UK and 14 agreed that they would help to recruit participants for the study. The recruitment target was based on numbers provided by the National Registry of Childhood Tumours (NRCT) of children who had been diagnosed in all 14 CCLG centres between 1999 and 2001. The study opened on 1$^{st}$ of February 2005 with eleven of the 14 centres taking part. This reduction, by three, in the number of centres taking part meant that the recruitment period had to be extended by one year in order to try to reach the recruitment target. There were several possible sources from which eligible patients could be identified but none were completely reliable. The NRCT data base was never up-to-date and completeness of the data at that time was estimated to be between 90% and 97%. Another source was the CCLG registry but, this data base was not able to provide numbers of children with a medulloblastoma in each centre who were specifically standard risk and the data base was not up-to-date either. Various other data bases at the CCLG were also incomplete.

Thus, the most reliable method of identifying all eligible patients for this investigation was for each participating hospital to identify their own patients. However, each hospital differed in the way electronic records were kept and the ability of each hospital to identify eligible patients varied. Initially recruitment was going to open to three groups of patients: newly diagnosed, one year post diagnosis (i.e. at the end of treatment for the medulloblastoma group), and two years post diagnosis. These three time frames would have been ideal in assessing the children with medulloblastoma at a time post diagnosis that was equivalent to the experience of children with an LGCA i.e. children with an LGCA following surgery received no further treatment therefore both groups would have been assessed at an equivalent time post-surgery. It was assumed that at this time children and parents in both groups would have been at a similar psychological state and not yet had sufficient time to adapt to their situation. In reality, this was not practical because of the small numbers of patients diagnosed each year. Therefore, by further limiting study entry criteria in this way, as well as the patient's age, recruitment would have been further reduced. Thus, I decided to recruit all patients irrespective of time since diagnosis as long as they had not been diagnosed more than three years previously.

Following the first assessment, all parents, children and teachers were re-contacted and assessed 12 months later (T2) and then again 12 months after that (T3). Due to this 12 month interval, for those children who had been treated for brain tumours, I first contacted the child's treating clinician at the hospital to ensure that the child had not relapsed or died in the intervening period. Also, participating teachers were different at each assessment due to children moving into higher classes or moving on to different schools.

## 2.6. Overall Analytic strategy

The distributions of the data were checked visually by plotting histograms and one sample Kolmogorov-Smirnov tests were conducted. These two methods in combination, informed judgements regarding normality of the data. It was decided not to remove outliers for reasons relating to the sample size of each group (< 40), i.e. the removal of data ran the risk of removing potentially important information about the array of characteristics of the children within the groups and also a removed outlier was likely to be replaced by another and so on. It was also decided not to transform non-normally distributed data sets due to the complexities of this issue evidenced by a lack of agreement between statisticians, described in Field (2009, pp. 155-156), as to the merit and appropriateness of performing data transformations.

Multiple testing is an issue in this study. One way of dealing with this is by applying the Bonferroni correction which adjusts the *p* value according to the number of analyses conducted. However, this is not recommended (Nakagawa, 2004; Perneger, 1998) as it is overly conservative and therefore runs the risk of artificially inflating the Type I error. An alternative solution is to use a 1% significance level instead of 5% (Altman, Machin, Bryant, Gardner, & 2002). However, the discussion regarding which significance level to use is purely academic, arbitrary and largely unjustified (see Field, 2009 p. 51 for a neat description of this issue). Field explains that the criterion for rejecting the experimental hypothesis if $p>.05$ came about from the critical values tables that Fisher produced at the beginning of the 20$^{th}$ century that were used for decades before the advent of computers and statistical software packages. Due to lack of space these tables contained critical values for only certain levels of probabilities (.05, .02, and .01) which researchers have reported ever since. According to Field (2009) Fisher himself considered this dogma to be silly and observed, "no scientific worker has a fixed level of significance at which from year to year, and in all circumstances, he rejects hypotheses; he rather gives his mind to each particular case in the light of his evidence and his ideas" (p. 51).

In light of the above discussion, and in view of the sample of children studied where even small changes or differences between groups that become apparent in children with newly acquired impaired functioning potentially have a large impact, even if $p>.05$, it was decided that precise *p* values would be shown but with a two-tailed 5% significance level cut off as the criterion for performing sub-analyses (see below). Importantly, confidence intervals, as recommended by the American Psychological Association (2003) and also Nakagawa (2004), are shown to allow the reader, in addition to looking at the *p* value, to make their own judgements regarding the precision of the estimated mean difference, rather than focussing solely on a particular arbitrary *p* value. The number of statistical analyses was kept to a minimum by only conducting subscale analyses when a significant overall effect was found. Having said this, one should be cautious when interpreting the results generated from the multiple tests conducted on subscales following a significant overall effect. All analyses were conducted using IBM SPSS version 19.0. For a detailed description of the analytic strategies see appendix A.

### 2.6.1. Analytic strategy for group comparisons of QoL

For each measure, the difference between the Total overall score (where applicable) across the three groups was examined using a one-way Analysis of Variance (ANOVA) for

parametric data or Kruskal-Wallis for non-parametric data. When there was a significant effect of group on the Total overall score, further analyses were conducted on the subscales to see which subscales accounted for the total score differences. Either multivariate analysis of variances (MANOVA), one-way ANOVAs, *t*-tests, the Kruskal-Wallis test or Mann-Whitney *U* tests were then conducted, as appropriate to the number of groups involved and number of outcome scores and whether the data met the assumptions of parametric analysis. All descriptive statistics are shown as means and standard deviations for consistency of presentation not only within this thesis but also for the review of published work including in the case of those data that were not normally distributed, for example, the HUI questionnaire (e.g. Boman et al., 2009; Penn et al., 2011).

### 2.6.2. Analytic strategy for changes in QoL over time

A complete-case analysis was conducted across time points and across informants to ensure that the same participants were included, but not across measures as this would have led to a greater reduction in the data available over time. Within group differences over time in the Total overall score for each measure were examined using one-way repeated-measures ANOVAs for parametric data followed by repeated-measures contrasts, or Friedman's ANOVA for non-parametric data, followed by Wilcoxon signed-rank tests, to identify which time points differed significantly. Following significant within group time point differences on the Total overall score, further analyses were conducted on the subscales to determine the time points between which these differed significantly. In order to reduce the number of tests due to the issue of multiple testing (see section 2.6), but to take full advantage of all time points to see where the greatest changes in scores took place, it was decided to first compare T3 to T1 for Total scores for each measure and if these showed significant change then compare T2 to T1 and T3 to T2.

### 2.6.3. Analytic strategy for parental mental health and child QoL

At each time point and in each group, separate simple linear regression models were used to assess whether parents' mental health, as measured by the GHQ-12, predicted parent-report PedsQL and SDQ Total scores, and child-report PedsQL Total score.

### 2.6.4. Analytic strategy for predictors of child HRQoL

Multiple regression was used to identify the important significant predictors of child-report and also parent-report HRQoL at each time point to see whether predictors changed or

remained the same over time and whether there were patterns of change or stability. Finally multiple regression was used to identify the significant predictors at T1 of child-report and also parent-report HRQoL at T3. Early predictors of subsequent HRQoL could be informative in a clinical setting to allocate resources efficiently and in a timely way to benefit the most needy children. As several predictors needed to be included in the models simultaneously, analyses were conducted in the whole study sample in order to ensure adequate sample sizes.

Firstly, SES, child's gender and age at assessment were included in the model. Group was not entered as a predictor because it had already been established earlier (in section 3.4) that there were significant differences between the three groups in HRQoL and I wanted to know what factors underlying intergroup differences, other than group, predicted HRQoL. Age at diagnosis or time since diagnosis were not included in the multiple regression models as the design of the study meant little variation in these two variables. Furthermore these variables could not apply to the Comparison group thereby reducing the sample size by a third. Also simple linear regression models including the two tumour groups only, showed that age at diagnosis significantly predicted child-report QoL at T1 and T3, but not by parent-report (chapter 6, table 58), but that it was highly significantly correlated with age at assessment at each time point. Thus, age at assessment rather than age at diagnosis seemed to be a more useful predictor to include in the multiple regression models. In addition, time since diagnosis did not significantly predict HRQoL in the tumour groups at any of the time points neither by child- nor by parent-report (chapter 6, table 59) and therefore it did not seem to be a useful predictor anyway.

To benefit fully from the data from all the subscales of all the measures, and also each informant, all the data were divided into six theoretically derived concepts (domains of function) for inclusion in the models. These domains of function were devised a priori by group consensus (me, a health psychologist, a paediatric neurologist, and two statisticians) and were chosen as they had previously been reported by others to be predictive of HRQoL and to be particularly important with regard to tumours of the cerebellum in relation to the cognitive affective syndrome. These domains were: Emotion, Behaviour, Social, Cognition, Motor and Sensory function, and Caregiver Mental Health. Then we looked at all the subscales and decided which ones went into which domain based on their face validity. We then combined those subscales which appeared similar (see Appendix B). I then conducted Cronbach's alpha analyses on these subscale scores for all the items

contributing to each domain of function. None of the items were deleted as even those with corrected item total correlations <.2 did not make a difference to the overall Cronbach's alpha if eliminated (see Appendix C). For each subscale, z-scores were then created (where the mean = 0 and the SD = 1) for the scores in the Comparison group on each subscale at each time point for each group of informants. Each domain of function was then created from the mean of the sum of the constituent subscales z-scores.

The models were constructed by firstly entering SES prior to diagnosis, child's gender and age at assessment of QoL at each time point and those predictors that were not significant were removed. The domains of function and Caregiver Mental Health were then included and those predictors that did not contribute significantly to the model were again removed and so on until only the significant predictors remained in the final model.

# CHAPTER 3 RESULTS: GROUP COMPARISONS

## 3.1. DEMOGRAPHIC CHARACTERISTICS OF THE THREE GROUPS AT TIME 1

A total of 115 families were contacted. Of these, five did not take part after receiving a full explanation of the study. The reasons for this were: one family wanted to complete only the questionnaires; another family, although willing to participate, never did because the child had posterior fossa syndrome which proved to be a great strain on the mum; the child in the third family had been blinded by the tumour and after some consideration, the mum decided not to participate; the child in the fourth family had become too old to be eligible by the time the mum decided to participate; and the fifth family decided not to participate after receiving the explanation of the study.

Thus the recruitment rate was 96% of those that I contacted. One hundred and ten families were recruited from eleven geographical areas in England and Wales (Table 1).

Table 1. Number of participants recruited from each geographical area

| Hospital and region | SRM | LGCA | Comparison | Total |
|---|---|---|---|---|
| Birmingham | 1 | 3 | 0 | 4 |
| Cambridge | 2 | 2 | 4 | 8 |
| Cardiff | 0 | 2 | 1 | 3 |
| Great Ormond St London | 4 | 7 | 4 | 15 |
| Leeds | 6 | 2 | 5 | 13 |
| Liverpool | 3 | 4 | 6 | 13 |
| Manchester | 4 | 0 | 2 | 6 |
| Newcastle-upon-Tyne | 7 | 3 | 4 | 14 |
| Nottingham | 0 | 6 | 1 | 7 |
| Royal Marsden London | 7 | 3 | 6 | 16 |
| Southampton | 3 | 3 | 5 | 11 |
| Total | 37 | 35 | 38 | 110 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

There were 37 children in the SRM group, 35 in the LGCA group and 38 in the Comparison group. Thus, the target of 111 families was almost reached with a short fall in the number of LGCA children by two and an extra child in the Comparison group. By T2 the sample size had reduced by 9% to 100 with 37, 32 and 31 in the Comparison, SRM and

LGCA groups respectively. By T3 the sample size had reduced further by 6% to 94 with 36, 29 and 29 in the Comparison, SRM and LGCA groups respectively.

The Comparison sample included a wide variety of children: one had been born prematurely, one was living with foster parents and had behavioural problems, one developed rheumatoid arthritis during the study period, one had parents who were immigrants from Iraq who had been living in the UK for ten years, one had sustained an injury to his hand resulting in the removal of the tips of three fingers, and one child was taking Ritalin for ADHD. Thus, recruitment of the Comparison group achieved the goal of providing a group of children representative of children of a similar age in the general population, rather than a 'healthy' Comparison group. Of the 38 children recruited to the Comparison group 25 (66%) agreed to participate after initial contact. The remaining 13 were recruited after subsequent random selections from the school year group.

In the SRM group a year after the first assessment, three families decided to drop out. The reasons for this were: one mother felt that they were now getting on well with their lives and wanted to put the experience of the child having a tumour behind them and not have reminders of it; one child did not want to take part as his first language was Welsh and he did not feel comfortable taking part in the English language; and one child had become upset during the interview at the first assessment and did not want to take part any more when contacted again for the second assessment. Unfortunately four children in this group had relapsed by the time the second assessment was due but in spite of this, three of the families wished to continue with the study, even though it was explained to them that it was undecided as to how their data would be used. Sadly one child in this group had died. By the time that the third assessments were due to be conducted (i.e. two years after the first meeting with the family) there were no further drop outs or relapses but a further two children had sadly died.

In the LGCA group three families had dropped out by the second assessment. One 13 year old no longer wanted to participate as she reported that she had found the questionnaires and WISC-IV childish; one child had become upset while filling in the questionnaires and no longer wanted to participate; and the mother of one child was going through a divorce and was unable to participate at that time. Unfortunately one of the children in this group had progression of residual tumour within the intervening period and by the second year another child had relapsed.

In the Comparison group one family had fostered the child who was shortly to move out of the foster home and by the second year one of the families had had moved away and was lost to follow-up. Overall, the rate of loss of participants (14%) from the study was close to but less than that which was predicted (i.e. 10% per annum).

At T1 the three groups were well matched in terms of child, parent and family characteristics (Table 2).

Table 2. Child and parent characteristics at Time 1

| Child characteristics | **SRM n=37** | **LGCA n=35** | **Comparison n=38** |
|---|---|---|---|
| Female (%) | 16 (43) | 23 (66) | 19 (50) |
| Mean age in years (SD) | 10.2 (1.8) | 10.4 (2.0) | 10.4 (1.8) |
| Mean age in years at diagnosis (SD) | 8.8 (2.0) | 9.2 (2.4) | N/A |
| Months from diagnosis (SD) | 16.2 (9.9) | 14.7 (9.3) | N/A |
| On treatment (%) | 15 (41) | 0 | N/A |
| Parent characteristics | | | |
| Mother/Father respondent | 35/2 | 32/2 | 33/4 |
| Respondent mean age in years (SD) | 39 (5.5) | 41 (8.1) | 41 (5.3) |
| Lone parent family (%) | 8 (22) | 3 (9) | 5 (11) |
| Siblings (%) | 27 (76) | 32 (89) | 34 (89) |
| Parent education (%): None/unknown | 1 (5) | 2 (6) | 2 (5) |
| School | 14 (38) | 5 (14) | 7 (18) |
| College | 15 (40) | 18 (54) | 21 (55) |
| University | 6 (16) | 10 (26) | 8 (21) |
| SES (%): Managerial & Professional | 7 (19) | 21 (60) | 18 (47) |
| Intermediate | 11 (30) | 8 (23) | 7 (18) |
| Routine & Manual | 6 (16) | 5 (14) | 10 (26) |
| Not working/unknown | 12 (35) | 1 (3) | 3 (8) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; SES, socioeconomic status; SD, standard deviation

Forty one per cent of the children in the SRM group were still receiving treatment at T1 whereas none of the children in the LGCA group was receiving treatment as they had all received surgery alone and no further treatment was required. There was a somewhat higher percentage of lone parents in the SRM group which may partly explain the higher

proportion of parents in this group who were not working. There was also a higher proportion of parents in the SRM group with school qualifications only. There appears to be no available systematic causes for these demographic differences.

### 3.2. CLINICAL NEUROLOGICAL FEATURES

Clinical neurological problems for children with SRM were more prevalent pre-operatively and showed a greater adverse change post-operatively than for those with LGCA. Of the 15 clinical features present before surgical resection of SRM, all except severe hydrocephalus and seizures were present in a greater number of children after surgery with the mean number of adverse clinical features per child increasing from 4.1 to 5.7 (Table 3). By contrast, the LGCA group had a lower mean number of clinical features both pre- (2.7) and post-operatively (2.9). Only eight of the 15 features affected a greater percentage of children and five features affected fewer children post-operatively than pre-operatively.

Table 3. Clinical neurological features before and after tumour resection

| | **SRM n=37** | | **LGCA n=35** | |
|---|---|---|---|---|
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| **Neurological feature** | **Pre op** | **Post op** | **Pre op** | **Post op** |
| Severe hydrocephalus | 17 (46) | 4 (11) | 12 (34) | 4 (11) |
| Visual impairment | 7 (19) | 9 (24) | 6 (17) | 4 (11) |
| Speech impairment | 3 (8) | 11 (30) | 1 (3) | 6 (17) |
| Upper limb ataxia | 19 (51) | 19 (51) | 12 (34) | 9 (26) |
| Truncal ataxia | 23 (62) | 24 (65) | 7 (20) | 8 (23) |
| Limb weakness | 1 (3) | 12 (32) | 2 (6) | 5 (14.3) |
| Balance impairment | 24 (64.9) | 27 (73.0) | 17 (48.6) | 9 (26) |
| Walking impairment | 15 (41) | 18 (49) | 11 (31) | 10 (29) |
| Seizures | 0 | 0 | 2 (6) | 0 |
| Posterior fossa syndrome | 0 | 12 (32) | 0 | 4 (11) |
| CNS/other infection | 0 | 8 (22) | 0 | 5 (14) |
| Mean no. of clinical features (SD) | 4.1 (2.8) | 5.7 (4.1) | 2.7 (2.2) | 2.9 (3.2) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebellar astrocytoma

### 3.3. EXTRA HELP RECEIVED AT SCHOOL

Table 4. Group comparisons of extra help given at school

| | SRM | | | LGCA | | | Comparison | | |
|---|---|---|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Help received** | **T1 n=35** | **T2 n=30** | **T3 n=28** | **T1 n=35** | **T2 n=31** | **T3 n=29** | **T1 n=38** | **T2 n=37** | **T3 n=35** |
| None | 8 (23) | 9 (30) | 9 (32) | 22 (63) | 23 (74) | 18 (62) | 36 (95) | 35 (95) | 32 (91) |
| similar to others | 7 (20) | 4 (13) | 3 (11) | 6 (17) | 2 (7) | 4 (14) | 1 (3) | 1 (3) | 2 (6) |
| specific | 14 (40) | 16 (53) | 16 (57) | 4 (11) | 6 (19) | 7 (24) | 1 (3) | 1 (3) | 1 (3) |
| not at school | 6 (17) | 1 (3) | 0 | 3 (9) | 0 | 0 | 0 | 0 | 0 |
| months absent* | 15.9 (1-30) | | | 7.8 (1-42) | | | N/A | | |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebellar astrocytoma; T1, time 1; T2, time 2; T3, time 3. *mean number of total months absent (and range) from full time education when ill initially and following surgery

Table 4 reveals that children in the SRM group had been absent from full time education for a mean of 15.9 months compared with 7.8 months in the LGCA group. The proportion of children in the SRM group who received extra help at school similar to that received by other children decreased over time, but the proportion of children who received specific extra help increased. The proportion of children in the LGCA group who received specific extra help also increased over time. The proportion of children in the Comparison group who received specific extra help was very low and remained stable over time.

## 3.4. COMPARISON OF QOL BETWEEN THE THREE GROUPS AT TIME 1

### 3.4.1. Child-report of PedsQL at Time 1

Table 5 shows that there was a significant effect of group on PedsQL Total score ($F(2, 104) = 15.7$, $p < .001$).

Table 5. Scale descriptive statistics for the child-report PedsQL Total scores, summary scores and subscales showing means and standard deviations in each group at Time 1

| | **SRM n=34** | **LGCA n=34** | **Comparison n=38** |
|---|---|---|---|
| Total Score | 60.2 (18.0) | 71.2 (20.4) | 82.1 (12.3) |
| Physical Health | 50.8 (24.8) | 71.1 (28.0) | 87.4 (10.0) |
| Psychosocial Health | 65.2 (17.2) | 71.2 (18.1) | 79.2 (15.3) |
| Emotional functioning | 69.3 (17.2) | 71.5 (20.1) | 75.5 (19.3) |
| Social functioning | 69.3 (19.5) | 79.6 (19.9) | 83.9 (15.3) |
| School functioning | 57.1 (24.1) | 62.6 (23.8) | 78.3 (15.8) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

Higher scores = better functioning

Table 6 demonstrates that PedsQL Total scores in the Comparison group were significantly higher (better) than those in the SRM group ($t(59.6) = 6.2$, $p < .001$) and significantly higher (better) than those in the LGCA group ($t(53.0) = 2.7$, $p = .010$). PedsQL Total scores in the SRM group were significantly lower (poorer) than those in the LGCA group ($t(65.4) = 2.5$, $p = .015$).

Table 6. Mean differences and confidence intervals for the child-report PedsQL Total scores between each group at Time 1

| | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| SRM vs Comparison | 22.4 | 15.1 to 29.7 | < .001 |
| LGCA vs Comparison | 10.8 | 2.8 to 18.9 | .010 |
| SRM vs LGCA | 11.6 | 2.3 to 20.8 | .015 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval

Table 7 reveals that the Physical Health Summary score was determined by group ($H(2) = 35.150$, $p < .001$). Children with SRM had a significantly lower (poorer) Physical Health Summary score than Comparisons ($Mdn = 46.9$ vs 89.1, $U = 116.0$, $p < .001$) and significantly lower (poorer) than children with LGCA ($Mdn = 79.7$, $U = 325.0$, $p = .001$). Also children with LGCA had a significantly poorer Physical Health Summary score than Comparisons ($U = 456.0$, $p = .031$).

Table 7. Mean differences and confidence intervals for the child-report Physical Health Summary scores of the PedsQL between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | 37.5 | 28.4 to 46.6 | < .001 |
| LGCA vs Comparison | 16.1 | 6.0 to 26.2 | .031 |
| SRM vs LGCA | 21.4 | 8.7 to 34.1 | .001 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p value for Mann-Whitney *U* tests

Table 8 reveals that there was a significant effect of group on the Psychosocial Health Summary score ($F(2, 104) = 6.7$, $p = .002$) accounted for by a significant difference between the SRM group and the Comparison group.

Table 8. Mean differences and confidence intervals for the child-report Psychosocial Health Summary scores of the PedsQL between each group at Time 1

| | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| SRM vs Comparison | 14.3 | 5.2 to 23.5 | .001 |
| LGCA vs Comparison | 8.0 | -1.5 to 17.6 | .116 |
| SRM vs LGCA | 6.3 | -3.5 to 16.1 | .320 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval

Table 9 shows that there was no significant difference between the SRM and Comparison groups in terms of Emotional Functioning ($t(71) = 1.464$, $p = .148$) but Social Functioning (*Mdn* = 70.0 vs 85.0, $U = 367.5$, $p = .001$) and School Functioning ($t(58.073) = 4.550$, $p < .001$) scores were significantly lower (poorer) in the SRM group.

Table 9. Mean differences and confidence intervals for the child-report Emotional, Social and School Functioning scales of the PedsQL between the SRM group and the Comparison group at Time 1

| | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| Emotional Functioning | 6.2 | -2.3 to 14.7 | .148 |
| Social functioning | 14.9 | 6.8 to 23.0 | .001 |
| School functioning | 21.9 | 12.2 to 31.5 | < .001 |

Abbreviation: CI, confidence interval

### 3.4.2. Parent-report of PedsQL Time 1

Table 10 demonstrates that there was a significant effect of group on PedsQL Total score ($H(2) = 39.088$, $p < .001$).

Table 10. Scale descriptive statistics for the parent-report PedsQL Total scores, summary scores and subscales showing means and standard deviations in each group at Time 1

| | **SRM n=34** | **LGCA n=34** | **Comparison n=38** |
|---|---|---|---|
| Total Score | 48.1 (21.7) | 68.2 (23.9) | 84.3 (11.0) |
| Physical Health | 36.1 (26.7) | 69.0 (31.6) | 90.3 (11.0) |
| Psychosocial Health | 54.5 (21.0) | 67.8 (21.1) | 81.1 (13.7) |
| Emotional functioning | 57.2 (22.8) | 65.3 (23.5) | 78.3 (16.8) |
| Social functioning | 59.0 (23.6) | 74.7 (22.9) | 85.4 (15.6) |
| School functioning | 47.4 (26.3) | 63.4 (25.0) | 79.6 (14.1) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

Higher scores = better functioning

Table 11 shows that children with SRM had significantly lower (poorer) PedsQL Total scores than Comparisons (*Mdn* = 45.7 vs 88.0, $U = 101.5$, $p < .001$) and significantly lower (poorer) than children with LGCA (*Mdn* = 71.7, $U = 331.5$, $p = .001$). Also children with LGCA had significantly lower (poorer) PedsQL Total scores than Comparisons ($U = 403.0$, $p = .004$).

Table 11. Mean differences and confidence intervals for the parent-report PedsQL Total scores between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | 35.6 | 27.4 to 43.8 | <.001 |
| LGCA vs Comparison | 15.7 | 6.9 to 24.5 | .004 |
| SRM vs LGCA | 19.8 | 9.0 to 30.7 | .001 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p values for Mann-Whitney *U* tests

Table 12 reveals that there was a significant effect of group on the Physical Health Summary score ($H(2) = 49.383$, $p < .001$). Children with SRM had a significantly lower (poorer) Physical Health Summary score than Comparisons (*Mdn* = 31.3 vs 93.8, $U = 42.5$, $p < .001$) and significantly lower (poorer) than children with LGCA (*Mdn* = 81.3, $U = 269.5$, $p = <.001$). Also children with LGCA had a significantly lower (poorer) Physical

Health Summary score than Comparisons ($U$ = 385.0, $p$ = .002).

Table 12. Mean differences and confidence intervals for the parent-report Physical Health Summary scores of the PedsQL between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | 53.2 | 43.3 to 63.0 | <.001 |
| LGCA vs Comparison | 20.8 | 9.6 to 32.1 | <.001 |
| SRM vs LGCA | 32.3 | 18.4 to 46.2 | <.001 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p value for Mann-Whitney *U* tests

Table 13 shows that there was a significant effect of group on the Psychosocial Health Summary score ($H$(2) = 27.720, $p$ < .001). Children with SRM had a significantly lower (poorer) Psychosocial Health Summary score than Comparisons (*Mdn* = 53.3 vs 85.8, $U$ = 193.0, $p$ < .001) and significantly lower (poorer) than children with LGCA (*Mdn* = 68.3, $U$ = 402.5, $p$ = .014). Also children with LGCA had a significantly lower (poorer) Psychosocial Health Summary score than Comparisons ($U$ = 412.5, $p$ = .005).

Table 13. Mean differences and confidence intervals for the parent-report Psychosocial Health Summary scores of the PedsQL between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | 26.2 | 17.9 to 34.5 | <.001 |
| LGCA vs Comparison | 13.0 | 4.7 to 21.3 | .005 |
| SRM vs LGCA | 13.2 | 3.2 to 23.1 | .014 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p values for Mann-Whitney *U* tests

Table 14 demonstrates that there was a significant effect of group on the Emotional Functioning score ($F$(2, 105) = 9.2, $p$ < .001), the Social Functioning score ($H$(2) = 15.451, $p$ < .001) and the School Functioning score ($H$(2) = 27.575, $p$ < .001). Children with SRM had a significantly lower (poorer) Social Functioning score than Comparisons (*Mdn* = 60.0 vs 90.0, $U$ = 244.5, $p$ < .001) and significantly lower (poorer) than children with LGCA (*Mdn* = 75.0, $U$ = 386.5, $p$ = .008). Children with LGCA had a significantly lower (poorer) social functioning score than Comparisons ($U$ = 488.0, $p$ = .048). Children with SRM had a significantly lower (poorer) School Functioning score than Comparisons (*Mdn* = 50.0 vs

85.0, $U = 191.5$, $p < .001$) and significantly lower (poorer) than children with LGCA (*Mdn* = 65.0, $U = 397.0$, $p = .011$). Children with LGCA had a significantly lower (poorer) Social Functioning score than Comparisons ($U = 426.5$, $p = .008$).

Table 14. Mean differences and confidence intervals for the parent-report Emotional, Social and School Functioning scales of the PedsQL between each group at Time 1

| | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| **SRM vs Comparison** | | | |
| Emotional Functioning | 20.7 | 8.8 to 32.6 | < .001 |
| Social Functioning | 25.8 | 16.4 to 35.3 | < .001***** |
| School Functioning | 32.0 | 22.1 to 42.0 | < .001***** |
| **LGCA vs Comparison** | | | |
| Emotional Functioning | 13.0 | 1.1 to 24.9 | .027 |
| Social Functioning | 10.7 | 1.7 to 19.7 | .048***** |
| School Functioning | 15.3 | 5.6 to 25.0 | .008***** |
| **SRM vs LGCA** | | | |
| Emotional Functioning | 7.7 | -4.4 to 19.8 | .330 |
| Social Functioning | 15.1 | 4.1 to 26.1 | .008***** |
| School Functioning | 16.7 | 4.5 to 28.9 | .011***** |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p values for Mann-Whitney *U* tests

## 3.5. COMPARISON OF HEALTH STATUS BETWEEN THE THREE GROUPS AT TIME 1

### 3.5.1. Child-report of HUI at Time 1

Table 15 reveals that there was a significant effect of group on the HUI3 overall HRQoL score ($H(2) = 8.782$, $p = .012$).

Table 15. Scale descriptive statistics for the child-report HUI3 overall health related quality of life scores and single attribute utility scores showing means and standard deviations in each group at Time 1

| | **SRM n=35** | **LGCA n=34** | **Comparison n=38** |
|---|---|---|---|
| HRQoL score | .62 (.31) | .71 (.33) | .85 (.13) |
| Vision | .97 (.17) | .94 (.15) | .99 (.02) |
| Hearing | .95 (.19) | .98 (.09) | 1.00 (.00) |
| Speech | .93 (.19) | .98 (.08) | .98 (.06) |
| Ambulation | .75 (.32) | .90 (.26) | 1.00 (.03) |
| Dexterity | .92 (.18) | .92 (.23) | 1.00 (.02) |
| Emotion | .96 (.07) | .94 (.09) | .96 (.07) |
| Cognition | .86 (.20) | .84 (.22) | .90 (.13) |
| Pain | .90 (.11) | .95 (.08) | .96 (.07) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; HRQoL, overall health related quality of life utility score

Higher scores = better functioning

Table 16 shows that children with SRM had significantly lower (poorer) HUI3 overall HRQoL scores than Comparisons (*Mdn* = .72 vs .87, *U* = 383.5, *p* = .002) but not significantly lower (poorer) than children with LGCA (*Mdn* = .85, *U* = 463.5, *p* = .113). Also children with LGCA did not have significantly lower (poorer) HUI3 overall HRQoL scores than Comparisons (*U* = 566.5, *p* = .366).

Table 16. Mean differences and confidence intervals for the child-report HUI3 overall health related quality of life scores between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | .23 | .12 to .35 | .002 |
| LGCA vs Comparison | .14 | .02 to .26 | .366 |
| SRM vs LGCA | .09 | -.06 to .25 | .113 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p values for Mann-Whitney *U* tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

Table 17 reveals that children with SRM had a significantly lower (poorer) ambulation utility score than Comparisons (*Mdn* = .83 vs 1.00, *U* = 335.0, *p* < .001), also a lower (poorer) dexterity score (*Mdn* = 1.00 vs 1.00, *U* = 472.0, *p* = .001) and a lower pain score,

i.e. more pain (*Mdn* = .92 vs 1.00, *U* = 438.5, *p* = .007).

Table 17. Mean differences and confidence intervals for the child-report HUI3 single attribute utility scores between the SRM and Comparison groups at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| Vision | .03 | -.03 to .08 | .812 |
| Hearing | .05 | -.01 to .12 | .067 |
| Speech | .05 | -.02 to .16 | .220 |
| Ambulation | .24 | .13 to .35 | < .001 |
| Dexterity | .08 | .06 to .14 | .001 |
| Emotion | .00 | -.03 to .03 | .984 |
| Cognition | .04 | -.04 to .11 | .565 |
| Pain | .06 | .01 to .10 | .007 |

Abbreviations: CI, confidence interval.

*p values for Mann-Whitney *U* tests

### 3.5.2. Parent-report of HUI at Time 1

Table 18 demonstrates that there was a significant effect of group on the HUI3 overall HRQoL score ($H(2) = 23.8$, $p < .001$).

Table 18. Scale descriptive statistics for the parent-report of the HUI3 overall health related quality of life scores and single attribute utility scores showing means and standard deviations in each group at Time 1

| | **SRM n=36** | **LGCA n=35** | **Comparison n=38** |
|---|---|---|---|
| HRQoL score | .52 (.37) | .77 (.29) | .90 (.16) |
| Vision | 1.00 (.01) | .98 (.11) | .99 (.02) |
| Hearing | .94 (.16) | 1.00 (.00) | 1.00 (.00) |
| Speech | .90 (.15) | .96 (.10) | .99 (.04) |
| Ambulation | .66 (.36) | .90 (.24) | 1.00 (.03) |
| Dexterity | .88 (.20) | .94 (.18) | 1.00 (.00) |
| Emotion | .89 (.20) | .96 (.07) | .96 (.12) |
| Cognition | .85 (.20) | .88 (.18) | .95 (.13) |
| Pain | .84 (.25) | .95 (.09) | .95 (.07) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; HRQoL, overall health related quality of life utility score

Higher scores = better functioning

Table 19 shows that children with SRM had significantly lower (poorer) HUI3 overall HRQoL scores than Comparisons (*Mdn* = .53 vs .95, *U* = 244.5, *p* < .001) and significantly lower (poorer) than children with LGCA (*Mdn* = .92, *U* = 355.0, *p* = .001). Children with LGCA did not have significantly lower (poorer) HUI3 overall HRQoL scores than Comparisons (*U* = 533.5, *p* = .138).

Table 19. Mean differences and confidence intervals for the parent-report HUI3 overall health related quality of life scores between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | .38 | .15 to .53 | < .001 |
| LGCA vs Comparison | .03 | .00 to .12 | .138 |
| SRM vs LGCA | .21 | .05 to .44 | .001 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p values for Mann-Whitney *U* tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

Table 20 reveals that children with SRM had a significantly lower (poorer) hearing utility score than Comparisons (*Mdn* = 1.00 vs 1.00, *U* = 589.0, *p* < .018), a lower (poorer) speech score (*Mdn* = 1.00 vs 1.00, *U* = 448.0, *p* < .001), a lower (poorer) ambulation score

(*Mdn* = .83 vs 1.00, *U* = 276.5, *p* < .001), a lower (poorer) dexterity score (*Mdn* = 1.00 vs 1.00, *U* = 399.0, *p* < .001), a lower (poorer) emotion score (*Mdn* = .96 vs 1.00, *U* = 510.5, *p* = .029), a lower (poorer) cognition score (*Mdn* = .92 vs 1.00, *U* = 412.5, *p* = .001), and a lower (i.e. more) pain score (*Mdn* = .92 vs 1.00, *U* = 465.0, *p* = .010). Compared with the LGCA group, children with SRM had a significantly lower (poorer) vision utility score than Comparisons (*Mdn* = 1.00 vs 1.00, *U* = 539.0, *p* = .043), a lower (poorer) hearing score (*Mdn* = 1.00 vs 1.00, *U* = 542.5, *p* = .023), a lower (poorer) speech score (*Mdn* = 1.00 vs 1.00, *U* = 479.5, *p* = .026), a lower (poorer) ambulation score (*Mdn* = .83 vs 1.00, *U* = 372.0, *p* = .001), a lower (poorer) emotion score (*Mdn* = .96 vs 1.00, *U* = 481.0, *p* = .049), and a somewhat lower (i.e. more) pain score (*Mdn* = .92 vs 1.00, *U* = 424.5, *p* = .010).

Table 20. Mean differences and confidence intervals for the parent-report HUI3 single attribute utility scores between the SRM group and the Comparison and LGCA groups at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| **SRM vs Comparison** | | | |
| Vision | .01 | -.01 to .00 | .104 |
| Hearing | .06 | .01 to .11 | .018 |
| Speech | .09 | .04 to .14 | < .001 |
| Ambulation | .34 | .22 to .46 | < .001 |
| Dexterity | .12 | .05 to .19 | < .001 |
| Emotion | .06 | -.01 to .14 | .029 |
| Cognition | .12 | .03 to .19 | .001 |
| Pain | .11 | .03 to .20 | .010 |
| **SRM vs LGCA** | | | |
| Vision | .02 | -.06 to .01 | .043 |
| Hearing | .06 | .01 to .11 | .023 |
| Speech | .06 | .00 to .12 | .026 |
| Ambulation | .24 | .10 to .38 | .001 |
| Dexterity | .06 | -.02 to .15 | .076 |
| Emotion | .07 | -.00 to .14 | .049 |
| Cognition | .04 | -.05 to .13 | .266 |
| Pain | .11 | .02 to .20 | .010 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p values for Mann-Whitney *U* tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

## 3.6. COMPARISON OF BEHAVIOUR BETWEEN THE THREE GROUPS AT TIME 1

### 3.6.1. Child-report of SDQ at Time 1

Table 21 shows that there was no significant effect of group on SDQ Total difficulties score ($F(2, 104) = 0.57$, $p = .568$).

Table 21. Scale descriptive statistics for the child-report SDQ Total Difficulties scores and subscales showing means and standard deviations in each group at Time 1

| | **SRM n=35** | **LGCA n=34** | **Comparison n=38** |
|---|---|---|---|
| Total Difficulties | 10.1 (5.2) | 10.0 (5.8) | 8.8 (5.5) |
| Emotional symptoms | 3.6 (2.5) | 3.0 (2.3) | 2.2 (2.0) |
| Conduct problems | 1.7 (1.5) | 1.9 (1.9) | 1.8 (1.6) |
| Hyperactivity/inattention | 3.0 (1.7) | 3.5 (2.5) | 3.3 (2.5) |
| Peer problems | 1.8 (1.5) | 1.5 (1.3) | 1.5 (1.4) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

Higher scores = poorer functioning

### 3.6.2. Parent-report of SDQ at Time 1

Table 22 reveals that there was no significant effect of group on SDQ Total difficulties score ($H(2) = 3.841$, $p = .147$).

Table 22. Scale descriptive statistics for the parent-report SDQ Total Difficulties scores and subscales showing means and standard deviations in each group at Time 1

| | **SRM n=36** | **LGCA n=35** | **Comparison n=38** |
|---|---|---|---|
| Total Difficulties | 10.9 (6.9) | 9.8 (6.0) | 8.1 (5.3) |
| Emotional symptoms | 3.7 (2.9) | 3.3 (2.5) | 1.8 (2.0) |
| Conduct problems | 1.9 (1.9) | 1.7 (1.4) | 0.8 (1.5) |
| Hyperactivity | 3.3 (2.1) | 3.5 (2.3) | 3.6 (2.4) |
| Peer problems | 2.1 (1.7) | 1.3 (1.7) | 1.9 (1.6) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

Higher scores = poorer functioning

### 3.6.3. Teacher-report of SDQ at Time 1

Table 23 reveals that there was a significant effect of group on the SDQ Total difficulties score ($H(2) = 13.475$, $p = .001$).

Table 23. Scale descriptive statistics for the teacher-report SDQ Total Difficulties scores showing means and standard deviations in each group at Time 1

| | **SRM n=33** | **LGCA n=32** | **Comparison n=37** |
|---|---|---|---|
| Total Difficulties | 8.9 (5.4) | 6.2 (5.1) | 4.7 (5.0) |
| Emotional symptoms | 4.0 (2.9) | 1.8 (2.2) | 1.0 (1.7) |
| Conduct problems | 0.5 (1.1) | 0.8 (1.4) | 0.5 (1.4) |
| Hyperactivity/inattention | 3.0 (2.4) | 2.7 (2.2) | 2.0 (2.4) |
| Peer problems | 1.4 (1.4) | 0.8 (1.1) | 1.2 (1.6) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

Higher scores = poorer functioning

Table 24 demonstrates that children with SRM had a significantly higher (poorer) SDQ Total difficulties score than Comparisons (*Mdn* = 9.0 vs 3.0, *U* = 310.5, *p* < .001) and higher (poorer) than the LGCA group (*Mdn* = 5.0, *U* = 356.0, *p* = .024).

Table 24. Mean differences and confidence intervals for the teacher-report SDQ Total Difficulties scores between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | 4.3 | 1.8 to 6.7 | <.001 |
| LGCA vs Comparison | 1.5 | -0.9 to 3.9 | .129 |
| SRM vs LGCA | 2.8 | 0.2 to 5.4 | .024 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

*p values for Mann-Whitney *U* tests

Table 25 shows that children with SRM had a significantly higher (poorer) Emotional symptoms score than Comparisons (*Mdn* = 4.0 vs 0.0, *U* = 208.0, *p* < .001) and a higher (poorer) hyperactivity/inattention score (*Mdn* = 3.0 vs 1.0, *U* = 445.0, *p* = .047) but there were no significant differences between the two groups for Conduct and Peer problems. Children with SRM also had a significantly higher (poorer) Emotional symptoms score than children with LGCA (*Mdn* = 1.0, *U* = 282.0, *p* = .001) but there were no significant differences between the two groups for Conduct, Hyperactivity/inattention or Peer problems.

Table 25. Mean differences and confidence intervals for the teacher-report Emotional, Social and School functioning scales of the PedsQL between the SRM group and the Comparison and LGCA groups at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| **SRM vs Comparison** | | | |
| Emotional symptoms | 3.0 | 1.9 to 4.1 | <.001 |
| Conduct problems | 0.1 | -0.5 to 0.7 | .724 |
| Hyperactivity/inattention | 1.0 | -0.2 to 2.2 | .047 |
| Peer problems | 0.2 | -0.5 to 1.0 | .280 |
| **SRM vs LGCA** | | | |
| Emotional symptoms | 2.2 | 0.9 to 3.5 | .001 |
| Conduct problems | 0.3 | -0.4 to 0.9 | .489 |
| Hyperactivity/inattention | 0.3 | -0.8 to 1.5 | .681 |
| Peer problems | 0.6 | -0.1 to 1.2 | .101 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval.

*p values for Mann-Whitney *U* tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

## 3.7. COMPARISON OF COGNITIVE FUNCTIONING BETWEEN THE THREE GROUPS AT TIME 1

### 3.7.1. Parent-report of BRIEF at T1

Table 26 shows that there was no significant effect of group on BRIEF GEC score ($H(2) = 4.396$, $p = .111$).

Table 26. Scale descriptive statistics for the parent-report BRIEF Global Executive Functioning Composite scores and subscale scores showing means and standard deviations in each group at Time 1

| | **SRM n=36** | **LGCA n=35** | **Comparison n=38** |
|---|---|---|---|
| GEC | 55.6 (12.5) | 56.0 (11.3) | 51.2 (10.0) |
| BRI | 56.3 (13.1) | 55.3 (12.0) | 49.7 (9.9) |
| Inhibit | 49.9 (9.4) | 51.0 (10.4) | 49.4 (9.6) |
| Shift | 57.1 (15.0) | 55.5 (12.3) | 49.6 (11.4) |
| Emotional control | 58.4 (12.8) | 57.4 (13.0) | 49.9 (9.5) |
| MI | 55.5 (12.3) | 55.7 (10.8) | 51.8 (10.2) |
| Initiate | 55.8 (13.0) | 55.4 (10.6) | 50.8 (9.5) |
| Working memory | 56.8 (14.1) | 56.4 (12.5) | 51.8 (10.1) |
| Plan/organise | 53.8 (11.9) | 55.4 (11.6) | 52.4 (10.9) |
| Organisation of materials | 49.8 (10.0) | 53.2 (8.7) | 52.0 (10.7) |
| Monitor | 53.7 (11.8) | 54.0 (11.5) | 49.7 (9.8) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; GEC, Global Executive Composite score; BRI, Behavioral Regulation Index; MI, Metacognition Index

Higher scores = poorer functioning

### 3.7.2. Teacher-report of BRIEF at Time 1

Table 27 reveals that there was a significant effect of group on the GEC score ($H(2) = 8.246$, $p = .016$).

Table 27. Scale descriptive statistics for the teacher-report of the BRIEF Global Executive Functioning Composite scores and subscale scores showing means and standard deviations in each group at Time 1

| | **SRM n=31** | **LGCA n=32** | **Comparison n=37** |
|---|---|---|---|
| GEC | 59.1 (13.3) | 56.9 (14.4) | 51.0 (9.0) |
| BRI | 56.7 (11.0) | 55.4 (12.5) | 50.6 (8.7) |
| Inhibit | 50.1 (6.9) | 52.0 (10.6) | 50.9 (9.3) |
| Shift | 59.9 (13.6) | 57.4 (13.6) | 50.6 (8.2) |
| Emotional control | 59.8 (14.2) | 55.2 (12.3) | 50.5 (8.0) |
| MI | 58.6 (14.5) | 57.0 (14.6) | 51.1 (8.8) |
| Initiate | 58.8 (14.4) | 57.3 (14.3) | 50.4 (8.5) |
| Working memory | 63.3 (18.2) | 57.8 (16.9) | 50.5 (8.4) |
| Plan/organise | 57.2 (12.3) | 56.0 (13.1) | 52.5 (9.3) |
| Organisation of materials | 54.5 (13.3) | 52.5 (11.8) | 49.9 (8.0) |
| Monitor | 55.7 (11.6) | 53.8 (11.6) | 51.3 (9.9) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; GEC, Global Executive Composite score; BRI, Behavioral Regulation Index; MI, Metacognition Index

Higher scores = poorer functioning

Table 28 shows that children with SRM had a significantly higher (poorer) GEC score than Comparisons (*Mdn* = 56.0 vs 48.0, *U* = 350.0, *p* = .006) but not significantly higher (poorer) than the LGCA group (*Mdn* = 52.5, *U* = 430.0, *p* = .364). Children with LGCA did not have a significantly poorer GEC score than Comparisons (*U* = 433.0, *p* = .055).

Table 28. Mean differences and confidence intervals for the teacher-report BRIEF Global Executive Functioning Composite scores between each group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| SRM vs Comparison | 8.1 | 2.4 to 13.7 | .006 |
| LGCA vs Comparison | 5.9 | -0.0 to 11.8 | .055 |
| SRM vs LGCA | 2.2 | -4.8 to 9.2 | .364 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

*p values for Mann-Whitney *U* tests

Table 29 demonstrates that children with SRM had a significantly higher (poorer) BRI score than Comparisons (*Mdn* = 54.0 vs 47.0, *U* = 369.5, *p* = .007) and also a higher (poorer) MI score than Comparisons (*Mdn* = 56.0 vs 49.0, *U* = 409.0, *p* = .043).

Table 29. Mean differences and confidence intervals for the teacher-report BRIEF Behavioural Regulation and Metacognition scores between the SRM group and the Comparison group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| Behavioural Regulation | 6.0 | 1.3 to 10.7 | .007 |
| Metacognition | 7.4 | 1.4 to 13.4 | .043 |

*p values for Mann-Whitney *U* tests

Table 30 shows that the SRM group had a significantly higher (poorer) Shift score than Comparisons (*Mdn* = 61.0 vs 49.0, *U* = 349.5, *p* = .003), a higher (poorer) Emotional control score (*Mdn* = 52.0 vs 46.0, *U* = 346.0, *p* = .003), a higher (poorer) Initiate score (*Mdn* = 58.0 vs 50.0, *U* = 405.0, *p* = .024), and a higher (poorer) Working memory score (*Mdn* = 60.0 vs 48.0, *U* = 318.0, *p* = .001).

Table 30. Mean differences and confidence intervals for the teacher-report of the BRIEF subdomains between the SRM group and the Comparison group at Time 1

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| Inhibit | 0.9 | -3.1 to 4.9 | .913 |
| Shift | 9.3 | 3.8 to 14.9 | .003 |
| Emotional control | 9.3 | 3.6 to 15.0 | .003 |
| Initiate | 8.4 | 2.6 to 14.2 | .024 |
| Working memory | 12.9 | 5.8 to 20.0 | .001 |
| Plan/organise | 4.7 | -0.6 to 10.0 | .133 |
| Organisation of materials | 4.5 | -0.9 to 10.0 | .169 |
| Monitor | 4.4 | -0.8 to 9.6 | .069 |

*p values for Mann-Whitney *U* tests

### 3.7.3. WISC®-IV UK at Time 1

Table 31 reveals that there was a significant effect of group on IQ ($F(2, 101) = 9.2$, $p < .001$).

Table 31. Scale descriptive statistics for the WISC Full Scale IQ and subscales showing means and standard deviations in each group at Time 1

| | **SRM n=32** | **LGCA n=34** | **Comparison n=38** |
|---|---|---|---|
| Full Scale IQ (FSIQ) | 86.2 (17.7) | 93.2 (15.0) | 101.9 (13.5) |
| Verbal comprehension (VCI) | 90.7 (14.1) | 96.5 (24.0) | 101.1 (12.1) |
| Perceptual reasoning (PRI) | 91.0 (16.9) | 95.3 (14.7) | 103.4 (12.0) |
| Working memory (WMI) | 90.8 (16.9) | 96.0 (13.7) | 99.4 (14.3) |
| Processing speed (PSI) | 79.4 (13.8) | 87.3 (16.3) | 98.7 (12.9) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma

Higher scores = better functioning

Table 32 demonstrates that IQ scores in the Comparison group were significantly higher (better) than those in the SRM group ($t(101) = 4.3$, $p < .001$) and higher (better) than those in the LGCA group ($t(101) = 2.4$, $p = .019$). IQ scores in the SRM group were not significantly lower (poorer) than those in the LGCA group ($t(101) = 1.9$, $p = .065$).

Table 32. Mean differences and confidence intervals for the WISC Full Scale IQ scores between each group at Time 1

| | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| SRM vs Comparison | 15.7 | 8.2 to 23.1 | < .001 |
| LGCA vs Comparison | 8.6 | 1.9 to 15.3 | .019 |
| SRM vs LGCA | 7.0 | -1.0 to 15.1 | .065 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval

Table 33 reveals that for comparisons between the SRM and Comparison groups, VCI ($t(69) = 3.339$, $p = .001$), PRI ($t(56.8$, $p = .001$), WMI ($t(69) = 2.324$, $p = .023$) and PSI ($t(68) = 6.036$, $p < .001$) scores were significantly lower (poorer) in the SRM group. For comparisons between the LGCA and Comparison groups, there was no significant difference in VCI ($t(70) = 1.034$, $p = .305$) or WMI ($t(70) = 1.036$, $p = .304$), but there was a difference in PRI ($t(70) = 2.580$, $p = .012$), and PSI ($t(70) = 3.299$, $p = .002$).

Table 33. Mean differences and confidence intervals for the subdomains of the WISC between the Comparison group and SRM and LGCA groups at Time 1

| | Mean difference | 95% CI | *P** |
|---|---|---|---|
| **SRM vs Comparison** | | | |
| Verbal comprehension | 10.4 | 4.2 to 16.6 | .001 |
| Perceptual reasoning | 12.4 | 5.3 to 19.5 | .001 |
| Working memory | 8.6 | 1.2 to 16.0 | .023 |
| Processing speed | 19.2 | 12.9 to 25.6 | <.001 |
| **LGCA vs Comparison** | | | |
| Verbal comprehension | 4.6 | -4.2 to 13.3 | .305 |
| Perceptual reasoning | 8.1 | 1.8 to 14.4 | .012 |
| Working memory | 3.4 | -3.2 to 10.0 | .304 |
| Processing speed | 11.4 | 4.5 to 18.2 | .002 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval

## 3.8. SUMMARY OF GROUP COMPARISONS OF QOL AT TIME 1

### 3.8.1. PedsQL

As predicted, at T1, by child- and parent-report, children with an SRM had a significantly poorer overall QoL than children with an LGCA and Comparisons. This overall poorer QoL was due to poorer physical health, compared with children with LGCA and also Comparisons, and poorer psychosocial health, compared with Comparisons, by child report, and compared with Comparisons and children with an LGCA, by parent-report. Social and school functioning accounted for this difference in psychosocial health, compared to Comparisons, and by parent-report, also emotional functioning. By parent-report, social and school functioning, but not emotional functioning, also accounted for the difference between the SRM and LGCA groups.

As predicted, compared with Comparisons, children with an LGCA had a significantly poorer overall QoL which was due to significantly poorer physical health, and in addition psychosocial health by parent-report only. Emotional, social and school functioning accounted for this difference in psychosocial health. Poorer scores in the LGCA group compared with those in the Comparison group indicates that damage to the cerebellum per se may have accounted for this difference caused by the presence of the tumour and

surgery.

### 3.8.2. HUI

By child-report, contrary to prediction, children with an SRM did not have a significantly poorer overall health status than children with an LGCA, but as predicted, it was poorer when compared with Comparisons. This overall poorer health status was due to significantly poorer ambulation, dexterity and more pain.

As predicted, according to parent-report, children with an SRM had a significantly poorer overall health status compared with Comparisons due to significantly poorer hearing, speech, ambulation, dexterity, emotion, cognition and more pain. Children with an SRM also had a significantly poorer overall health status compared with children with an LGCA due to significantly poorer vision, hearing, speech, ambulation, emotion, and more pain. Contrary to prediction, by child- and parent-report, children with an LGCA did not have a significantly poorer overall health status compared with Comparisons.

### 3.8.3. SDQ

Contrary to the prediction, according to child- and parent-report, children with an SRM did not have significantly poorer behaviour than children with an LGCA or Comparisons, and children with an LGCA did not have significantly poorer behaviour than Comparisons.

Consistent with the prediction according to teacher-report children with SRM had significantly poorer behaviour than Comparisons and the LGCA group. This was due to children in the SRM group having significantly more emotional symptoms than Comparisons and more hyperactivity and inattention, but there were no significant differences between the two groups for conduct and peer problems. Children with SRM also had a significantly higher (poorer) Emotional symptoms score than children with LGCA but there were no significant differences between the two groups for Conduct, Hyperactivity/inattention or Peer problems. By teacher-report children with an LGCA did not have significantly poorer behaviour than Comparisons.

### 3.8.4. BRIEF and WISC®-IV UK

By parent-report, contrary to prediction, children with an SRM did not have significantly poorer executive functioning than children with an LGCA or Comparisons, and children

with an LGCA did not have poorer executive functioning than Comparisons.

By teacher-report, as predicted, children with an SRM had significantly poorer executive functioning than Comparisons. Both behavioural regulation and metacognition accounted for this difference. Specifically children with an SRM had significant problems with shifting attention, controlling their emotions, initiating actions, and with working memory.

There was no significant difference in executive functioning between children with an SRM and those with an LGCA and children with an LGCA did not have poorer executive functioning than Comparisons.

As predicted, children with an SRM had a significantly lower IQ than Comparisons and so did children with an LGCA. Contrary to prediction, children with an SRM did not have IQ scores that were lower than children with an LGCA. The difference in IQ between the SRM and Comparison groups were due to significantly poorer verbal comprehension, perceptual reasoning, working memory, and processing speed. The difference in IQ between the LGCA and Comparison groups was due to poorer perceptual reasoning and processing speed in the LGCA group.

# CHAPTER 4 RESULTS: CHANGES IN QOL OVER TIME

## 4.1. WITHIN GROUP CHANGES IN QOL OVER TIME

### 4.1.1. Child-report of PedsQL over time

Figure 2 and table 34 show that PedsQL Total scores increased significantly over time in the SRM group ($F(2,50) = 7.114$, $p = .002$) and in the Comparison group ($F(2,70) = 5.423$, $p = .006$) but not in the LGCA group ($F(2,54) = 2.824$, $p = .068$).

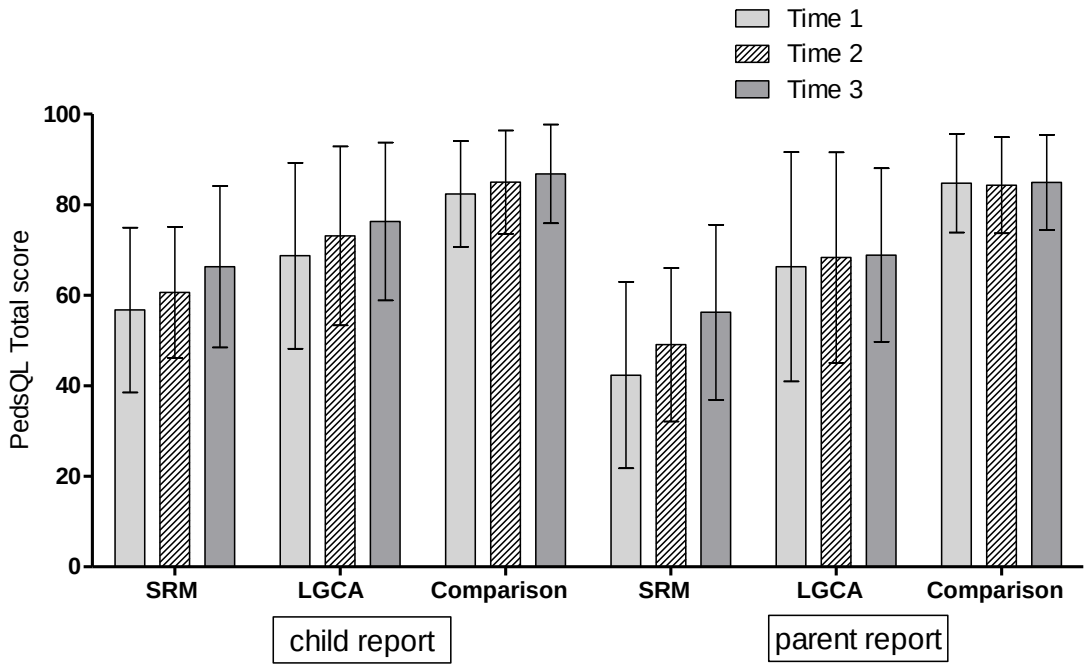


Figure 2. Child- and parent-report PedsQL Total mean scores and standard deviations arranged by group and time. Higher scores = better functioning. (SRM n = 26, LGCA n = 28, Comparison n = 36.)

Table 34. Complete case analysis showing means and standard deviations for child- and parent-report PedsQL Total scores for each group at each time point and numbers of children in the at risk category

| | **SRM n=26** | | | **LGCA n=28** | | | **Comparison n=36** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Child** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** |
| Mean | 56.7 | 60.6 | 66.3 | 68.7 | 73.1 | 76.3 | 82.4 | 85.0 | 86.8 |
| (SD) | (18.2) | (14.5) | (17.8) | (20.5) | (19.8) | (17.4) | (11.7) | (11.4) | (10.9) |
| No. (%) | 19 | 19 | 15 | 13 | 9 | 7 | 4 | 7 | 2 |
| at risk | (73.1) | (73.1) | (57.7) | (46.4) | (32.1) | (25.0) | (11.1) | (19.4) | (5.6) |
| **Parent** | | | | | | | | | |
| Mean | 42.3 | 49.1 | 56.2 | 66.3 | 68.3 | 68.9 | 84.8 | 84.3 | 84.9 |
| (SD) | (20.6) | (17.0) | (19.3) | (25.3) | (23.3) | (19.2) | (10.9) | (10.6) | (10.5) |
| No. (%) | 22 | 21 | 17 | 10 | 12 | 10 | 3 | 2 | 3 |
| at risk | (84.6) | (80.8) | (65.4) | (35.7) | (42.9) | (35.7) | (8.3) | (5.6) | (8.3) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebellar astrocytoma; T1, time 1; T2, time 2; T3, time 3.

Table 35 reveals that in the SRM group PedsQL Total scores were significantly higher at T3 compared with T1 ($F(1, 25) = 13.672$, $p = .001$), and at T3 compared with T2 ($F(1,25) = 6.174$, $p = .020$) but not at T2 compared with T1 ($F(1,25) = 1.986$, $p = .171$). In the Comparison group PedsQL Total scores were significantly higher at T3 compared with T1 ($F(1,35) = 7.693$, $p = .009$) and at T2 compared with T1 ($F(1,35) = 4.443$, $p = .042$) but not at T3 compared with T2 ($F(1,35) = 2.384$, $p = .132$).

Table 35. Mean differences and confidence intervals for the child-report PedsQL Total scores between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the SRM and Comparison groups

| | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| **SRM** | | | |
| T1 vs T3 | 9.6 | 4.2 to 14.9 | .001 |
| T1 vs T2 | 3.9 | -1.8 to 9.6 | .171 |
| T2 vs T3 | 5.7 | 1.0 to 10.4 | .020 |
| **Comparison** | | | |
| T1 vs T3 | 4.4 | 1.2 to 7.7 | .009 |
| T1 vs T2 | 2.6 | 0.1 to 5.1 | .042 |
| T2 vs T3 | 1.8 | -0.6 to 4.3 | .132 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

Figure 3 and table 36 demonstrate that Physical Health scores in the SRM group were significantly higher at T3 compared with T1 (*Mdn* = 57.8 vs 37.5, *T* = 26.00, *p*< .001) and at T3 compared with T2 (*Mdn* = 51.6, *T* = 48.50, *p* = .004) but in the Comparison group there was no difference between T1 and T3 (*Mdn* = 89.1 vs 93.8, *T* = 156.00, *p* = .070) or between T1 and T2 (*Mdn* = 90.6, *T* = 174.00, *p* = .144).

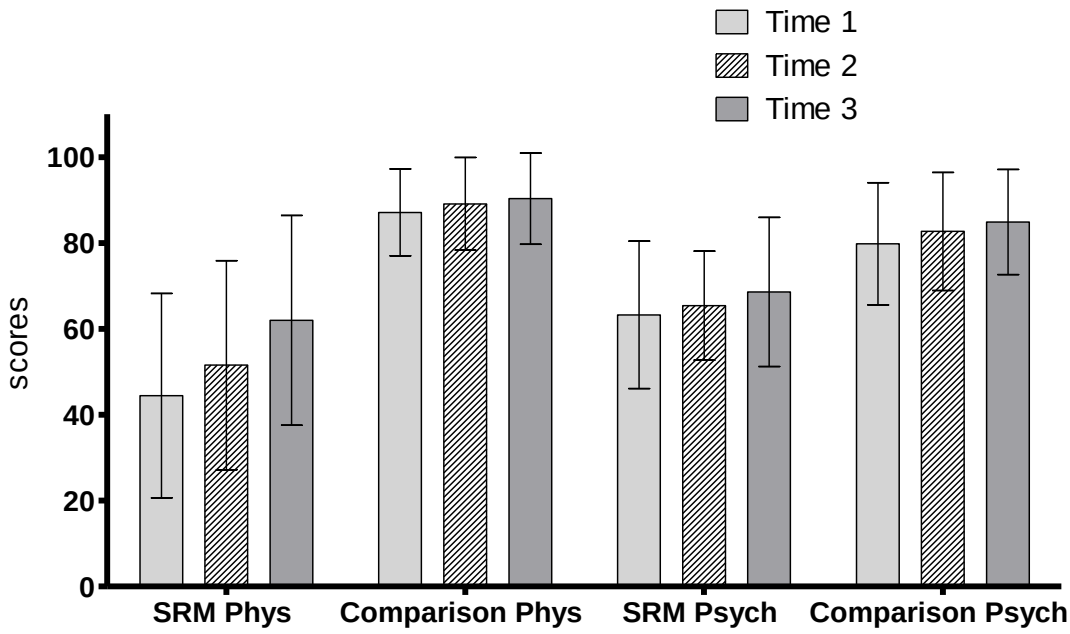


Figure 3. Child-report PedsQL Physical Health and Psychosocial Health mean scores and standard deviations arranged by group and time. Higher scores = better functioning. (SRM n = 26, Comparison n = 36.)

Table 36. Mean differences and confidence intervals for the child-report Physical Health Summary scores of the PedsQL between Time 1 and Time 3, and Time 2 and Time 3 for the SRM group and between Time 1 and Time 3, and Time 1 and Time 2 for the Comparison group

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| **SRM** | | | |
| T1 vs T3 | 17.5 | 9.3 to 25.8 | <.001 |
| T2 vs T3 | 10.5 | 4.1 to 16.8 | .004 |
| **Comparison** | | | |
| T1 vs T3 | 3.2 | -0.3 to 6.7 | .070 |
| T1 vs T2 | 2.0 | -1.0 to 4.0 | .144 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests

Figure 3 and table 37 show that in the SRM group Psychosocial Health scores increased significantly between T1 and T3 ($t(25) = 2.149$, $p = .041$) but not between T2 and T3 ($t(25) = 1.241$, $p = .226$) and in the Comparison group Psychosocial Health scores increased significantly between T1 and T3 (*Mdn* = 79.2 vs 85.8, $T = 162.50$, $p = .007$) but not between T1 and T2 (*Mdn* = 85.8, $T = 180.00$, $p = .072$).

Table 37. Mean differences and confidence intervals for the child-report Psychosocial Health Summary scores of the PedsQL between Time 1 and Time 3, and Time 2 and Time 3 for the SRM group and between Time 1 and Time 3, and Time 1 and Time 2 for the Comparison group

| | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| **SRM** | | | |
| T1 vs T3 | 5.3 | 0.2 to 10.4 | .041 |
| T2 vs T3 | 3.1 | -2.1 to 8.4 | .226 |
| **Comparison** | | | |
| T1 vs T3 | 5.1 | 1.3 to 8.9 | .007* |
| T1 vs T2 | 2.9 | -0.2 to 6.1 | .072* |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests

Figure 4 and table 38 reveal that in the SRM group Emotional functioning scores did not significantly increase between T1 and T3 ($t(25) = 0.389$, $p = .700$), nor did they increase for Social functioning (*Mdn* = 67.5 vs 70.0, $T = 86.50$, $p = .191$) but they did for School

functioning (*Mdn* = 55.0 vs 60.0, *T* = 57.50, *p* = .014). In the Comparison group Emotional functioning scores did increase significantly between T1 and T3 (*Mdn* = 80.0 vs 85.0, *T* = 109.50, *p* = .006) and so did Social functioning (*Mdn* = 85.0 vs 95.0, *T* = 49.50, *p* = .001) but School functioning did not (*Mdn* = 80.0 vs 85.0, *T* = 201.00, *p* = .719).

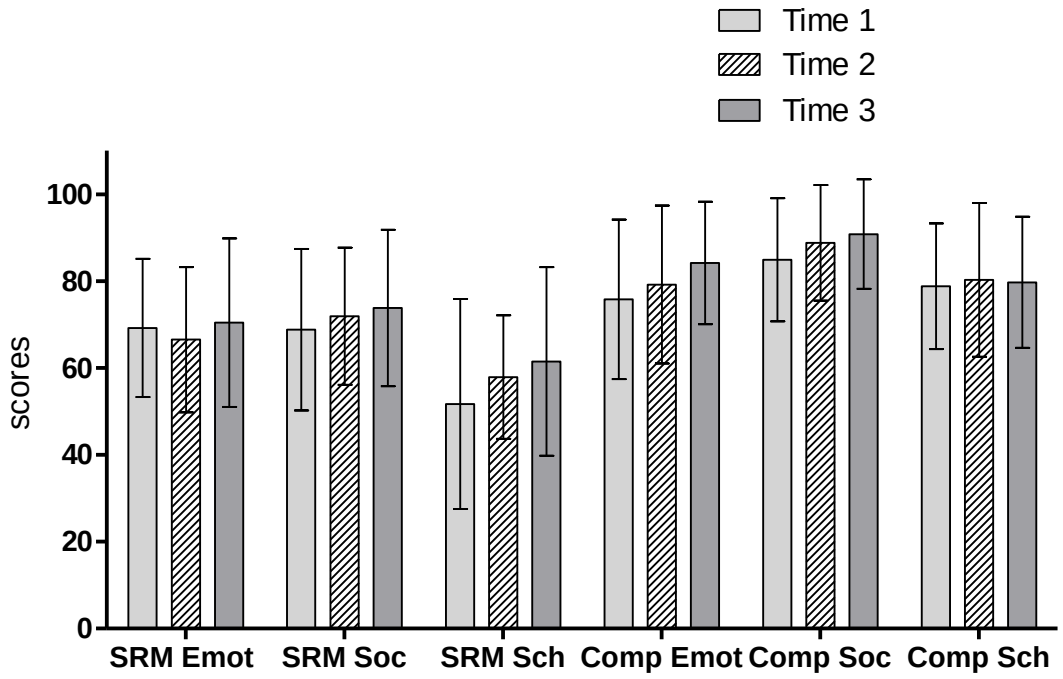


Figure 4. Child-report PedsQL Emotional, Social and School functioning mean scores and standard deviations arranged by group and time. Higher scores = better functioning. (SRM n = 26, Comparison n = 36.)

Table 38. Mean differences and confidence intervals for the child-report Emotional, Social and School functioning subscale scores of the PedsQL between Time 1 and Time 3 for the SRM and Comparison groups

| T1 vs T3 | Mean difference | 95% CI | *P* |
|---|---|---|---|
| **SRM** | | | |
| Emotional Functioning | 1.2 | -5.0 to 7.3 | .700* |
| Social Functioning | 5.0 | -2.3 to 12.3 | .191 |
| School Functioning | 9.8 | 2.3 to 17.3 | .014 |
| **Comparison** | | | |
| Emotional Functioning | 8.3 | 2.5 to 14.1 | .006 |
| Social Functioning | 6.0 | 2.5 to 9.4 | .001 |
| School Functioning | 1.0 | -3.7 to 5.7 | .719 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T3, Time 3

*$p$ value for dependent $t$ test

### 4.1.2. Parent-report of PedsQL over time

Figure 2 and table 34 demonstrate that PedsQL Total scores changed significantly over time in the SRM group ($\chi^2(2) = 18.554$, $p < .001$) but not in the LGCA group ($\chi^2(2) = 0.019$, $p = .991$) or the Comparison group ($\chi^2(2) = 0.273$, $p = .872$). Table 39 shows that in the SRM group PedsQL Total scores increased significantly between T1 and T3 (*Mdn* = 40.8 vs 58.7, $T = 21.00$, $p <.001$) between T1 and T2 (*Mdn* = 44.0, $T = 73.50$, $p = .010$) and between T2 and T3 ($T = 63.0$, $p = .007$).

Table 39. Mean differences and confidence intervals for the parent-report PedsQL Total scores between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the SRM group

| SRM | Mean difference | 95% CI | *P** |
|---|---|---|---|
| T1 vs T3 | 13.8 | 7.2 to 20.6 | <.001 |
| T1 vs T2 | 3.9 | -1.8 to 9.6 | .010 |
| T2 vs T3 | 5.7 | 1.0 to 10.4 | .007 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

*$p$ value for Wilcoxon tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

Figure 5 and table 40 reveal that Physical Health scores changed significantly over time ($\chi^2(2) = 20.688$, $p < .001$). They increased significantly between T1 and T3 (*Mdn* = 20.3 vs 46.9, $T = 16.50$, $p < .001$), between T1 and T2 (*Mdn* = 32.8, $T = 39.0$, $p = .003$) and between T2 and T3 ($T = 40.0$, $p = .002$).

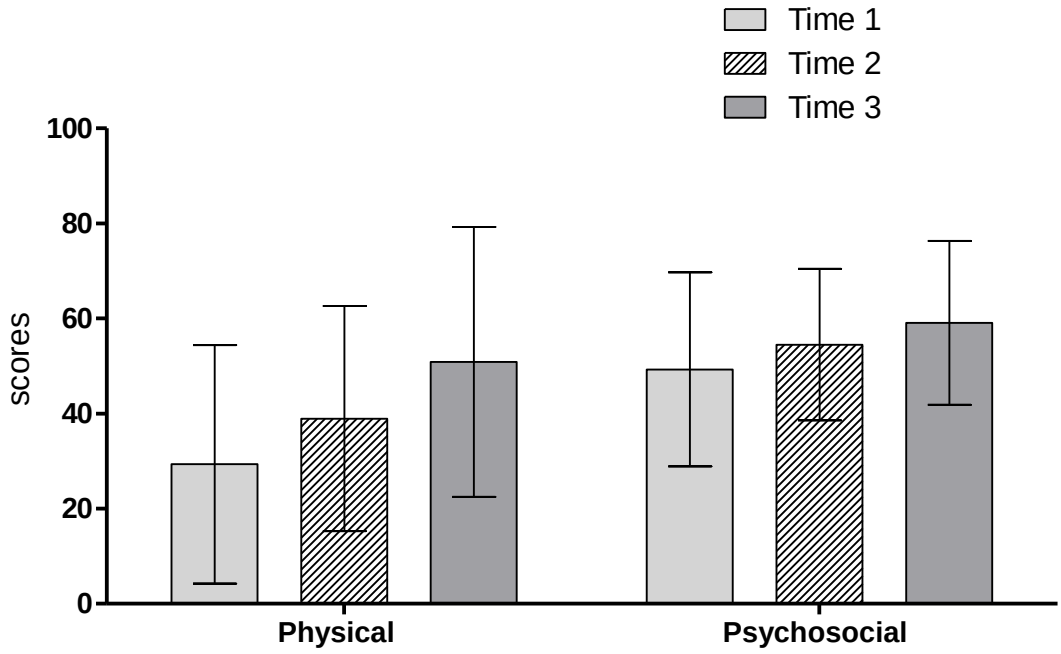


Figure 5. Parent-report PedsQL Physical Health and Psychosocial Health mean scores and standard deviations at each time point in the SRM group. Higher scores = better functioning. (n = 26)

Table 40. Mean differences and confidence intervals for the parent-report Physical Health Summary scores of the PedsQL between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the SRM group

| **SRM** | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| T1 vs T3 | 21.5 | 11.6 to 31.4 | <.001 |
| T1 vs T2 | 9.6 | 3.8 to 15.4 | .003 |
| T2 vs T3 | 11.9 | 4.7 to 19.1 | .002 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests

Figure 5 and table 41 demonstrate that Psychosocial Health scores changed significantly over time ($\chi^2(2) = 8.143$, $p = .017$). They increased significantly between T1 and T3 (*Mdn* = 49.2 vs 60.0, $T = 38.50$, $p = .002$) and between T1 and T2 (*Mdn* = 52.5, $T = 85.00$, $p = .037$) but not between T2 and T3 ($T = 104.50$, $p = .192$).

Table 41. Mean differences and confidence intervals for the parent-report Psychosocial Health Summary scores of the PedsQL between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the SRM group

| **SRM** | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| T1 vs T3 | 9.8 | 4.0 to 15.7 | .002 |
| T1 vs T2 | 5.2 | -0.5 to 10.9 | .037 |
| T2 vs T3 | 4.6 | -0.3 to 9.5 | .192 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

Figure 6 and table 42 demonstrate that Emotional functioning scores increased significantly between T1 and T3 (*Mdn* = 52.5 vs 65.0, *T* = 28.50, *p* = .002) but not between T1 and T2 (*t*(25) = 0.944, *p* =.354). Social functioning scores did not increase significantly between T1 and T3 (*t*(25) = 1.439, *p* =.163) nor between T1 and T2 (*Mdn* = 57.5 vs 60.0, *T* = 120.00, *p* = .832). School functioning scores increased significantly between T1 and T3 (*t*(25) = 3.699, *p* =.001) and between T1 and T2 (*t*(25) = 3.469, *p* =.002).

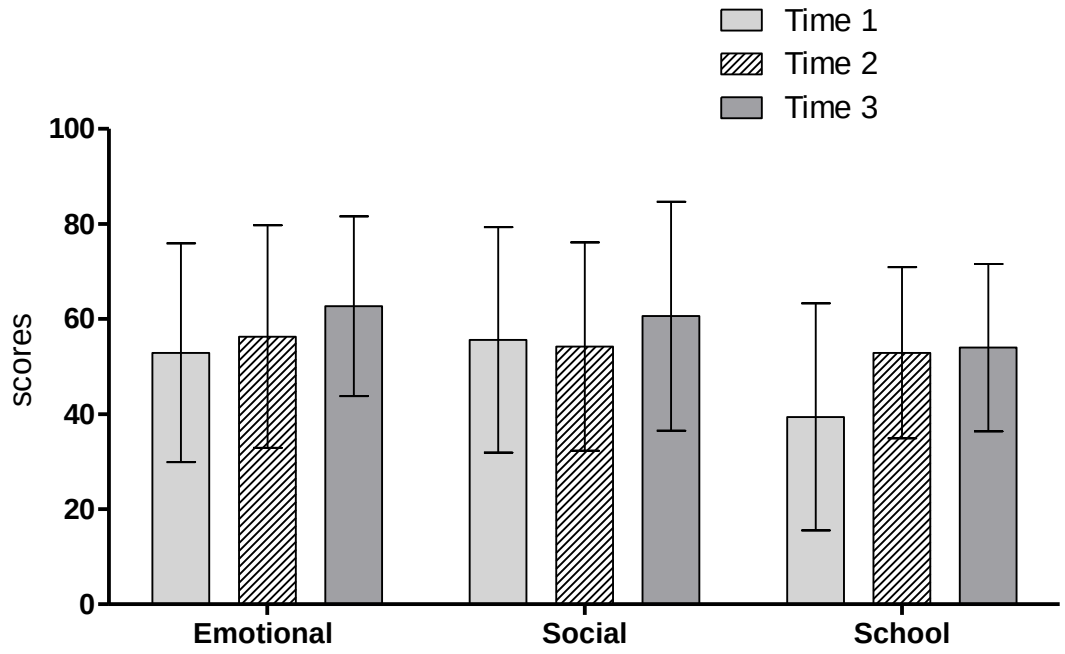


Figure 6. Parent-report PedsQL Emotional, Social and School functioning mean scores and standard deviations for the SRM group at each time point. Higher scores = better functioning. (n = 26.)

Table 42. Mean differences and confidence intervals for the parent-report Emotional, Social and School functioning subscale scores of the PedsQL between Time 1 and Time 3, and Time 1 and Time 2 for the SRM group

| **SRM** | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| **T1 vs T3** | | | |
| Emotional Functioning | 9.8 | 4.1 to 15.6 | .002* |
| Social Functioning | 5.0 | -2.2 to 12.2 | .163 |
| School Functioning | 14.6 | 6.5 to 22.8 | .001 |
| **T1 vs T2** | | | |
| Emotional Functioning | 3.5 | -4.1 to 11.0 | .163 |
| Social Functioning | 1.3 | -4.9 to 7.6 | .832* |
| School Functioning | 13.5 | 5.5 to 21.5 | .002 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T3, Time 3

**p* value for Wilcoxon test

## 4.2. WITHIN GROUP CHANGES IN HEALTH STATUS OVER TIME

### 4.2.1. Child-report of HUI over time

Figure 7 and table 43 show that HUI3 overall HRQoL scores changed significantly over time in the SRM group ($\chi^2(2) = 6.137$, $p = .046$) but not in the LGCA group ($\chi^2(2) = 0.766$, $p = .682$) nor in the Comparison group ($\chi^2(2) = 4.839$, $p = .089$).

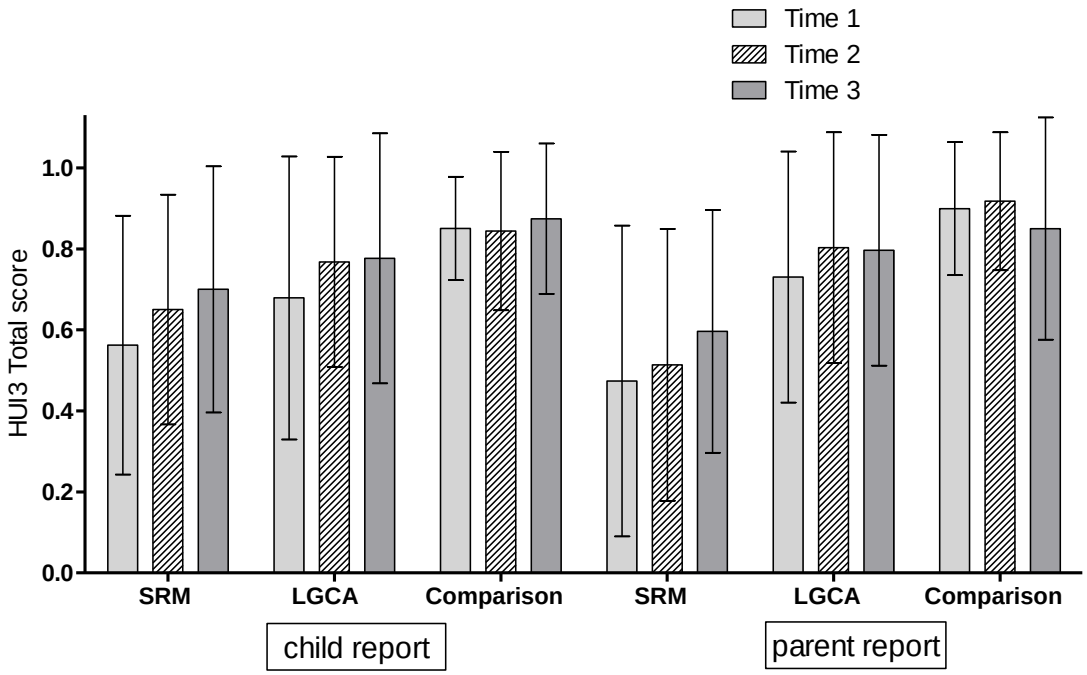


Figure 7. Child- and parent-report HUI3 overall health related quality of life mean scores and standard deviations arranged by group and time. Higher scores = better functioning. (SRM n = 27, LGCA n = 28, Comparison n = 36.)

Table 43. Complete case analysis showing means and standard deviations for child- and parent-report HUI overall HRQoL scores for each group at each time point

| | **SRM n=26** | | | **LGCA n=28** | | | **Comparison n=36** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Child** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** |
| Mean | 0.56 | 0.65 | 0.70 | 0.68 | 0.77 | 0.78 | 0.85 | 0.84 | 0.87 |
| (SD) | (0.32) | (0.29) | (0.30) | (0.35) | (0.26) | (0.31) | (0.13) | (0.20) | (0.19) |
| **Parent** | | | | | | | | | |
| Mean | 0.47 | 0.51 | 0.60 | 0.73 | 0.80 | 0.80 | 0.90 | 0.92 | 0.85 |
| (SD) | (0.38) | (0.34) | (0.30) | (0.31) | (0.28) | (0.29) | (0.16) | (0.17) | (0.27) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebellar astrocytoma; T1, time 1; T2, time 2; T3, time 3.

Table 44 shows that in the SRM group HUI3 overall HRQoL scores did not increase to a significant extent between T1 and T3 (*Mdn* = 0.55 vs 0.82, *T* = 99.00, *p* = .088) nor between T1 and T2 (*Mdn* =0.74, *T* = 124.00, *p* = .191) nor between T2 and T3 (*T* = 114.0, *p* = .192).

Table 44. Mean differences and confidence intervals for the child-report HUI3 overall health related quality of life scores between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the SRM group

| SRM | Mean difference | 95% CI | *P** |
|---|---|---|---|
| T1 vs T3 | 0.14 | -0.20 to 0.30 | .088 |
| T1 vs T2 | 0.09 | -0.04 to 0.21 | .191 |
| T2 vs T3 | 0.05 | -0.08 to 0.18 | .192 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests

### 4.2.2. Parent-report of HUI over time

Figure 7 and table 43 reveal that HUI3 overall HRQoL scores changed significantly over time in the SRM group ($\chi^2(2) = 10.738$, $p = .005$) but not in the LGCA group ($\chi^2(2) = 0.892$, $p = .640$) nor in the Comparison group ($\chi^2(2) = 3.449$, $p = .178$). Table 45 demonstrates that in the SRM group HUI3 overall HRQoL scores increased significantly between T1 and T3 (*Mdn* =0.53 vs 0.59, $T = 91.00$, $p = .019$), and between T2 and T3 (*Mdn* =0.48, $T = 56.0$, $p = .007$) but not between T1 and T2 ($T = 143.0$, $p = .600$).

Table 45. Mean differences and confidence intervals for the parent-report HUI3 overall health related quality of life scores between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the SRM group

| SRM | Mean difference | 95% CI | *P** |
|---|---|---|---|
| T1 vs T3 | 0.12 | -0.01 to 0.26 | .019 |
| T1 vs T2 | 0.04 | -0.08 to 0.16 | .600 |
| T2 vs T3 | 0.08 | -0.02 to 0.19 | .007 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

Figure 8 and table 46 demonstrate that between T1 and T3 vision decreased significantly (*Mdn* =1.00 vs 1.00, $T = 0.00$, $p = .034$), ambulation improved (*Mdn* =0.83 vs 0.83, $T = 10.00$, $p = .008$), and so did dexterity (*Mdn* =1.00 vs 1.00, $T = 2.50$, $p = .027$) and pain (*Mdn* =0.92 vs 1.00, $T = 34.00$, $p = .007$). Between T2 and T3 there were no significant changes in any of these scores.

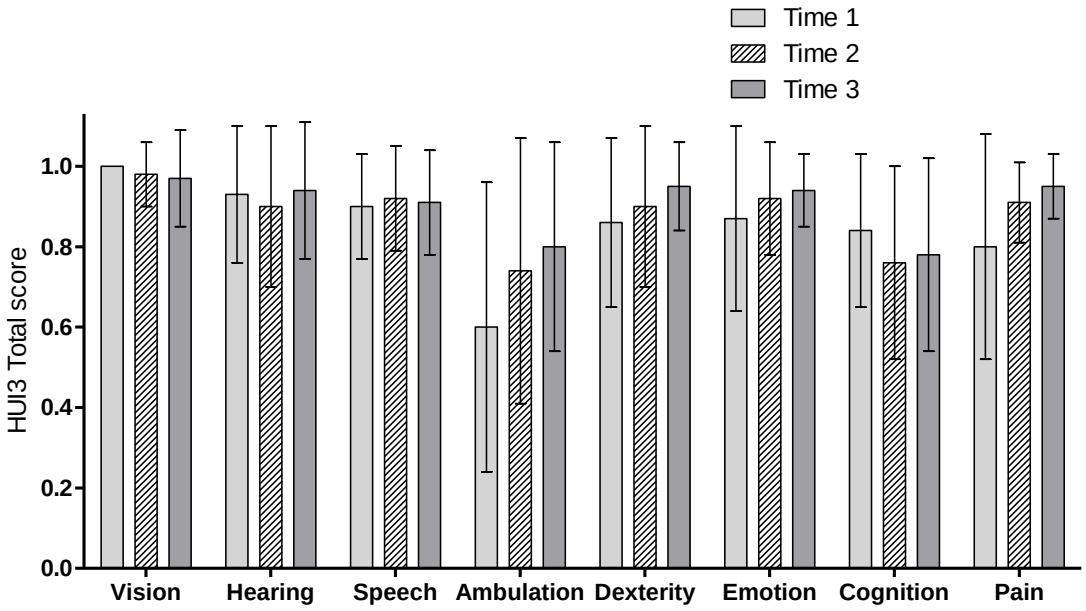


Figure 8. Parent-report HUI3 vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain single attribute mean utility scores and standard deviations at each time point in the SRM group. Higher scores = better functioning. (n = 27)

Table 46. Mean differences and confidence intervals for the parent-report HUI3 single attribute utility scores between Time 1 and Time 3, and Time 2 and Time 3 for the SRM group

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| **Vision** | | | |
| T1 vs T3 | 0.03 | -0.02 to 0.08 | .034 |
| T2 vs T3 | 0.01 | -0.04 to 0.07 | .336 |
| **Hearing** | | | |
| T1 vs T3 | 0.01 | -0.05 to 0.08 | .461 |
| T2 vs T3 | 0.04 | -0.01 to 0.09 | .102 |
| **Speech** | | | |
| T1 vs T3 | 0.01 | -0.04 to 0.05 | .605 |
| T2 vs T3 | 0.01 | -0.04 to 0.06 | .740 |
| **Ambulation** | | | |
| T1 vs T3 | 0.20 | 0.07 to 0.33 | .008 |
| T2 vs T3 | 0.06 | -0.03 to 0.16 | .198 |
| **Dexterity** | | | |
| T1 vs T3 | 0.09 | 0.01 to 0.16 | .027 |
| T2 vs T3 | 0.05 | -0.01 to 0.12 | .121 |
| **Emotion** | | | |
| T1 vs T3 | 0.06 | -0.03 to 0.15 | .321 |
| T2 vs T3 | 0.02 | -0.04 to 0.09 | .702 |
| **Cognition** | | | |
| T1 vs T3 | 0.06 | -0.02 to 0.15 | .139 |
| T2 vs T3 | 0.02 | -0.08 to 0.12 | .462 |
| **Pain** | | | |
| T1 vs T3 | 0.14 | 0.03 to 0.25 | .007 |
| T2 vs T3 | 0.04 | -0.00 to 0.08 | .080 |

Abbreviations: CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

## 4.3. WITHIN GROUP CHANGES IN BEHAVIOURAL FUNCTIONING OVER TIME

### 4.3.1. Child-report of SDQ over time

Figure 9 and table 47 show that SDQ Total Difficulties scores changed significantly over

time in the Comparison group ($F(2,60) = 7.266$, $p = .001$) but not in the SRM group ($F(2,46) = 0.175$, $p = .840$) nor in the LGCA group ($F(1.539, 36.924) = 0.164$, $p = .793$).

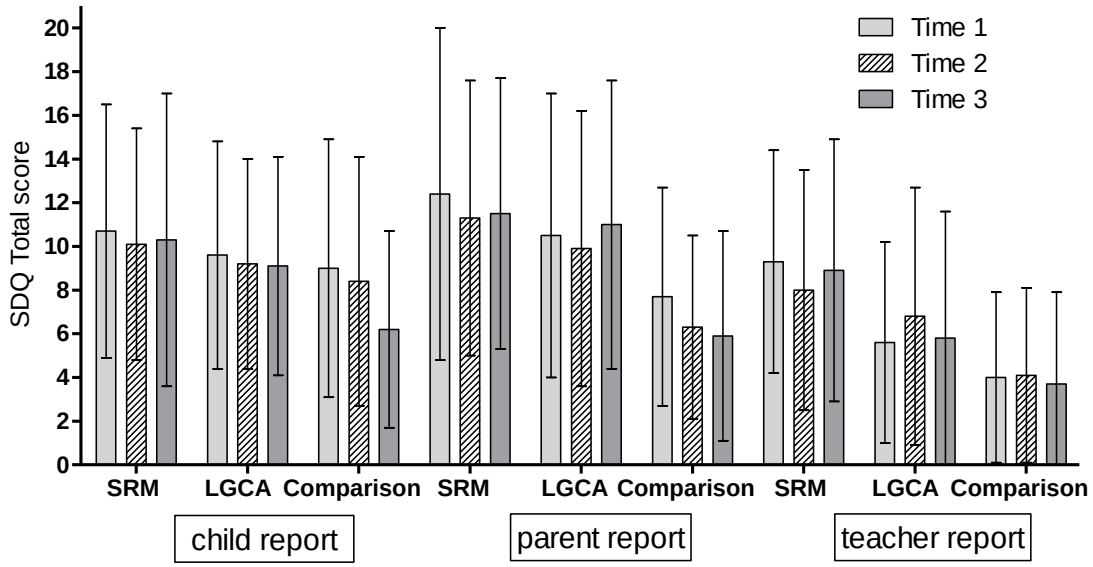


Figure 9. Child- , parent-, and teacher-report SDQ Total Difficulties mean scores and standard deviations arranged by group and time. Higher scores = poorer functioning. (SRM n = 24, LGCA n = 25, Comparison n = 31.)

Table 47. Complete case analysis showing means and standard deviations for child- parent- and teacher-report SDQ Total Difficulties scores and numbers with borderline/abnormal scores for each group at each time point

| | SRM n=24 | | | LGCA n=25 | | | Comparison n=31 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Child** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** |
| Mean | 10.7 | 10.1 | 10.3 | 9.6 | 9.2 | 9.1 | 9.0 | 8.4 | 6.2 |
| (SD) | (5.8) | (5.3) | (6.7) | (5.2) | (4.8) | (5.0) | (5.9) | (5.7) | (4.5) |
| No. (%) | 4 | 5 | 5 | 4 | 2 | 3 | 5 | 4 | 1 |
| bord/abn | (16.7) | (20.8) | (20.8) | (16.0) | (8.0) | (12.0) | (16.1) | (12.9) | (3.2) |
| **Parent** | | | | | | | | | |
| Mean | 12.4 | 11.3 | 11.5 | 10.5 | 9.9 | 11.0 | 7.7 | 6.3 | 5.9 |
| (SD) | (7.6) | (6.3) | (6.2) | (6.5) | (6.3) | (6.6) | (5.0) | (4.2) | (4.8) |
| No. (%) | 9 | 8 | 8 | 6 | 8 | 11 | 5 | 3 | 2 |
| bord/abn | (37.5) | (33.3) | (33.3) | (24.0) | (32.0) | (44.0) | (16.1) | (9.7) | (6.5) |
| **Teacher** | | | | | | | | | |
| Mean | 9.3 | 8.0 | 8.9 | 5.6 | 6.8 | 5.8 | 5.0 | 4.1 | 3.7 |
| (SD) | (5.1) | (5.5) | (6.0) | (4.6) | (5.9) | (5.8) | (3.9) | (4.0) | (4.2) |
| No. (%) | 7 | 5 | 6 | 2 | 4 | 4 | 2 | 2 | 1 |
| bord/abn | (29.2) | (20.8) | (25.0) | (8.0) | (16.0) | (16.0) | (6.5) | (6.5) | (3.2) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebellar astrocytoma; T1, time 1; T2, time 2; T3, time 3; bord/abn, borderline/abnormal scores

Table 48 demonstrates that in the Comparison group SDQ Total Difficulties scores decreased significantly between T1 and T3 ($F(1,30) = 12.439$, $p = .001$) and between T2 and T3 ($F(1,30) = 9.279$, $p = .005$) but did not change between T1 and T2 ($F(1,30) = 0.959$, $p = .447$).

Table 48. Mean differences and confidence intervals for the child-report SDQ Total Difficulties scores between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the Comparison group

| **Comparison** | **Mean difference** | **95% CI** | ***P*** |
|---|---|---|---|
| T1 vs T3 | 2.8 | 1.2 to 4.4 | .001 |
| T1 vs T2 | 0.6 | -1.0 to 2.2 | .447 |
| T2 vs T3 | 2.2 | 0.7 to 3.6 | .005 |

Abbreviations: CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

Figure 10 and table 49 show that between T1 and T3 Emotional symptoms decreased significantly (*Mdn* = 2.0 vs 1.0, $T = 31.00$, $p = .017$) and so did Conduct problems (*Mdn* =

1.0 vs 1.0, $T$ = 23.50, $p$ = .006). Emotional symptoms also decreased between T2 (*Mdn* = 1.0) and T3 ($T$ = 31.0, $p$ = .016), and so did Peer problems (*Mdn* = 1.0 vs 2.0, $T$ = 52.0, $p$ = .007).

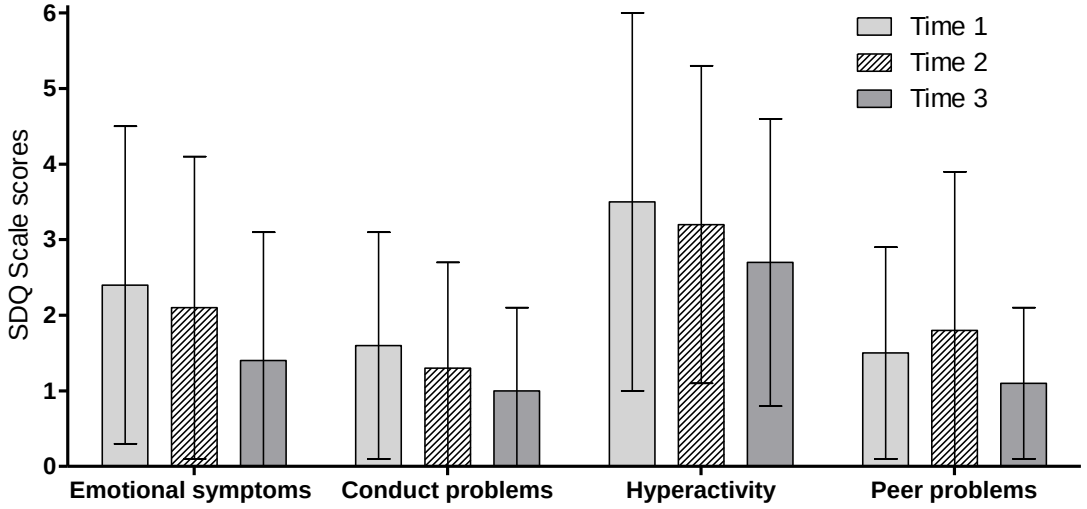


Figure 10. Child-report Emotional symptoms, Conduct problems, Hyperactivity/inattention and Peer problems mean scores and standard deviations at each time point in the Comparison group. Higher scores = poorer functioning (n = 31).

Table 49. Mean differences and confidence intervals for the child-report SDQ Emotional symptoms, Conduct problems, Hyperactivity/inattention and Peer problems scores between Time 1 and Time 3, and Time 2 and Time 3 for the Comparison group

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| **T1 vs T3** | | | |
| Emotional Symptoms | 0.9 | 0.2 to 1.7 | .017 |
| Conduct Problems | 0.6 | 0.2 to 1.1 | .006 |
| Hyperactivity/inattention | 0.9 | 0.0 to 1.7 | .067 |
| Peer Problems | 0.3 | -0.2 to 0.8 | .152 |
| **T2 vs T3** | | | |
| Emotional Symptoms | 0.7 | 0.2 to 1.2 | .016 |
| Conduct Problems | 0.3 | -0.1 to 0.7 | .106 |
| Hyperactivity/inattention | 0.5 | -0.1 to 1.1 | .105 |
| Peer Problems | 0.7 | 0.3 to 1.2 | .007 |

Abbreviations: CI, confidence interval

**p* value for Wilcoxon tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

### 4.3.2. Parent-report of SDQ over time

Figure 9 and table 47 demonstrate that SDQ Total Difficulties scores changed significantly over time in the Comparison group ($\chi^2(2) = 8.052$, $p = .018$) but not in the SRM group ($F(2,46) = 0.860$, $p = .430$) nor in the LGCA group ($F(2,48) = 0.791$, $p = .459$). Table 50 shows that in the Comparison group SDQ Total Difficulties scores decreased significantly between T1 and T3 ($Mdn = 6.0$ vs 6.0, $T = 97.50$, $p = .009$) but not between T1 and T2 ($Mdn = 4.0$, $T = 121.5$, $p = .062$) or between T2 and T3 ($T = 134.5$, $p = .185$).

Table 50. Mean differences and confidence intervals for the parent-report SDQ Total Difficulties scores between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the Comparison group

| **Comparison** | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| T1 vs T3 | 1.8 | 0.5 to 3.1 | .009 |
| T1 vs T2 | 1.4 | 0.0 to 2.8 | .062 |
| T2 vs T3 | 0.4 | -0.7 to 1.4 | .185 |

Abbreviations: CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests calculated by ranking data may not necessarily correspond to CIs calculated using mean scores.

Figure 11 and table 51 reveal that between T1 and T3 Hyperactivity/inattention decreased

significantly (*Mdn* = 3.0 vs 2.0, *T* = 65.00, *p* = .004) but there were no other changes for any of the other subscales.

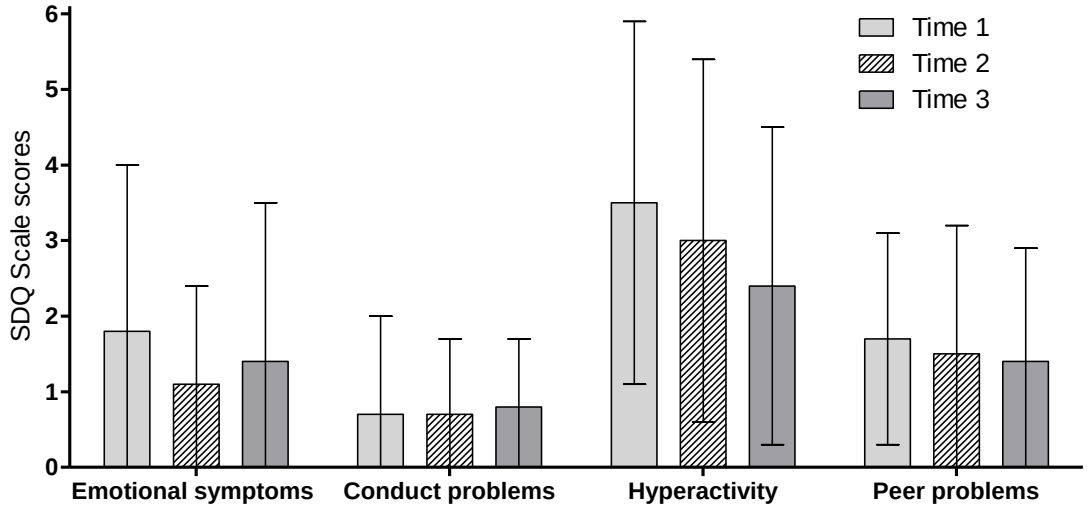


Figure 11. Parent-report SDQ Emotional symptoms, Conduct problems, Hyperactivity/inattention and Peer problems mean scores and standard deviations at each time point in the Comparison group. Higher scores = poorer functioning (n = 31).

Table 51. Mean differences and confidence intervals for the parent-report SDQ Emotional symptoms, Conduct problems, Hyperactivity/inattention and Peer problems scores between Time 1 and Time 3 for the Comparison group

| | **Mean difference** | **95% CI** | ***P**** |
|---|---|---|---|
| **T1 vs T3** | | | |
| Emotional Symptoms | 0.5 | -0.4 to 1.3 | .220 |
| Conduct Problems | 0.1 | -0.3 to 0.4 | .572 |
| Hyperactivity/inattention | 1.1 | 0.4 to 1.7 | .004 |
| Peer Problems | 0.3 | -0.2 to 0.8 | .256 |

Abbreviations: T1, Time 1; T3, Time 3; CI, confidence interval

**p* value for Wilcoxon tests

### 4.3.3. Teacher-report of SDQ over time

Figure 9 and table 47 show that SDQ Total Difficulties scores did not change significantly over time in the SRM group ($F(2,46) = 0.407$, $p = .668$) nor in the LGCA group ($\chi^2(2) = 0.467$, $p = .792$) or the Comparison group ($\chi^2(2) = 0.789$, $p = .674$).

## 4.4. WITHIN GROUP CHANGES IN COGNITIVE FUNCTIONING OVER TIME

### 4.4.1. Parent-report of BRIEF over time

Figure 12 and table 52 reveal that parent-report BRIEF GEC scores did not change significantly over time in the SRM group ($F(2, 40) = 0.427$, $p = .655$) nor in the LGCA group ($\chi^2(2) = 0.837$, $p = .653$) or the Comparison group ($\chi^2(2) = 3.076$, $p = .215$).

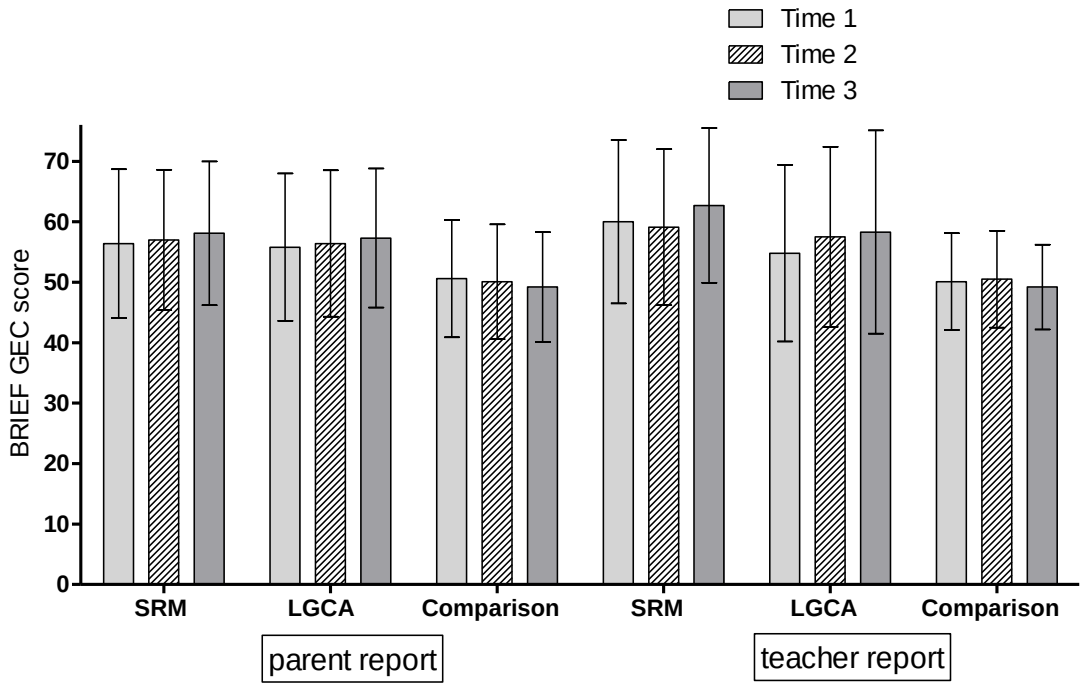


Figure 12. Parent- and teacher-report BRIEF Global Executive Functioning Composite mean scores and standard deviations arranged by group and time. Higher scores = poorer functioning. (SRM n = 21, LGCA n = 22, Comparison n = 31.)

Table 52. Complete case analysis showing means and standard deviations for parent- and teacher-report BRIEF Global Executive Functioning Composite scores for each group at each time point and the number of children in the clinically significant range

| | SRM n=21 | | | LGCA n=22 | | | Comparison n=31 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parent** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** |
| Mean | 56.4 | 57.0 | 58.1 | 54.8 | 55.9 | 56.6 | 50.6 | 50.1 | 49.2 |
| (SD) | (12.3) | (11.6) | (11.9) | (11.4) | (12.1) | (11.3) | (9.7) | (9.5) | (9.1) |
| No. (%) | 6 | 7 | 6 | 5 | 6 | 3 | 4 | 3 | 1 |
| clin. sig. | (28.6) | (33.3) | (28.6) | (22.7) | (27.3) | (13.6) | (12.9) | (9.7) | (3.2) |
| **Teacher** | | | | | | | | | |
| Mean | 60.0 | 59.1 | 62.7 | 53.0 | 55.6 | 57.8 | 50.1 | 50.5 | 49.2 |
| (SD) | (13.5) | (12.9) | (12.8) | (11.8) | (11.9) | (17.0) | (8.0) | (8.0) | (7.0) |
| No. (%) | 8 | 8 | 8 | 3 | 6 | 8 | 3 | 3 | 1 |
| clin. sig. | (38.1) | (38.1) | (38.1) | (13.6) | (27.3) | (36.4) | (9.7) | (9.7) | (3.2) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebellar astrocytoma; T1, time 1; T2, time 2; T3, time 3; clin. sig., clinically significant impairment

### 4.4.2. Teacher-report of BRIEF over time

Figure 12 and table 52 reveal that GEC scores changed significantly over time in the SRM group ($\chi^2(2) = 6.146$, $p = .046$) but not in the LGCA group ($\chi^2(2) = 0.292$, $p = .864$) nor the Comparison group ($\chi^2(2) = 1.369$, $p = .504$). However, table 53 shows that in this group GEC scores were not significantly different between T1 and T3 (*Mdn* =60.00 vs 63.00, $T = 83.50$, $p = .266$), T1 and T2 (*Mdn* =56.00, $T = 91.50$, $p = .888$) or between T2 and T3 ($T = 68.50$, $p = .102$).

Table 53. Mean differences and confidence intervals for the teacher-report BRIEF Global Executive Functioning Composite scores between Time 1 and Time 3, Time 1 and Time 2, and Time 2 and Time 3 for the SRM group

| SRM | Mean difference | 95% CI | *P** |
|---|---|---|---|
| T1 vs T3 | 1.5 | -1.6 to 4.5 | .266 |
| T1 vs T2 | 0.9 | -4.6 to 6.3 | .888 |
| T2 vs T3 | 3.6 | -1.2 to 8.4 | .102 |

Abbreviations: SRM, standard risk medulloblastoma; CI, confidence interval; T1, Time 1; T2, Time 2; T3, Time 3

**p* value for Wilcoxon tests

### 4.4.3. WISC®-IV UK over time

Figure 13 and table 54 demonstrate that FSIQ scores did not change significantly over time in the SRM group ($\chi^2(2) = 2.324$, $p = .313$) nor in the LGCA group ($\chi^2(2) = 1.585$, $p = .453$) nor in the Comparison group ($F(2, 68) = 1.490$, $p = .233$).

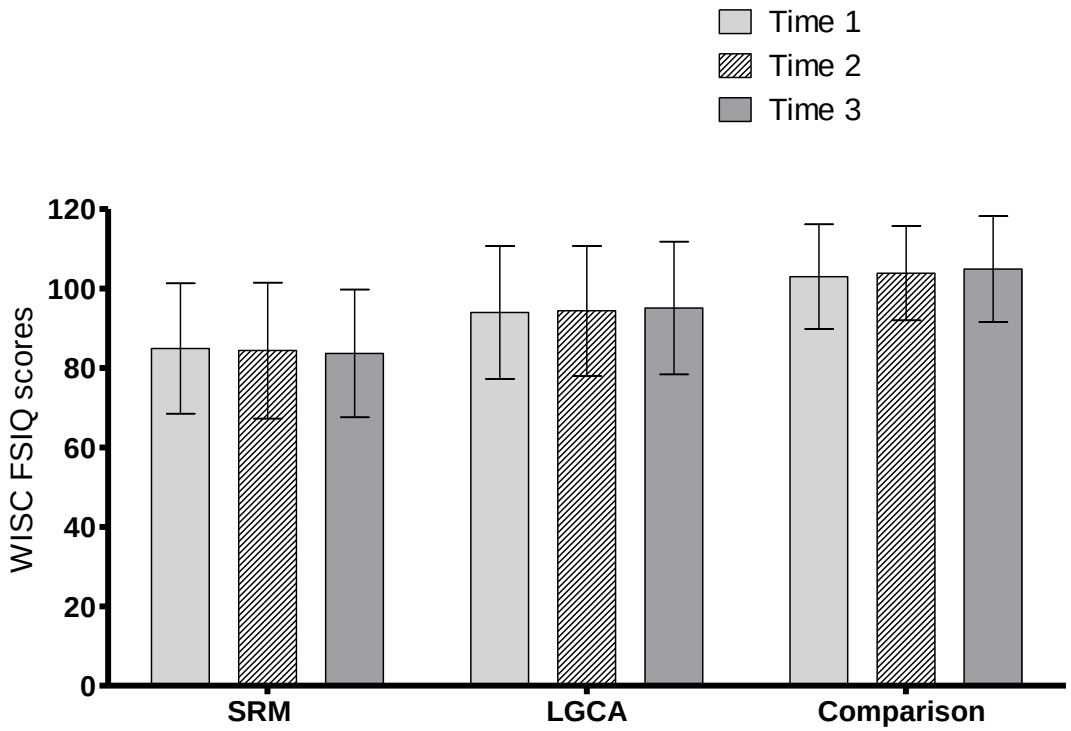


Figure 13. WISC FSIQ mean scores and standard deviations for each group over time. Higher scores = poorer functioning. (SRM n = 18, LGCA n = 27, Comparison n = 35.)

Table 54. Complete case analysis showing means and standard deviations for WISC FSIQ scores for each group at each time point

| | **SRM n=18** | | | **LGCA n=27** | | | **Comparison n=35** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** |
| Mean | 84.9 | 84.4 | 83.7 | 94.0 | 93.4 | 95.1 | 103.0 | 103.9 | 104.9 |
| (SD) | (16.4) | (17.1) | (16.1) | (16.7) | (16.4) | (16.7) | (13.2) | (11.9) | (13.3) |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebellar astrocytoma; T1, time 1; T2, time 2; T3, time 3.

## 4.5. SUMMARY OF CHANGES IN QOL OVER TIME

### 4.5.1. PedsQL

As predicted, by child- and also parent-report, QoL improved over time in the SRM group but contrary to prediction, it did not improve in the LGCA group. It did improve in the

Comparison group but by child-report only. This improvement in QoL in the SRM group occurred between the first and third assessment, a period of 24 months, and between the second and third assessment, a period of 12 months, and was due to a significant improvement in physical health and also psychosocial health over 24 months. The improvement in psychosocial health was due to improved school functioning. In the Comparison group the improvement in QoL occurred between the first and third assessment, over a period of 24 months, and between the first and second assessment, over a period of 12 months. This improvement was not due to an improvement in physical health but due to an improvement in psychosocial health over 24 months which was accounted for by improved emotional and social functioning over this time period.

Similarly to child-report, as predicted, by parent-report, QoL improved over time in the SRM group and remained the same in the Comparison group. However, contrary to prediction, it did not improve in the LGCA group. This improvement in QoL in the SRM group was significant between each time point which was due to improved physical functioning and also due to improved psychosocial functioning over the 24 months between the first and third assessment and also over the first 12 months between the first and second assessment. This improvement in psychosocial functioning was due to an improvement in emotional and school functioning over 24 months and an improvement in school functioning over the first 12 months.

### 4.5.2. HUI

As predicted, according to child-report, health status improved overall over time in the SRM group and remained the same in the Comparison group but contrary to prediction, it remained the same in the LGCA group. This improvement in overall health status in the SRM group did not achieve significance between any of the specific time points.

As predicted, according to parent-report, health status improved overall over time in the SRM group and remained the same in the Comparison group but contrary to prediction, it also remained the same in the LGCA group. This improvement in health status in the SRM group occurred over the 24 months between the first and third assessments which was accounted for by an improvement in ambulation, dexterity and pain although vision declined over this period. There was also an overall improvement over the 12 months between the second and third assessments but none of the single attributed utility scores accounted specifically for this improvement.

### 4.5.3. SDQ

Contrary to prediction, by child-report, behavioural functioning did not improve over time in the SRM group nor in the LGCA group, but it did improve in the Comparison group. Their improvement occurred over the 24 months between the first and third assessment and was due to an improvement in emotional symptoms and conduct problems. Behavioural functioning also improved during the 12 months between the second and third assessment which was due to an improvement in emotional symptoms and also peer problems.

Contrary to prediction, according to parent-report, behavioural functioning did not improve over time in the SRM group nor in the LGCA group but it did improve in the Comparison group. Their improvement occurred over the 24 month period between the first and third assessments and was due to an improvement in hyperactivity and attention.

Contrary to prediction, according to teacher-report, behavioural functioning did not improve over time in the SRM group nor in the LGCA group and, as predicted, it remained the same in the Comparison group.

### 4.5.4. BRIEF and WISC®-IV UK

As predicted, according to parent-report, executive functioning did not change over time in the LGCA or Comparison groups and contrary to prediction it did not decline in the SRM group.

As predicted, according to teacher-report, executive functioning did not change over time in the LGCA or Comparison groups and it did decline in the SRM group overall but not between any particular time point.

As predicted, cognitive functioning, as measured by the WISC remained the same over time in the LGCA and Comparison groups, but contrary to prediction, it did not decline in the SRM group.

# CHAPTER 5 RESULTS: THE RELATIONSHIP BETWEEN PARENTAL MENTAL HEALTH AND CHILD QOL

## 5.1. GHQ-12 AND PARENT-REPORT OF PEDSQL

Table 55 shows that at T1, T2 and T3 parent's mental health significantly predicted their report of their child's QoL in the LGCA group but not in the SRM or Comparison groups.

Table 55. Simple linear regression models predicting parent-report PedsQL Total scores from ratings of their own mental health in each group at each time point

| **T1** | **$R^2$** | **B** | **SE B** | **Beta** | ***F*** | **95% CI** | ***P*** |
|---|---|---|---|---|---|---|---|
| SRM (n=35) | .050 | -0.912 | 0.695 | -.223 | 1.724 | -2.326, 0.501 | .198 |
| LGCA (n=35) | .126 | -1.226 | 0.561 | -.355 | 4.767 | -2.368, -0.084 | .036 |
| Comparison (n=37) | .070 | -0.551 | 0.341 | -.264 | 2.615 | -1.243, 0.141 | .115 |
| **T2** | | | | | | | |
| SRM (n=31) | .048 | -0.648 | 0.535 | -.220 | 1.468 | -1.743, 0.446 | .235 |
| LGCA (n=31) | .243 | -2.878 | 0.948 | -.493 | 9.322 | -4.805, -0.950 | .005 |
| Comparison (n=36) | .026 | -0.355 | 0.370 | -.162 | 0.922 | -1.107, 0.397 | .344 |
| **T3** | | | | | | | |
| SRM (n=29) | .053 | -0.769 | 0.626 | -.230 | 1.509 | -2.054, 0.516 | .230 |
| LGCA (n=29) | .152 | -1.693 | 0.770 | -.390 | 4.837 | -3.272, -0.114 | .037 |
| Comparison (n=36) | .027 | -0.301 | 0.310 | -.164 | 0.940 | -0.932, 0.330 | .339 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval for B; T1, Time 1; T2, Time 2; T3, Time 3

## 5.2. GHQ-12 AND PARENT-REPORT OF SDQ

Table 56 reveals that at T1, T2 and T3 parent's mental health did not significantly predict their report of their child's behavioural functioning in any of the three groups.

Table 56. Simple linear regression models predicting parent-report of SDQ Total Difficulties scores from ratings of their own mental health in each group at each time point

| **T1** | **$R^2$** | **B** | **SE B** | **Beta** | ***F*** | **95% CI** | ***P*** |
|---|---|---|---|---|---|---|---|
| SRM (n=36) | .010 | 0.129 | 0.225 | .098 | 0.330 | -0.327, 0.585 | .570 |
| LGCA (n=35) | .024 | 0.135 | 0.151 | .154 | 0.797 | -0.173, 0.443 | .379 |
| Comparison (n=37) | .086 | 0.298 | 0.164 | .294 | 3.300 | -0.035, 0.631 | .078 |
| **T2** | | | | | | | |
| SRM (n=31) | .080 | 0.329 | 0.208 | .282 | 2.511 | -0.096, 0.754 | .124 |
| LGCA (n=31) | .096 | 0.510 | 0.291 | .310 | 3.073 | -0.085, 1.106 | .090 |
| Comparison (n=36) | .003 | -0.052 | 0.150 | -.059 | 0.119 | -0.356, 0.252 | .732 |
| **T3** | | | | | | | |
| SRM (n=29) | .042 | 0.246 | 0.226 | .205 | 1.180 | -0.218, 0.710 | .287 |
| LGCA (n=29) | .071 | 0.388 | 0.271 | .266 | 2.057 | -0.167, 0.944 | .163 |
| Comparison (n=36) | .005 | 0.066 | 0.157 | .072 | 0.177 | -0.253, 0.385 | .676 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval for B; T1, Time 1; T2, Time 2; T3, Time 3

### 5.3. GHQ-12 AND CHILD-REPORT OF PEDSQL

Table 57 reveals that at T1 and T2 parents' mental health significantly predicted child-report QoL in the LGCA group but not in the SRM or Comparison groups. At T3 parents' mental health predicted child-report QoL in the SRM group only.

Table 57. Simple linear regression models predicting child-report PedsQL Total scores from ratings of parent mental health in each group at each time point

| **T1** | **$R^2$** | **B** | **SE B** | **Beta** | ***F*** | **95% CI** | ***P*** |
|---|---|---|---|---|---|---|---|
| SRM (n=35) | .057 | -0.816 | 0.580 | -.238 | 1.980 | -1.996, 0.364 | .169 |
| LGCA (n=34) | .132 | -1.065 | 0.484 | -.363 | 4.847 | -2.051, -0.080 | .035 |
| Comparison (n=37) | .029 | -0.392 | 0.383 | -.170 | 1.043 | -1.170, 0.387 | .314 |
| **T2** | | | | | | | |
| SRM (n=31) | .005 | -0.188 | 0.472 | -.074 | 0.158 | -1.154, 0.778 | .694 |
| LGCA (n=30) | .165 | -1.967 | 0.835 | -.407 | 5.552 | -3.678,-0.257 | .026 |
| Comparison (n=36) | .049 | -0.531 | 0.402 | -.221 | 1.746 | -1.348, 0.286 | .195 |
| **T3** | | | | | | | |
| SRM (n=28) | .242 | -1.673 | 0.581 | -.492 | 8.290 | -2.868, -0.479 | .008 |
| LGCA (n=28) | .091 | -1.184 | 0.733 | -.302 | 2.609 | -2.691, 0.323 | .118 |
| Comparison (n=36) | .011 | -0.203 | 0.325 | -.107 | 0.393 | -0.863, 0.456 | .535 |

Abbreviations: SRM, standard risk medulloblastoma; LGCA, low grade cerebella astrocytoma; CI, confidence interval for B; T1, Time 1; T2, Time 2; T3, Time 3

### 5.4. SUMMARY OF PARENTAL MENTAL HEALTH AND CHILD QOL

As predicted, at T1, T2 and T3 parents' mental health significantly predicted their report of their child's QoL in the LGCA group but contrary to prediction this was not evident in the SRM or Comparison groups. Parents' mental health did not predict behavioural functioning at any time in any of the groups. At T1 and T2 parents' mental health predicted the child-report QoL in the LGCA group only and at T3 in the SRM group.

Table 58 demonstrates that age at diagnosis significantly predicted child-report QoL at T1 and T3, but not by parent-report and it was highly significantly correlated with age at assessment at each time point (T1 $r_s(72) = .904$, $p = <.001$; T2 $r_s(63) = .903$, $p = <.001$; T3 $r_s(58) = .887$, $p = <.001$).

Table 58. Simple linear regression models predicting child- and parent-report PedsQL Total scores from age at diagnosis at each time point in the two tumour groups combined

| PedsQL | $R^2$ | B | SE B | Beta | *F* | 95% CI | *P* |
|---|---|---|---|---|---|---|---|
| **Child-report** | | | | | | | |
| T1 (n=69) | .074 | -2.445 | 1.057 | -.272 | 5.352 | -4.555, -0.336 | .024 |
| T2 (n=62) | .036 | -1.509 | 1.002 | -.191 | 2.268 | -3.512, 0.495 | .137 |
| T3 (n=56) | .110 | -2.852 | 1.102 | -.332 | 6.698 | -5.061, -0.643 | .012 |
| **Parent-report** | | | | | | | |
| T1 (n=70) | .031 | -1.983 | 1.335 | -.177 | 2.206 | -4.646, 0.681 | .142 |
| T2 (n=62) | .047 | -2.202 | 1.278 | -.217 | 2.967 | -4.759, 0.355 | .090 |
| T3 (n=58) | .042 | -1.895 | 1.213 | -.204 | 2.441 | -4.325, 0.535 | .124 |

Abbreviations: CI, confidence interval for B; T1, Time 1; T2, Time 2; T3, Time 3

Table 59 shows that time since diagnosis did not significantly predict QoL at any of the time points neither by child- nor by parent-report.

Table 59. Simple linear regression models predicting child- and parent-report PedsQL Total scores from time since diagnosis at each time point in the two tumour groups combined

| PedsQL | $R^2$ | B | SE B | Beta | *F* | 95% CI | *P* |
|---|---|---|---|---|---|---|---|
| **Child-report** | | | | | | | |
| T1 (n=69) | .021 | 0.308 | 0.256 | .145 | 1.445 | -0.203, 0.819 | .234 |
| T2 (n=62) | .005 | 0.130 | 0.236 | .073 | 0.321 | -0.330, 0.590 | .573 |
| T3 (n=56) | .008 | 0.170 | 0.256 | .090 | 0.440 | -0.343, 0.682 | .510 |
| **Parent-report** | | | | | | | |
| T1 (n=70) | .000 | 0.031 | 0.311 | .012 | 0.010 | -0.590, 0.652 | .921 |
| T2 (n=62) | .005 | -0.154 | 0.293 | -.068 | 0.277 | -0.740, 0.432 | .601 |
| T3 (n=58) | .028 | -0.334 | 0.262 | -.168 | 1.623 | -0.858, 0.191 | .208 |

Abbreviations: CI, confidence interval for B; T1, Time 1; T2, Time 2; T3, Time 3

## 6.1. PREDICTORS OF CHILD-REPORT QOL

### 6.1.1. Time 1

Table 60 demonstrates that Emotional and Motor and Sensory functioning at T1 predicted child-report QoL at T1 but contrary to prediction Behaviour, Social functioning, and Cognition did not, and neither did Caregiver Mental Health. The model showed that an increase in the Emotional functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .472 of a standard deviation. It also showed that an increase in the Motor and Sensory functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .494 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the values in the model would vary little across different samples. These two predictors at T1 together accounted for 65% of the variance in child-report QoL scores at T1. $R^2$ adjusted was very similar to $R^2$ indicating that not only was the model a good fit but also that it was generalisable to other populations.

Table 60. Forced entry regression model for T1 predictors of T1 child-report PedsQL using z scores

| **Step 1** N=106, $R^2$=.073, $R^2_{adj}$=.046, *p*=.051 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.334 | .153 | -.209 | -.638 to -.030 | .031 |
| Child's gender | -.222 | .301 | -.071 | -.820 to .375 | .462 |
| Child's age | -.144 | .081 | -.171 | -.304 to .016 | .077 |
| **Step 2** N=95, $R^2$=.686, $R^2_{adj}$=.660, *p*<.001 | | | | | |
| SES | -.019 | .096 | -.013 | -.210 to .172 | .843 |
| Emotion | -.145 | .029 | -.411 | -.202 to -.089 | <.001 |
| Behaviour | -.010 | .037 | -.027 | -.083 to .063 | .784 |
| Social | -.023 | .032 | -.062 | -.087 to .040 | .467 |
| Motor and Sensory | -.025 | .005 | -.384 | -.035 to -.015 | <.001 |
| Cognition | -.010 | .009 | -.123 | -.027 to .008 | .274 |
| Caregiver Mental Health | -.080 | .087 | -.059 | -.252 to .092 | .357 |
| **Final model** N=101, $R^2$=.653, $R^2_{adj}$=.646, *p*<.001 | | | | | |
| Emotion | -.163 | .022 | -.472 | -.207 to -.118 | <.001 |
| Motor and Sensory | -.031 | .004 | -.494 | -.039 to -.023 | <.001 |

### 6.1.2. Time 2

Table 61 reveals that Emotional and Motor and Sensory functioning at T2 predicted child-report QoL at T2 but contrary to prediction Behaviour, Social functioning, and Cognition did not and neither did Caregiver Mental Health. The model showed that an increase in the Emotional functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .526 of a standard deviation, and that an increase in the Motor and Sensory functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .467 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the values in the model would vary little across different samples. These two predictors at T2 together accounted for 67% of the variance in child-report QoL scores at T2. $R^2$ adjusted was very similar to $R^2$ indicating that not only was the model a good fit but also that it was generalisable to other populations.

Table 61. Forced entry regression model for T2 predictors of T2 child-report PedsQL using z scores

| **Step 1** N=99, $R^2$=.070, $R^2_{adj}$=.040, *p*=.076 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.352 | .151 | -.231 | -.653 to -.052 | .022 |
| Child's gender | -.246 | .307 | -.080 | -.856 to .364 | .426 |
| Child's age | -.099 | .082 | -.120 | -.262 to .064 | .232 |
| **Step 2** N=89, $R^2$=.689, $R^2_{adj}$=.662, *p*<.001 | | | | | |
| SES | -.015 | .095 | -.010 | -.203 to .173 | .875 |
| Emotion | -.108 | .024 | -.379 | -.155 to -.060 | <.001 |
| Behaviour | -.042 | .034 | -.116 | -.110 to .025 | .217 |
| Social | -.012 | .032 | -.034 | -.076 to .052 | .713 |
| Motor and Sensory | -.030 | .006 | -.382 | -.041 to -.019 | <.001 |
| Cognition | -.009 | .008 | -.117 | -.025 to .007 | .283 |
| Caregiver Mental Health | -.136 | .099 | -.094 | -.332 to .061 | .174 |
| **Final model** N=94, $R^2$=.669, $R^2_{adj}$=.662, *p*<.001 | | | | | |
| Emotion | -.146 | .018 | -.526 | -.181 to -.110 | <.001 |
| Motor and Sensory | -.037 | .005 | -.467 | -.047 to -.027 | <.001 |

### 6.1.3. Time 3

Table 62 demonstrates that Emotional and Motor and Sensory functioning, and Cognition at T3, predicted child-report QoL at T3 but contrary to prediction behaviour and social functioning did not, and neither did caregiver Mental Health. The model showed that an increase in the Emotional functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .342 of a standard deviation, an increase in the Motor and Sensory functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .354 of a standard deviation, and an increase in the Cognition z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .357 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the values in the model would vary little across different samples. These three predictors at T3 together accounted for 76% of the variance in child-report QoL scores at T3. $R^2$ adjusted was very similar to $R^2$ indicating that not only was the model a good fit but also that it was generalisable to other

populations.

Table 62. Forced entry regression model for T3 predictors of T3 child-report PedsQL using z scores

| **Step 1** N=92, $R^2$=.121, $R^2_{adj}$=.091, *p*=.010 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.471 | .162 | -.292 | -.793 to -.148 | .005 |
| Child's gender | .086 | .332 | .026 | -.575 to .746 | .797 |
| Child's age | -.188 | .088 | -.215 | -.363 to .014 | .035 |
| **Step 2** N=84, $R^2$=.780, $R^2_{adj}$=.757, *p*<.001 | | | | | |
| SES | -.128 | .099 | -.076 | -.325 to .069 | .200 |
| Child's age | -.088 | .050 | -.100 | -.188 to .013 | .086 |
| Emotion | -.140 | .032 | -.360 | -.203 to -.076 | <.001 |
| Behaviour | .031 | .026 | .105 | -.021 to .083 | .243 |
| Social | -.013 | .025 | -.042 | -.063 to .036 | .596 |
| Motor and Sensory | -.051 | .010 | -.343 | -.070 to -.032 | <.001 |
| Cognition | -.029 | .008 | -.357 | -.045 to -.012 | .001 |
| Caregiver Mental Health | -.031 | .104 | -.017 | -.237 to .176 | .766 |
| **Final model** N=84, $R^2$=.761, $R^2_{adj}$=.752, *p*<.001 | | | | | |
| Emotion | -.133 | .030 | -.342 | -.193 to -.073 | <.001 |
| Motor and Sensory | -.053 | .009 | -.354 | -.071 to -.034 | <.001 |
| Cognition | -.029 | .006 | -.357 | -.041 to -.016 | <.001 |

### 6.1.4. Time 1 predictors of Time 3 PedsQL

Table 63 shows that Emotional functioning and Cognition at T1 predicted child-report QoL at T3 along with the child's age, but contrary to prediction Motor and Sensory functioning, Behaviour and Social functioning did not and neither did Caregiver Mental Health. The model showed that an increase in age by one standard deviation was associated with a decrease in the PedsQL Total z-score by .169 of a standard deviation, an increase in the Emotional functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .268 of a standard deviation, and an increase in the Cognition z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .483 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the

values in the model would vary little across different samples. These three predictors at T1 together accounted for 54% of the variance in child-report QoL scores at T3. $R^2$ adjusted was very similar to $R^2$ indicating that not only was the model a good fit but also that it was generalisable to other populations.

Table 63. Forced entry regression model for T1 predictors of T3 child-report PedsQL using z-scores

| **Step 1** N=92, $R^2$=.123, $R^2_{adj}$=.094, *p*=.009 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.472 | .162 | -.293 | -.794 to -.150 | .005 |
| Child's gender | .092 | .332 | .028 | -.567 to .752 | .781 |
| Child's age | -.195 | .088 | -.221 | -.371 to -.019 | .030 |
| **Step 2** N=81, $R^2$=.575, $R^2_{adj}$=.528, *p*<.001 | | | | | |
| SES | -.087 | .124 | -.060 | -.333 to .160 | .486 |
| Child's age | -.132 | .066 | -.164 | -.263 to -.002 | .047 |
| Emotion | -.084 | .040 | -.231 | -.164 to -.005 | .038 |
| Behaviour | -.018 | .055 | -.044 | -.128 to .091 | .739 |
| Social | -.040 | .043 | -.105 | -.126 to .045 | .353 |
| Motor and Sensory | -.009 | .006 | -.139 | -.021 to .004 | .172 |
| Cognition | -.025 | .012 | -.315 | -.048 to -.001 | .039 |
| Caregiver Mental Health | -.016 | .114 | -.011 | -.242 to .211 | .891 |
| **Final model** N=81, $R^2$=.541, $R^2_{adj}$=.523, *p*<.001 | | | | | |
| Child's age | -.136 | .063 | -.169 | -.262 to -.010 | .035 |
| Emotion | -.098 | .039 | -.268 | -.175 to -.021 | .014 |
| Cognition | -.038 | .008 | -.483 | -.055 to -.021 | <.001 |

## 6.2. PREDICTORS OF PARENT-REPORT QOL

### 6.2.1. Time 1

Table 64 demonstrates that Emotional, Motor and Sensory functioning, and Cognition at T1 predicted parent-report QoL at T1 but contrary to prediction Behaviour and Social functioning did not and neither did Caregiver Mental Health. The model showed that an increase in the Emotional functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .404 of a

standard deviation, an increase in the Motor and Sensory functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .400 of a standard deviation, and an increase in the Cognition z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .255 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the values in the model would vary little across different samples. These three predictors at T1 together accounted for 72% of the variance in parent-report QoL scores at T1. $R^2$ adjusted was very similar to $R^2$ indicating that not only was the model a good fit but also that it was generalisable to other populations.

Table 64. Forced entry regression model for T1 predictors of T1 parent-report PedsQL using z scores

| **Step 1** N=107, $R^2$=.060, $R^2_{adj}$=.033, *p*=.094 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.460 | .216 | -.204 | -.889 to -.031 | .036 |
| Child's gender | -.024 | .424 | -.005 | -.864 to .816 | .956 |
| Child's age | -.180 | .114 | -.151 | -.407 to .047 | .118 |
| **Step 2** N=94, $R^2$=.738, $R^2_{adj}$=.716, *p*<.001 | | | | | |
| SES | .014 | .122 | .007 | -.230 to .257 | .911 |
| Emotion | -.187 | .037 | -.376 | -.260 to -.114 | <.001 |
| Behaviour | .088 | .047 | .167 | -.006 to .182 | .067 |
| Social | -.069 | .041 | -.132 | -.151 to .012 | .094 |
| Motor and Sensory | -.033 | .006 | -.357 | -.045 to -.020 | <.001 |
| Cognition | -.033 | .010 | -.297 | -.056 to -.010 | .005 |
| Caregiver Mental Health | -.127 | .110 | -.067 | -.346 to .092 | .251 |
| **Final model** N=96, $R^2$=.724, $R^2_{adj}$=.715, *p*<.001 | | | | | |
| Emotion | -.201 | .036 | -.404 | -.273 to -.130 | <.001 |
| Motor and Sensory | -.036 | .006 | -.400 | -.048 to -.025 | <.001 |
| Cognition | -.025 | .009 | -.225 | -.042 to -.008 | .005 |

### 6.2.2. Time 2

Table 65 reveals that Emotional, Motor and Sensory functioning, and Cognition at T2 predicted parent-report QoL at T2 but contrary to prediction Behaviour and Social functioning did not and neither did Caregiver Mental Health. The model showed that an increase in the Emotional functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .305 of a standard deviation, an increase in the Motor and Sensory functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .322 of a standard deviation, and an increase in the Cognition z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .301 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the values in the model would vary little across different samples. These three predictors at T1 together accounted for 58% of the variance in parent-report QoL scores at T1. $R^2$ adjusted was very similar to $R^2$ indicating

that not only was the model a good fit but also that it was generalisable to other populations.

Table 65. Forced entry regression model for T2 predictors of T2 parent-report PedsQL using z scores

| **Step 1** N=99, $R^2$=.068, $R^2_{adj}$=.038, *p*=.082 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.444 | .207 | -.215 | -.854 to -.034 | .034 |
| Child's gender | -.134 | .418 | -.032 | -.963 to .696 | .750 |
| Child's age | -.191 | .113 | -.169 | -.414 to .033 | .094 |
| **Step 2** N=89, $R^2$=.604, $R^2_{adj}$=.569, *p*<.001 | | | | | |
| SES | .074 | .148 | .037 | -.220 to .368 | .618 |
| Emotion | -.108 | .037 | -.275 | -.182 to -.033 | .005 |
| Behaviour | .020 | .053 | .039 | -.086 to .125 | .712 |
| Social | -.013 | .050 | -.027 | -.114 to .087 | .794 |
| Motor and Sensory | -.035 | .009 | -.320 | -.053 to -.017 | <.001 |
| Cognition | -.031 | .013 | -.299 | -.056 to -.006 | .017 |
| Caregiver Mental Health | -.305 | .154 | -.153 | -.613 to .002 | .051 |
| **Final model** N=90, $R^2$=.581, $R^2_{adj}$=.566, *p*<.001 | | | | | |
| Emotion | -.119 | .037 | -.305 | -.192 to -.046 | .002 |
| Motor and Sensory | -.035 | .009 | -.322 | -.052 to -.018 | <.001 |
| Cognition | -.031 | .010 | -.301 | -.051 to -.011 | .003 |

### 6.2.3. Time 3

Table 66 reveals that Motor and Sensory functioning and Cognition at T3 predicted parent-report QoL at T3 but contrary to prediction Emotion, Behaviour and Social functioning did not and neither did Caregiver Mental Health. The model showed that an increase in the Motor and Sensory functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .265 of a standard deviation, and an increase in the Cognition z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .677 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the values in the model would vary little across different samples. These three predictors at T1 together accounted for 68% of the variance in parent-report QoL

scores at T1. $R^2$ adjusted was very similar to $R^2$ indicating that not only was the model a good fit but also that it was generalisable to other populations.

Table 66. Forced entry regression model for T3 predictors of T3 parent-report PedsQL using z scores

| **Step 1**<br>N=94, $R^2$=.086, $R^2_{adj}$=.056, *p*=.043 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.456 | .191 | -.242 | -.836 to -.076 | .019 |
| Child's gender | -.179 | .389 | -.047 | -.951 to .593 | .646 |
| Child's age | -.183 | .104 | -.179 | -.390 to .023 | .081 |
| **Step 2**<br>N=84, $R^2$=.706, $R^2_{adj}$=.679, *p*<.001 | | | | | |
| SES | .085 | .125 | .046 | -.163 to .333 | .497 |
| Emotion | -.050 | .040 | -.117 | -.131 to 0.030 | .218 |
| Behaviour | .060 | .033 | .186 | -.005 to .126 | .068 |
| Social | -.022 | .031 | -.063 | -.084 to .041 | .491 |
| Motor and Sensory | -.040 | .012 | -.245 | -.064 to -.016 | .001 |
| Cognition | -.063 | .010 | -.716 | -.083 to -.044 | <.001 |
| Caregiver Mental Health | .006 | .131 | .003 | -.255 to .267 | .963 |
| **Final model**<br>N=84, $R^2$=.683, $R^2_{adj}$=.676, *p*<.001 | | | | | |
| Motor and Sensory | -.043 | .011 | -.265 | -.066 to -.021 | <.001 |
| Cognition | -.060 | .006 | -.677 | -.072 to -.048 | <.001 |

### 6.2.4. Time 1 predictors of Time 3 PedsQL

Table 67 demonstrates that Emotional functioning, Motor and Sensory functioning and Cognition at T1 predicted parent-report QoL at T3 but contrary to prediction Behaviour and Social functioning did not and neither did Caregiver Mental Health. The model showed that an increase in the Emotional functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .246 of a standard deviation, an increase in the Motor and Sensory functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .239 of a standard deviation, and an increase in the Cognitive functioning z-score by one standard deviation (i.e. more difficulties) was associated with a decrease in the PedsQL Total z-score by .447 of a standard deviation. The standard error for beta for each of these predictors was very small indicating that the values in the model would vary

little across different samples. These three predictors at T1 together accounted for 65% of the variance in child-report QoL scores at T3 and $R^2$ adjusted was very similar to $R^2$ indicating that the model was generalisable to other populations.

Table 67. Forced entry regression model for T1 predictors of T3 parent-report PedsQL using z scores

| **Step 1** N=94, $R^2$=.089, $R^2_{adj}$=.059, *p*=.037 | B | SE B | β | 95% CI for B | *p* |
|---|---|---|---|---|---|
| SES | -.458 | .191 | -.243 | -.838 to -.079 | .019 |
| Child's sex | -.174 | .388 | -.045 | -.944 to .597 | .655 |
| Child's age | -.194 | .104 | -.188 | -.402 to .013 | .066 |
| **Step 2** N=81, $R^2$=.663, $R^2_{adj}$=.631, *p*<.001 | | | | | |
| SES | .032 | .134 | .018 | -.235 to .299 | .813 |
| Emotion | -.093 | .044 | -.204 | -.180 to -.006 | .037 |
| Behaviour | .030 | .060 | .057 | -.089 to .149 | .621 |
| Social | -.085 | .046 | -.179 | -.178 to .007 | .069 |
| Motor and Sensory | -.015 | .007 | -.198 | -.029 to -.002 | .029 |
| Cognition | -.041 | .013 | -.426 | -.067 to -.016 | .002 |
| Caregiver Mental Health | -.120 | .125 | -.070 | -.369 to .129 | .340 |
| **Final model** N=81, $R^2$=.646, $R^2_{adj}$=.632, *p*<.001 | | | | | |
| Emotion | -.112 | .042 | -.246 | -.196 to -.027 | .010 |
| Motor and Sensory | -.019 | .007 | -.239 | -.032 to -.006 | .006 |
| Cognition | -.043 | .010 | -.447 | -.063 to -.023 | <.001 |

## 6.3. SUMMARY OF PREDICTORS OF CHILD QOL

Considering the data cross-sectionally, at T1, T2 and T3 emotion and motor and sensory functioning consistently predicted child-report QoL and by T3 cognition became a significant predictor too. According to parents, emotion, motor and sensory functioning, and cognition predicted QoL at T1 and T2 but by T3 even though motor and sensory functioning and cognition remained significant predictors, emotion did not.
Considering the data longitudinally, T1 predictors of child-report QoL at T3 were the child's age, emotion, and cognition, and for parent-report emotion, motor and sensory functioning, and cognition. Thus children and parents agreed that motor and sensory functioning had a consistent impact on QoL over time but for children, in addition,

emotion was an important consistent predictor, and for parents cognition was. When early predictors of later QoL were examined, children and parents agreed that emotion and cognition were significant, and for children, in addition, older age was a significant predictor, and for parents motor and sensory functioning was.

# CHAPTER 7 DISCUSSION

By addressing previous methodological limitations, and taking into consideration common themes identified in previous research this study aimed to investigate:

- whether HRQoL in the first five years after tumour diagnosis differs between children treated for cerebellar tumours, who are old enough to report reliably on their HRQoL, and a comparable representative sample of children in the general population;
- whether there are differences between HRQoL in the children treated for SRM from those treated for LGCA associated with their differing treatments, but common for location in the cerebellum;

The study also aimed to investigate:

- whether QoL in these children changes over time and the factors that impact on QoL and whether these differ over time; and
- whether early predictors that might be amenable to alteration by interventions were predictive of subsequent HRQoL.

Each of these questions will be answered in turn in the light of findings from the present study and evidence from the literature. Inter-informant agreement will also be discussed as well as the sensitivity of the measures used. As this is the first multicentre longitudinal study of comparison of HRQoL in children treated for SRM, LGCA, and a contemporaneous typically developing non-tumour comparison group, and also to investigate early predictors of subsequent HRQoL, direct comparisons with other studies are not possible. Inconsistencies in findings between studies and with the present one may be accounted for by the good sample size in the present study and the two tumour groups were homogenous in terms of tumour type, treatment, child's age, time period in which treatment was given, and interval from diagnosis. By tightly controlling these variables, in the present study, which have been found to affect outcome in these children, in some studies, as discussed in the literature review, adds reliability to the results. The finding that children and parents similarly reported poorer QoL in the SRM group also adds weight to the reliability of the results.

In this study a homogenous sample of children were recruited from a wide geographic area in the UK who had been treated with either surgery alone or surgery plus adjuvant therapy, for tumours at just one location in the brain, the cerebellum. They had all been diagnosed within the previous three years prior to enrolment and were all of sufficient age to provide

reliable self-report but young enough to remain of school-age throughout the study. By studying participants in their home environment, at dates and times that were convenient for them, high levels of participation over a 24 month period were maintained. Attrition over this time was low and mainly due to relapse. In studying a homogeneous group of survivors, it was possible to eliminate the many confounders that have limited the findings from previous studies. I also looked at multiple issues relating to QoL and drew upon three different perspectives, the child's, the parent's and the teacher's. Different informants tended to agree adding weight to the reliability of responses but they also provided different but complementary information. This was particularly true of teachers who provided information about the children's functioning at school.

In addition normative data were not used in the present study but rather a randomly selected appropriate non-tumour comparison group was recruited. This consisted of a representative sample of children of a similar age from the same schools as the children with tumours who completed the questionnaires concurrently. This is essential if a true comparison is to be achieved (Kendall & Sheldrick, 2000). In this way cohort and geographic effects were controlled for.

This study identified early predictors of subsequent QoL. These predictors were theoretically derived and constructed from all the subscales from the questionnaires into domains of function. These domains had good construct reliability and were based on well validated measures with good psychometric properties. This information is critical in the early identification and rehabilitation of patients at risk for impaired QoL given the prevalence of difficulties in later life as mentioned in section 1.1 and also the risk that brain tumour patients may attend fewer follow-up visits (Barakat et al., 2012) thereby reducing their opportunities for interventions over time.

## 7.1. DID QOL DIFFER BETWEEN CHILDREN TREATED FOR CEREBELLAR TUMOURS AND A COMPARISON GROUP?

### 7.1.1. QoL

The finding that children with an SRM and also those with an LGCA had a significantly poorer overall QoL than Comparisons is consistent with that of Bhat et al. (2005) who reported poorer QoL in a heterogeneous sample of children treated for brain tumours, including those with medulloblastoma, in comparison with a sample of healthy children. It

is also consistent with the study of Ribi et al. (2005) who studied survivors of medulloblastoma in comparison to normative data. The finding is however, inconsistent with that of Maddrey et al. (2005) who reported no difference in QoL between normative data and 16 adolescent and young adult survivors treated with different regimens for medulloblastoma. This inconsistency may be accounted for by the homogeneity of the SRM sample in the present study in terms of treatment. Also, the sample in the present study consisted of children who, at T1, were aged eight to 14 years and had all been diagnosed within the previous three years prior to entry to the study, making them relatively homogeneous.

Inconsistencies in outcome can be partly accounted for by the use of different measures in different studies, some of which have low sensitivity to detect intergroup differences. Similarly to Bhat et al. (2005) and Ribi et al. (2005) the present study used the PedsQL to measure HRQoL, a psychometrically sound age appropriate measure, that has been reviewed along with other well-known measures and deemed the best available in terms of its development and psychometric properties (Banks et al., 2008; Eiser & Morse, 2001b).

The finding that compared with the Comparison group, children with an LGCA had significantly poorer overall QoL is consistent with the findings of Pompili et al. (2002) and Aarsen et al. (2006) who also studied survivors of LGCA in comparison with a healthy control group but inconsistent with that of Zuzak et al. (2008), Musial-Bright et al. (2011), Daszkiewicz et al. (2009), and Korinthenberg et al. (2011) who used a variety of measures and compared with published norms their heterogeneous sample of children with LGCA or low grade glioma in a variety of brain regions.

### 7.1.2. Health status

Children in the SRM group had poorer physical health than Comparisons according to both the PedsQL and the HUI. This is understandable given the relatively short interval from diagnosis in which 41% of the children were still on treatment or recovering from treatment. The HUI showed that ambulation, dexterity, pain (by child- and parent-report), hearing and speech (by parent-report) were particularly affected in this group. This finding adds to the evidence that the children were still in a period of treatment or recovery in which fatigue may affect ambulation and some pain may still be present due to treatment related symptoms. It is possible that participants were responding to the ambulation questions in the HUI not because of an inability to walk per se but due to an inability to

walk far due to fatigue. On the other hand, the finding that ambulation, dexterity, and speech were particularly affected may reflect the location of the tumour in the cerebellum which coordinates muscle movements. These domains would have been particularly affected in the 32% of children in this group who had posterior fossa syndrome. Hearing impairment in the SRM group is likely to have been induced by cisplatin in the treatment regimen (Orgel et al., 2012; Yancey et al., 2012).

According to the PedsQL, children with an LGCA had significantly poorer physical functioning compared with Comparisons (by child- and parent-report) but overall health status measured using the HUI was similar to Comparisons. This difference in measures highlights the issue mentioned above that different questionnaires may produce different results. It is possible that a lack of evidence of poorer health status using the HUI could be indicative that it is not sensitive enough to elicit subtle affects or the affects that are particularly pertinent to children with brain tumours. The children in the LGCA group were not free from physical problems post-operatively and had neurological status been measured in the Comparison group and presented alongside the tumour groups, the incidence of physical problems measured in this way, would certainly have been close to zero. Thus, the presence or absence of difficulties depends on what is measured and when.

### 7.1.3. Behavioural functioning

At T1 using the SDQ, by child- and parent-report, children in the SRM and LGCA groups had similar behaviour to Comparisons. However, 38% of children in the SRM group by parent-report had borderline or abnormal scores which is consistent with the finding of Ribi et al. (2005) who reported behavioural problems in 42% of survivors of medulloblastoma. Also the percentage of children in both tumour groups with borderline or abnormal scores was higher than Comparisons by parent-report. By teacher-report children in the SRM group only, had significantly poorer behaviour than Comparisons and this was reflected in the higher percentage of children in the SRM group with borderline or abnormal scores compared with the small proportion of children in the Comparison group. Using the BRIEF teachers also reported poorer behavioural regulation in the SRM group compared with Comparisons. These findings indicate that the children in the SRM group had behavioural difficulties in the school environment that were not apparent at home when compared with the Comparison group. This finding contrasts with that of Upton and Eiser (2006) who reported more behavioural problems at home than at school in children treated for various brain tumours. However, as already mentioned, it all depends on how

one looks at the data. In the present sample of children treated for SRM, although behavioural difficulties scores were higher at home than at school, there was a greater difference in scores compared with the Comparison group at school. This highlights again the importance of including a Comparison sample to help with the interpretation of findings.

Although no difference was found in behavioural functioning in the LGCA group compared with Comparisons, 24% of children in the LGCA group had borderline or abnormal scores at T1 by parent-report. This is consistent with the findings of Steinlin et al. (2003) and Daszkiewicz et al. (2009) who reported behavioural difficulties in 33% and 50% respectively of patients treated for benign cerebellar tumours. Unlike the SRM group, the LGCA group, by teacher-report seemed to be functioning within the normal range at school when comparing the percentages of borderline or abnormal scores compared with the Comparison group.

The finding that behavioural difficulties in the SRM group were particularly apparent in the school environment may partly be due to the amount of time that the children had been absent from full time education during initial illness due to the tumour and following surgery (Upton & Eiser, 2006) coupled with the importance that children ascribe to getting good marks at school (Mares & Neusar, 2010). The children in the SRM group were having significant difficulties at school by child- and by parent-report according to the PedsQL whereas in the LGCA group, difficulties at school were reported only by parents and not by children themselves. The finding that teachers reported behavioural problems in the SRM group and that the children themselves reported difficulties at school as well, whereas teachers did not report behavioural difficulties at school in the LGCA and these children did not report difficulties at school themselves, indicates that the behavioural problems at school were related to having an SRM rather than an LGCA.

### 7.1.4. Social and school functioning

Children in both tumour groups had poorer psychosocial health than Comparisons by child- (in the SRM group only) and also by parent-report (in both tumour groups) which was accounted for by social and school functioning. As already mentioned, at T1 many of the children in the SRM group and a few in the LGCA group were still in a period of treatment or recovery and this period was characterised by school absences and as a result, social isolation (Upton & Eiser, 2006). Social isolation can be further exacerbated by

rejection by peers (Noll, Ris, Davies, Bukowski, & Koontz, 1992), although there was no evidence of this in the present study from child-, parent-, and teacher-report using the SDQ. In addition cognitive impairment may affect a child's ability to understand social cues and relationships (Nassau & Drotar, 1997) further exacerbating social difficulties. This finding showing early difficulties with schooling and social relationships is important and may have far reaching consequences (Kupersmidt et al., 1990) given the significance of school to feelings of achievement in children (Mares & Neusar, 2010), as already mentioned.

### 7.1.5. Emotional functioning

At T1 according to the PedsQL and HUI (in the SRM group only) by parent-report only, children in both tumour groups had significantly poorer emotional functioning compared with Comparisons. Teachers also reported in the SRM group difficulties in terms of the children experiencing emotional symptoms (according to the SDQ) and controlling their emotions (according to the BRIEF) at school. The children themselves did not report emotional difficulties. Thus, were emotional difficulties present or not in these children? It could be that emotional difficulties were present but the cross-informant variance may be due to the children not being at a developmental level to understand the emotional impact of their illness (Landgraf & Abetz, 1996) and also having an underdeveloped awareness of their psychological self, including emotional functioning (Cremeens et al., 2006, 2007; De Civita et al., 2005). On the other hand, it could be that emotional difficulties were absent and parents over-reported emotional difficulties due to them being unaware of their children's emotional functioning (Morrow et al., 2012; Sprangers & Aaronson, 1992) although it is more likely that they were more aware of their sick child's emotional functioning (De Bolle et al., 2008; Eiser & Morse, 2001a) especially in light of their young age (April et al., 2006; Guyatt et al., 1997; Jokovic et al., 2004) and involvement with their children particularly during this period of recovery (Jokovic et al., 2004). Thus the evidence indicates that parent-report in the present study was reliable and the children were experiencing emotional difficulties, in particular in the SRM group as evidenced also by teacher-report. The finding that emotional difficulties in the LGCA group were only apparent according to the PedsQL may indicate that this measure is more sensitive than the HUI or the BRIEF.

### 7.1.6. Cognitive functioning

At T1 by parent-report (but not child-report) of the HUI, teacher-report of the BRIEF, and the children's performance on the WISC, children in the SRM group had significantly poorer cognitive functioning, executive functioning and IQ compared with Comparisons. In the LGCA group, only the WISC showed a significant difference in IQ scores compared with Comparisons. This difference was due to poorer perceptual reasoning and processing speed in the LGCA group. Children with an SRM had significant problems with shifting attention (according to the BRIEF and SDQ), controlling their emotions, initiating actions, working memory (according to the BRIEF and the WISC) verbal comprehension, perceptual reasoning, and processing speed. Teacher-report of executive functioning was likely to be accurate as the ratings ascribed to the Comparison group were around 50 with a standard deviation of ten which is equivalent to normative data. It is possible that teachers can provide more accurate knowledge of deficits in executive functioning due to having more opportunities to observe typically developing children. The lack of reporting of cognitive difficulties on the HUI by the children in the SRM group could show a lack of awareness of their own cognitive difficulties. These findings support previous findings of cognitive deficit in children treated for medulloblastoma (George et al., 2003; Grill et al., 1999; Kieffer-Renaux et al., 2000; Mulhern et al., 1998; Palmer et al., 2001; Saury & Emanuelson, 2011). The finding that children with LGCA also experienced cognitive deficits in particular in relation to perceptual reasoning and processing speed provides further evidence for the cerebellum being involved with cognitive functioning (Schmahmann & Sherman, 1998). The children treated for LGCA in the present study, did not show cognitive deficits to the extent that has been reported in some previous studies of older survivors and this could be due to the short interval from diagnosis which means that the children had not yet grown into deficits (Aarsen et al., 2006; Levisohn et al., 2000). In some survivors of LGCA, cognitive deficits do not become apparent until many years post diagnosis (Aarsen et al., 2009).

### 7.2. DID QOL DIFFER BETWEEN CHILDREN TREATED FOR SRM AND LGCA?

Children in the SRM group had a poorer QoL than those in the LGCA group. By parent-report, children with an SRM also had significantly poorer physical functioning according to the PedsQL and poorer overall health status according to the HUI compared with children with an LGCA. This was due to poorer vision, hearing, speech, ambulation, emotion, and more pain. This finding is consistent with that of Bhat et al. (2005), Benesch et al. (2009), and Roncadin et al. (2008) and is understandable given the short interval from diagnosis in the present study. As already mentioned, some of the children in the SRM

group were still on treatment during this time and the others who had finished treatment were still in a period of recovery, whereas those in the LGCA group had received no other treatment following surgery.

A higher proportion of children in the SRM group had more clinical neurological problems pre-operatively and showed a greater adverse change post-operatively than children in the LGCA group. Although Roncadin et al. (2008) reported that children treated for medulloblastoma or cerebellar astrocytoma presented similarly at diagnosis and experienced similar perioperative events, that study may have had a selection bias towards patients with fewer events peri-operatively: fewer of the medulloblastoma survivors in their sample had had cerebellar mutism compared to the sample in the present study (17% vs 32%) or other large studies of children with medulloblastoma (e.g. Robertson et al., 2006). As already mentioned, the sample in the present study consisted of children who had been recruited consecutively, some of whom later relapsed and therefore was representative of a typical group of children diagnosed with SRM.

Compared with those in the LGCA group, a much higher proportion of children in the SRM group experienced severe pre-operative hydrocephalus, upper limb and truncal ataxia, and impaired balance. This difference could be due to faster growth of malignant tumours causing more rapid progression of hydrocephalus and other neurological symptoms (Dorner, Fritsch, Stark, & Mehdorn, 2007). The greater adverse change in neurological problems post-operatively in the medulloblastoma group reflects a higher risk of surgical complications: Cerebellar astrocytomas are mostly well circumscribed, more laterally located (i.e. arising from the cerebellar hemispheres rather than the cerebellar vermis or brain stem) and more easily resected than medulloblastomas without damage to healthy tissue (Nejat, El Khashab, & Rutka, 2008). In addition, neurosurgeons may feel under more pressure to achieve a complete resection of a medulloblastoma because of the associated higher risk of relapse with residual tumour leading rapidly to death in most cases (Nejat et al., 2008).

Using the SDQ, by child- and also parent-report, behaviour in both tumour groups was similar but by teacher-report, children in the SRM group had significantly poorer behaviour than children in the LGCA group at school which was accounted for by poorer emotional functioning. An inter-group difference in emotional functioning was not identified using any of the other measures. This may indicate that the children in the SRM

group were having a more difficult time at school than those in the LGCA group. There was some evidence of this from the parent-report PedsQL which showed poorer school functioning in the SRM group compared with the LGCA group. Parents, but not children, also reported significantly poorer social functioning in the children treated for SRM compared with the LGCA group. This difference was not identified in other measures but does show the relationship perceived by the parents between school and social functioning.

The finding that there was no significant difference in executive functioning or IQ between children with SRM and those with LGCA is important. This coupled with the finding that children with LGCA had significantly lower IQ than the Comparison group, that IQ remained the same at each time point in each group, and that cognitive functioning was a significant predictor of QoL shows that cognitive deficits were evident from an early stage in the LGCA group and persist in the same way as they do in the SRM group. These findings show evidence of the cognitive affective syndrome (Levisohn et al., 2000) and are consistent with other studies (Aarsen et al., 2009; Aarsen et al., 2006; Beebe et al., 2005; Hirsch et al., 1979; LeBaron et al., 1988; Pompili et al., 2002; Riva & Giorgi, 2000; Steinlin et al., 2003) which also reported cognitive deficits in children treated with surgery alone for LGCA.

### 7.3. DID QOL CHANGE OVER TIME?

The finding showing steady improvement in QoL, health status, physical health, particularly ambulation, dexterity and pain, and school functioning in the SRM group by both child- and parent-report shows that these children have the capacity to improve within the first few years following diagnosis, at least. These improvements may reflect transient effects of treatment from which the children are able to recover. However, these findings must be viewed in the context of very poor HRQoL and health status reported at T1. At T3, over two thirds of children in the SRM group still had scores within the 'at significant risk' category for poor HRQoL. Behavioural functioning was similar to the Comparison group at T1 and did not change over time which indicates that behavioural difficulties were not an issue for these children or their parents at home.

However, at school, behavioural functioning was significantly poorer than the Comparison group at T1 and did not improve showing that difficulties at school in the SRM group persisted. Also executive functioning in these children declined by teacher-report and although IQ did not decline, it did remain the same and was significantly poorer than the

Comparison group at T1. Children's experience of school however, seemed to improve as evidenced by their reported improvement in school functioning. This may be due to the finding that some of the children improved at school and no longer required extra help while others who were in need changed from receiving help similar to other children to receiving specific help. Thus, although teachers reported continued difficulties at school, children's experience of school improved.

Although children in the LGCA group had significantly better HRQoL and health status than those in the SRM group and also higher IQ, these were significantly poorer compared with the Comparison group at T1 and there was no improvement over time. This lack of improvement is surprising and also concerning given that QoL improved not only in the SRM group but also in the Comparison group (see below possible reasons for this). This may indicate that the capacity for recovery in this group may be limited. By T3 a quarter to a third of the children in the LGCA group were still within the 'at significant risk' category for poor QoL. This does not show evidence of response shift (Hays, 2005) and may show that these children are not adapting in the same way as the ones in the SRM group. These findings could indicate that the relatively less obvious problems experienced by these children compared with those experienced by children with an SRM were overlooked by health professionals and also teachers leading to a lack of attention to these children's needs and therefore a lack of support. The findings of LeBaron et al. (1988) that some deficits may not necessarily be evident to trained professionals without proper evaluation is in keeping with this explanation. This oversight is exacerbated by the expectation by professionals that children having had surgery alone for LGCA and no adjuvant treatment, once recovered, can resume their previous activities as before. Evidence from the present study clearly puts into question this assumption. This lack of support would also explain the consistent relationship between parental mental health and HRQoL in this group. Behavioural and executive functioning, which were similar to the Comparison group at T1, did not change in the LGCA group which indicates that these were not an issue in these children.

Lack of improvement in the LGCA group could indicate that the deficits experienced are due to damage of healthy tissue caused by the tumour and or surgery from which the child may have limited capacity to recover over time. In addition, the follow-up period of the study may not have been long enough to allow the emergence of further deficits that Aarsen et al. (2009) had found. The improvements observed in the SRM group in the

present study may reflect gradual recovery from the effects of treatment which may take time. This provides hope of further recovery for children with SRM and indicates that for children with LGCA it is imperative that help be given early on as improvement is likely to be limited.

The finding that QoL, in particular emotional and social function, in the Comparison group improved over time by child-report was surprising. In contrast, parent-reported scores showed remarkable consistency. It is difficult to explain why child-report QoL would have improved in this group. It could be due to the particularly vulnerable time that children go through during development when more demands are placed on them in the school environment as they make the transition from primary to secondary school (Carmen, Waycott, & Smith, 2011; Lanson & Marcotte, 2012; Lester, Cross, Shaw, & Dooley, 2012; Rice, Frederickson, & Seymour, 2011) and the effect this may have on the child's psychosocial functioning. This may also explain why children self-reported increasing age as a predictor of poorer HRQoL in the sample of eight to 14 year olds in the present study. This could also be due to older children in the tumour groups having a better formed memory or an idealised memory of their former HRQoL which negatively affected their post tumour ratings of their current HRQoL. These findings highlight the importance of including a contemporaneous typically developing group whose scores may reflect events in the social context common to all children. Children diagnosed with a tumour around this time may therefore suffer particularly during adolescence and therefore special provision needs to be made for them to reduce the impact on their HRQoL by providing timely support at school.

The findings in the present study are discrepant with those of Penn et al. (2008) and Penn et al. (2009) who reported improved HRQoL within the first year following diagnosis in their heterogeneous sample which mainly consisted of 17 low grade astrocytoma patients and in the present study there was no improvement in this group. The important difference between the two studies is the short follow-up period of one, six and 12 months post diagnosis in their study in which the children will have still been recovering from surgery and gradually returning to school, compared with 16, 27, and 36 months in the present study where the children will have recovered as much as they were likely to and all were back at school.

### 7.4. WHAT WERE THE PREDICTORS OF QOL?

In the SRM group there was a higher proportion of lone parents, parents who were not working, and parents with school qualifications only. There appears to be no systematic reasons for these demographic differences and the finding that SES was not a predictor of the child's QoL shows that these differences were not important. The child's sex did not predict QoL either. These findings are consistent with some studies (Aarsen et al., 2006; Bhat et al., 2005; Eiser, Vance, Horne, Glaser, & Galvin, 2003; Penn et al., 2009; Pogorzala et al., 2010; Ribi et al., 2005; Russell et al., 2006; Shankar et al., 2005) whereas others have reported poorer QoL in females (Alessi et al., 2007; Hudson et al., 2003; Nathan et al., 2007; Reulen et al., 2007; Sands et al., 2012) but who were all older than in the present study and treated for a variety of malignancies. It's possible therefore that greater deficits in HRQoL in females may become apparent in the present sample with time but only further follow-up would answer this question. The multiple regression models showed that parental mental health, similar to the finding of Penn et al. (2009), and the child's behaviour were not predictive of QoL either.

Cross-sectionally, at each time point, by child- and parent-report, motor and sensory functioning consistently predicted QoL. For children, in addition, emotion was a consistent predictor and for parents, cognition was. By T3, for children, cognition became a significant predictor too and for parents, although emotion was important at T1 and T2 by T3 it no longer was. Longitudinally, for children and parents, emotion and cognition at T1 significantly predicted QoL at T3 and additionally for children, age, and for parents, motor and sensory functioning. These findings in combination show that better emotion, cognition, and motor and sensory functioning are associated with better QoL and older children are more vulnerable.

These findings confirm the significant contribution of emotional functioning in combination with cognitive functioning to the concept of QoL as reported by others (Cramm & Nieboer, 2012; Ellenberg et al., 2009; Flouri & Panourgia, 2011; Koenen et al., 2009; Pine & Freedman, 2009) especially in those children treated for tumours of the cerebellum (LeBaron et al., 1988; Levisohn et al., 2000; Ribi et al., 2005; Schmahmann & Sherman, 1998; Zuzak et al., 2008). The cognitive reserve hypothesis (Stern, 2002) that good cognitive functioning skills protect against mental illness can also shed light on these findings in that the children in the present study have a high risk of acquired brain injury from having a tumour and also the surgery to remove it and then those with an SRM have an additional risk from adjuvant treatment. They therefore have a high risk of losing the

ability to problem solve effectively and therefore do not possess the resources to overcome their difficulties by finding appropriate strategies. It is hardly surprising then that these children suffer poorer QoL.

### 7.5. WAS THERE INTER-INFORMANT AGREEMENT?

The lower HRQoL scores reported by parents relative to their ill children is consistent with previous findings (e.g. De Bolle et al., 2008; Kuhlthau et al., 2012; Levi & Drotar, 1999; Ribi et al., 2005; Russell et al., 2006; Upton, Lawford, & Eiser, 2008) but cross-informant variance for psychosocial functioning was greater in the SRM group than in the Comparison group. Although I did not look at statistical differences between child and parent report, the mean differences in the SRM group between the psychosocial, school functioning and emotional functioning domains were 10.7, 9.7 and 12.1. These are large differences when compared with differences between child- and parent-report in the Comparison group of 1.9, 1.3 and 2.8 with parents reporting higher scores than their children. However, the parents of the children in the non-tumour comparison group seemed to be unaware of the change over time in their children's QoL due to improvements in social and emotional functioning, domains that may not easily be observable by parents (Sprangers & Aaronson, 1992).

Compared with ratings in the LGCA group, parents of children in the SRM group rated their psychosocial functioning much lower than their children. The groups differed only with regard to the addition of adjuvant therapy in the SRM group and this may have been the reason for this difference. Prolonged treatment in the SRM group as described in the child's account in section 1.1 and the constant threat of relapse especially early on may have affected the parents mental health causing them to perceive their child's psychosocial functioning poorer than their children did (Arnaud et al., 2008; Cramm & Nieboer, 2012; Giannakopoulos et al., 2009). However, parental mental health was not found to be a predictor of HRQoL in the SRM group cross-sectionally or longitudinally and either parent ratings were not influenced by their own feelings or the GHQ-12 was not sensitive enough.

The children and parents agreed on the differences between the three groups in terms of physical functioning measured using the PedsQL but the mean differences between the groups were greater in the parent-report. This may be explained by the general tendency of parents of ill children to overestimate their child's difficulties compared with the children themselves (Sprangers & Aaronson, 1992) and for parents of 'healthy' children to

underestimate difficulties thus increasing the mean differences between the groups in parental reports (Eiser & Morse, 2001a). This agreement between parents and children provides evidence for inter-rater reliability between child- and parent-report of these domains of HRQoL. Although there was a significant difference between each group in terms of overall physical health by child-report, when more precise attributes of physical functioning were examined using the HUI questionnaire, children reported differences only between the SRM and Comparison groups and only in terms of ambulation and dexterity whereas parents reported a greater number of differences in attributes affected between not only the SRM and Comparison groups (hearing, speech, ambulation and dexterity) but also between the SRM and LGCA groups which include vision in addition but not dexterity. Parents and children agreed that the biggest mean difference between the Comparison and SRM groups is ambulation followed by dexterity. The differences between the child and parent views using the HUI questionnaire again seems to reflect that the parents of the ill children viewed their functioning as being poorer than the children do themselves. It could be that parents are better observers of their children's physical states than the children are of their own physical states when they are ill. Parents may possibly become more acutely aware than the children do themselves.

Children and parents agreed that motor and sensory functioning had a consistent impact on QoL over time but for children, in addition, emotion was an important consistent predictor and for parents cognition was. When early predictors of later QoL were examined, children and parents agreed that emotion and cognition were significant and for children, in addition, older age was a significant predictor and for parents motor and sensory functioning was. Cross-informant consistency of some findings shows reliability of the reports and where there is variance between reports, it shows that children and parents may focus on different domains and the information should be viewed as being complementary rather than unreliable (Achenbach et al., 1987; Guyatt et al., 1997).

However, there were remarkably similar patterns of scores between respondents and time points even if not significant. This similarity between respondents provides evidence for reliability especially for teacher-report when the accuracy of their responses is reflected in the scores given to the Comparison group which were in the expected normal range and in the case of the BRIEF, remarkably similar to the score of 50 that would be expected as the mean average for this questionnaire.

Higher percentages of children with impaired QoL were reported by parent- than by child-report in all groups. According to child-report, cognitive and emotional function measured early along with the child's age significantly predicted subsequent QoL and accounted for a large proportion of the variance in scores. By parent-report the predictors were emotional, motor and sensory and cognitive functioning, which accounted for a larger proportion of the variance in scores than by child-report.

### 7.6. HOW SENSITIVE WERE THE MEASURES?

The PedsQL appears to have distinguished well between the three groups of children and shown that children with an SRM had a significantly poorer overall QoL than children with an LGCA or Comparisons. It captured well the differences between the groups in terms of physical health which was found to be significantly poorer in the children with an SRM. This was to be expected given that these children were still either on treatment or recovering from it at a mean interval of 16 months post diagnosis.

The PedsQL also captured well differences between the groups in terms of psychosocial functioning. The children in the SRM group differed significantly from Comparisons, but not from the children in the LGCA group, in terms of social and school functioning but not emotional functioning. The children in the SRM group were absent from full-time education for around 16 months, and those in the LGCA group for eight months, which would have limited their social contact.

The fact that health status by child-report, as measured by the HUI was similar in both tumour groups but physical functioning measured by the PedsQL showed poorer functioning in the SRM group, may indicate that the PedsQL is a more sensitive instrument for detecting child-report physical functioning.

The SDQ did not detect differences between the groups by child- or parent-report but did detect differences by teacher-report. It is possible that the children in particular had lack of insight into their own behaviours or that parents and children were showing denial of difficulties (Carpentieri et al., 2003) or showing social desirability bias, or the questions themselves may not have been sensitive enough to detect specific behavioural difficulties or personality changes in children treated for cerebellar tumours characterised by blunted affect, and disinhibited and inappropriate behaviour (Schmahmann & Sherman, 1998) or irritability (Daszkiewicz et al., 2009; Riva & Giorgi, 2000) or autistic like behaviours

(Riva & Giorgi, 2000). Teachers, on the other hand can be more objective. When answering questions about their pupils, they are less likely to be influenced by denial or social desirability. They may also have better insight into children's behaviour as a result of being able to draw on their observations of many children in the school environment. These reasons may also account for the apparent lack of sensitivity of the BRIEF to distinguish between the groups by parent-report, but not by teacher-report.

### 7.7. LIMITATIONS OF THE STUDY

The sample size in this study was similar to that expected and larger than in many studies reviewed. However, a larger sample would have been desirable but not possible within the deliberate constraints to limit heterogeneity of the sample with regard to age and tumour location and within the population of England and Wales. A reduction in the number of participants is inevitable in a longitudinal study and this one was no exception. However, there was a high rate of enrolment among those informed about the study of 96% within the tumour groups which reflected families' motivation to take part in such a study. Participant drop out was in fact mainly due to relapse. The high participation and retention rates increase the likelihood that the findings generalizable to the population of children surviving cerebellar tumours given that most families took part. In order to increase the sample size while maintaining homogeneity of the sample, and ensure generalizability by including the whole population, and to follow progress over a longer period of time, ideally the study would have been conducted in a treatment trial.

At T1 41% of the sample of children in the medulloblastoma group were still on treatment. Interval from diagnosis in both tumour groups ranged between 1 and 35 months. This means that some of the children in the medulloblastoma group were still poorly at this time but nevertheless they were all well enough to take part in the research, even the children who had had posterior fossa syndrome. This may have accounted for the improvement in QoL over time that was not observed in the LGCA group. It is possible that the improvement in QoL observed in the SRM group would have plateaued given a longer follow-up period.

Because it was crucial not to over burden families, questionnaires were completed by respondents before each home visit to reduce the time of the visit. This meant that it was not possible to monitor directly how the questionnaires were completed. However, before mailing the questionnaires to families, at each time point, I tried to reduce possible

unwanted effects by explaining by telephone the importance of being as honest as possible with their answers. I also tried to reduce parental influence by emphasizing to parents that if the child required help with their questionnaires then this should only be to help them read and not to help them choose answers even if the child responded in ways that the parent did not agree with. I emphasized that they should not react to 'strange' choices of items but just to accept and respect their child's choices. I emphasized that I was very interested in the children's views and that they should not influence their child's choices in any way. Parents and children were highly motivated to participate as evidenced by the high retention rate. They also took their participation seriously and therefore in spite of the limitations of using questionnaires, I believe that the responses were genuine and therefore reliable.

Respondents are restricted by the items on questionnaires which are created for the average person who in reality does not exist and questionnaires can only enquire about common situations rather than a whole gamut of experiences. This means that some issues may not have been adequately covered. However, the selection of the questionnaires and the domains of functioning were based on theory and the issues that had been perceived to be important in previous research. Some of the questionnaires may not have been sensitive enough to identify particular issues pertinent to children with brain tumours. This may be why the SDQ, for example, or the BRIEF by child- and parent-report did not show differences between the groups but nevertheless provided valuable information from teachers. There is always the temptation to include other factors of interest but it is important not to overburden participants, especially children who are unwell or tired from treatment.

An important advantage of questionnaires relative to direct assessment is that they are non-confrontational in the sense that the respondent can complete them in their own time and not feel pressured or rushed or embarrassed. This is a particularly important point regarding assessment of the children in this study who on the whole had had reduced cognitive functioning and in particular processing speed.

A direct assessment of executive functioning would have been a desirable addition but impractical due to time constraints on home visits. It took at least an hour to administer the WISC which was the limit for some children's ability to concentrate and to sit still at a table. The WISC was not administered in optimum circumstances in participants' homes

but any context effects should have been equal across groups. However, optimal circumstances for administering the WISC are not always achieved in a clinical setting either. Some of the children who had been treated for brain tumours found completing the WISC difficult due deficits in cognitive functioning (!), feeling emotional and being aware of their own failings especially on some of the tests where there is a need to fail several times before testing can be stopped. This latter point is important because unlike children with congenital deficits who have never known being any different, children with brain tumours that present in the second half of childhood are fully aware of their former better functioning selves. Being tested with the WISC simply served to highlight to them their failings and some children found this difficult which raises the issue of whether it is ethical to test these children with such direct assessments. It also meant that I was not always able to follow standard administration rules due to the overriding need to put the child at ease. For these reasons I would not favour using the WISC in future studies but perhaps a simpler form such as the WASI.

### 7.8. FUTURE DIRECTIONS

It is clear from these findings that HRQoL difficulties become apparent at an early stage and persist not only in the short term but also in the longer term as evidenced by the studies mentioned in section 1.1. The best way forward for future research into HRQoL in children treated for brain tumours is to systematically assess HRQoL within the context of large multicentre paediatric brain tumour treatment trials. In this context, all the children receive the same treatment for the same type of tumour and progress can be monitored over time. This will overcome many of the limitations inherent in research in this field as discussed in this thesis. By prospectively studying children in this way, it will be possible to really see how their HRQoL changes over time and the factors that affect it that may be amenable to intervention. In addition, HRQoL information may help to inform clinicians as to the best treatment to use where survival rates are similar between treatment arms. Steps have already been taken to do this by the Children's Oncology Group in the United States and also by the Quality of Survival Group in European treatment trials conducted by the Brain Tumour Group of the International Society of Paediatric Oncology.

Some of the discrepancies in findings between studies could be eliminated if common ground was established in terms of measures used to assess children. A common set of psychometrically sound age appropriate measures should be used to enable comparison between studies, and that can be applied using an efficient method to encourage continued

participation over time. This can be problematic cross nationally but the questionnaires used in this study, the SDQ, BRIEF, PedsQL and HUI are available in many languages. Difficulties identified in cohorts of children within the context of large treatment trials are more likely to be reliable and can inform the development of appropriate intervention strategies with the aim of reducing deficits in survivors in the long term.

The present study has shown that children with SRM may be particularly vulnerable in the school environment, especially those who are older and going through the transition from primary to secondary school, which is a vulnerable time for all children. Futures studies should focus on developing interventions that will maximise good reintegration into school post treatment, the transition from primary to secondary school, and also to help children manage with the demands of the school environment. Some cognitive remediation and other interventions are already available, and to an extent have been successfully used in children with brain tumours in the short and medium term (Butler, Copeland, et al., 2008; Butler, Sahler, et al., 2008; Carmen et al., 2011; Patel, Katz, Richardson, Rimmer, & Kilian, 2009; Rey-Casserly & Meadows, 2008) although cognitive remediation programmes aiming to improve attention, memory and/or executive functioning in children with acquired brain injury shows inconclusive evidence for the efficacy of such interventions (Limond & Leeke, 2005). Therefore, there is still a lot of work to be done in this field of research.

The data set gathered for the present study is rich. I had to make difficult choices regarding which data to analyse and how to analyse it keeping in mind the hypotheses to be tested and the issue of multiple testing. This is not to preclude alternative analyses that could be performed on the data in the future. For example, statistical analysis could further examine the longitudinal relationships between variables to identify mediators and moderators. This could be achieved using various techniques such as structural equation or multilevel modelling and multiple or logistic regression. In addition sub-group analyses could be performed with regard to post-operative morbidity. For example, the differences between those children with and without cerebellar mutism could be explored. Other important analyses to consider, given detailed neurosurgical data, are the relationships between anatomical differences within the cerebellum itself in terms of specific location of the tumour and neurosurgical damage caused to the structures of the cerebellum. This may serve to identify in particular those children with LGCA who had received no adjuvant therapy but who nevertheless experienced persistent impairments in QoL and IQ.

## 7.9. CONCLUDING REMARKS

This thesis opened with a quote from the WHO, 'The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being…' The right to health does not mean the right to be healthy but rather the right to access services to increase an individual's chances of being healthy. Governments must provide health services, healthy and safe working conditions, adequate housing and nutritious food to improve the chances of all members of society to be as healthy as possible.

Many of the children in this study were not enjoying the health that they were entitled to. They had certainly received the medical interventions necessary to save their lives but their persistent post treatment poor QoL showed a definite need for early psychosocial interventions, especially in older children, to improve their chances of reaching 'the highest attainable standard of health', in the widest sense of the term. Early intervention is vital to help these children experience a QoL that is commensurate with their peers. However, in spite of a growing body of evidence of neurocognitive and other deficits among survivors, and increased awareness among relevant professionals of the need for aftercare justifying regular cognitive assessment, delays in the identification of difficulties persist (Aukema, Last, Schouten-van Meeteren, & Grootenhuis, 2011) and are perpetuated by guidelines recommending psychological assessment only when concerns are raised by teachers or parents (Lancashire et al., 2010). Risk screening at diagnosis and annually may be achieved using questionnaires at follow-up clinics and by teachers at school, or easily and speedily administered tools that correlate with IQ (Castellino, Tooze, Flowers, & Parsons, 2011; Krull, Okcu, et al., 2008). Those children screening positive for abnormally elevated scores could then be referred to psychology services for further more in depth investigations.

In view of the findings from the investigation described in this thesis, particularly the unexpected finding showing that HRQoL in children with an LGCA did not improve over time, I would make the following recommendations for practice and policy:

- Given that 65% of children with SRM and 36% of those with LGCA were at significant risk of poor QoL more than three years post diagnosis, all children following surgery for a tumour, regardless of type, should be systematically assessed at their first and subsequent outpatient appointments using the child- and

parent-report PedsQL as lower scores (see below) on this questionnaire could indicate important underlying cognitive and emotional difficulties in the child.

- Given that the proportion of children receiving specific extra help at school increased steadily over time from 40% to 57% in children with SRM and from 11% to 24% in those with LGCA, that teachers reported borderline or abnormal behaviour more than three years post diagnosis in 25% of children with SRM and 16% of those with LGCA compared with only 3% in the Comparison group, and that teachers reported that the proportion of children with executive dysfunction in the SRM group remained relatively high at 38% and increased steadily over time in the LGCA group from 14% to 36%, and that over time IQ did not change and remained poorer than Comparisons in both tumour groups, once the child is back at school, the SDQ and the BRIEF should be given to the member of staff who knows the child best. The child and parent will be able to identify this person easily. This person may be different at subsequent appointments and this will need to be checked with the child and parent.
- These three questionnaires are familiar to clinical and educational psychologists and could easily be scored and also interpreted by them. The cut off scores for clinical risk described in this thesis and also in the scoring instructions for each of the questionnaires could be used as an indicator for further in depth investigation of a child at risk and subsequent intervention. For the PedsQL a total score of < 69.7 for self-report and < 65.4 for parent-report is recommended; for the teacher-report SDQ a total score of >11; and for the teacher-report BRIEF a total score of >65 is recommended.
- These recommendations have implications for the availability of psychological services for each child assessing positively for further in depth psychological assessment on the aforementioned measures. This would require a change in policy from a reactive one to a pro-active one and would be a step nearer to a package of rehabilitation services that should be available to all children treated for brain tumours, similar to the practice in France where all these children are systematically assessed and monitored over time. In this way, a reduction in the relative risk of poorer social outcomes described by Boman et al. (2010) may be achieved in survivors thereby reducing the impact on society.

Assessing and addressing deficits early is vital particularly cognitive and emotional functioning which were found to be early predictors of HRQoL in this study. Given that

most children will survive into adulthood and live long term with the physical, psychosocial, and economic consequences of having had a brain tumour in childhood, early interventions need to be implemented to improve their subsequent life chances.

## Appendix A. Detailed analytic strategies

### Analytic strategy for child-report of PedsQL

The PedsQL Total score data were normally distributed and so a one-way ANOVA was conducted to test for differences in overall QoL scores between the three groups. Planned contrasts for unequal variances then revealed significant differences between the three groups. Further tests were conducted to establish which of the two summary scores, Physical Health or Psychosocial Health, accounted for these differences in overall QoL between the three groups.

For the Physical Health Summary score the distribution of the data was not normal in any of the three groups and so a Kruskal-Wallis test was conducted to test for overall group differences. Mann-Whitney *U* tests were conducted following the significant Kruskal-Wallis test to see which specific groups differed in physical health. For the Psychosocial Health Summary score the data in each group were normally distributed so a one-way ANOVA was conducted to test for overall group differences. Following the significant effect of group, post hoc tests were conducted using the Games-Howell procedure, which is used in circumstances where there are unequal variances and small differences in sample sizes.

Further analyses were conducted to see which of the three scales: Emotional, Social or School Functioning significantly contributed to the significant difference in the Psychosocial Health Summary score found between the SRM and Comparison groups. For the Emotional and School Functioning subscale, the scores were normally distributed in both groups but for the Social Functioning subscale the scores were not normally distributed. Therefore for the two former subscales, *t* tests were conducted and for the latter subscale a Mann-Whiney *U* test was conducted to test for differences between the two groups.

### Analytic strategy parent-report of PedsQL

For the PedsQL Total score the data were normally distributed in the SRM group but not in the Comparison or LGCA groups. Therefore a Kruskal-Wallis test was conducted to test for differences in the PedsQL Total scores between the three groups. Following a significant effect of group, Mann-Whitney *U* tests were conducted to follow-up this finding. Following a significant difference between the three groups further tests were

conducted to establish which of the two summary scales, Physical Health or Psychosocial Health, accounted for these differences in overall QoL between the three groups.
For the Physical Health Summary score the data in each group were not normally distributed. For the Psychosocial Health Summary score the data in the SRM and LGCA groups were normally distributed but not in the Comparison group. Thus, for both the Physical Health Summary score and for the Psychosocial Health Summary score a Kruskal-Wallis test was conducted to test for differences between the three groups. There was an effect of group for both summary scores so Mann-Whitney *U* tests were conducted to follow-up these findings.

Further analyses were conducted to see which of the three scales: Emotional, Social or School Functioning significantly contributed to the significant difference in the Psychosocial Health Summary score found between each of the three groups. For the Emotional Functioning subscale, the data were normally distributed in each of the three groups, for the Social Functioning subscale the data were normally distributed in the SRM group but not in the LGCA or Comparison groups and for the School Functioning subscale, the data were normally distributed in the SRM and Comparison groups but not in the LGCA group. Thus, for the Emotional Functioning subscale, a one-way ANOVA was conducted, and for the Social Functioning and School Functioning subscales a Kruskal-Wallis test was conducted.

Following an overall effect of group on emotional functioning, post hoc tests using Gabriel's procedure, which is used in circumstances where there are small differences in sample sizes, were conducted to test for specific group differences. Following an overall effect of group on social and school functioning, Mann-Whitney *U* tests were conducted to follow up these findings.

**Analytic strategy child-report of HUI**

For the HUI3 overall HRQoL score the data were highly negatively skewed in each group. Therefore a Kruskal-Wallis test was conducted to test for differences in the HUI3 overall HRQoL scores between the three groups. Following a significant group effect, Mann-Whitney *U* tests were conducted to follow-up this finding. Further tests were conducted to establish which of the single attribute utility scores accounted for the differences in HUI3 overall HRQoL scores between the Comparison and the SRM groups. As the data were not normally distributed, Mann-Whitney *U* tests were conducted to test for differences.

**Analytic strategy parent-report of HUI**

For the HUI3 overall HRQoL score the data were highly negatively skewed in each group. Therefore a Kruskal-Wallis test was conducted to test for differences in the HUI3 overall HRQoL scores between the three groups. Mann-Whitney *U* tests were conducted to follow-up this finding. Further tests were conducted to establish which of the single attribute utility scores accounted for these differences in HUI3 overall HRQoL scores between the SRM group and the Comparison and LGCA groups. As the data were not normally distributed, Mann-Whitney *U* tests were conducted to test for differences.

**Analytic strategy child-report of SDQ**

The SDQ Total difficulties score data were normally distributed and so a one-way ANOVA was conducted to test for differences in overall behavioural functioning scores between the three groups. As there was not an effect of group, no subscale analyses were conducted.

**Analytic strategy parent-report of SDQ**

For the SDQ Total difficulties score the distribution of the data in the SRM and Comparison groups was normal whereas the data in the LGCA group were not normally distributed. Thus, a Kruskal-Wallis test was conducted to test for differences in overall behavioural functioning between the three groups. As there was not an effect of group, no subscale analyses were conducted.

**Analytic strategy teacher-report of SDQ**

For the SDQ Total difficulties score the distribution of the data in the SRM group was normal whereas the data in the LGCA and Comparison groups were not normally distributed. Thus, a Kruskal-Wallis test was conducted to test for group differences in overall behavioural functioning. Mann-Whitney *U* tests were conducted to follow-up the significant effect of group. Further tests were conducted to establish which of the SDQ subscales, Emotional symptoms, Conduct problems, Hyperactivity/inattention or Peer problems accounted for the differences in the SDQ Total difficulties score between the SRM group and the Comparison and LGCA groups. None of the data for any of the subscales were normally distributed therefore Manny-Whitney *U* tests were conducted for these analyses.

**Analytic strategy parent-report of BRIEF**

For the Global Executive Functioning Composite (GEC) score the data were not normally distributed in the SRM and LGCA groups but were in the Comparison group. Therefore a Kruskal-Wallis test was conducted to test for differences in the GEC scores between the three groups. As there was not an effect of group, no subscale analyses were conducted.

**Analytic strategy teacher-report of BRIEF**

For the GEC score the data were not normally distributed in any of the three groups. Therefore a Kruskal-Wallis test was conducted to test for overall group differences in the GEC scores. Following an overall effect of group, Mann-Whitney *U* tests were conducted to follow-up this finding. Further tests were conducted to establish which of the two supra-ordinate scales, Behavioural Regulation (BRI) or Metacognition (MI), accounted for the differences in GEC scores between the SRM and Comparison groups. For the BRI and the MI the distribution of the data in both groups was not normal. Thus, Mann-Whitney *U* tests were conducted to test for differences between the two groups, both of which were found to be significant. Further analyses were then conducted using Mann-Whitney *U* tests, as none of the data were normally distributed, to see which of the seven subdomains: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/organize, Organization of Materials, and Monitor significantly contributed to the significant differences in the BRI and MI scores found between the SRM and Comparison groups.

**Analytic strategy WISC®-IV UK**

The Full Scale IQ (FSIQ) data were normally distributed and so a one-way ANOVA was conducted to test for differences in IQ scores between the three groups. Following a significant effect of group, planned contrasts were conducted for equal variances to test for differences between groups. Following this, further tests were conducted to establish which of the four cognitive domains, verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI) or processing speed (PSI), accounted for these differences in FSIQ between each of the tumour groups and the comparison group. For each of the four domains the distribution of the data in each group was normal. Because the comparisons were bivariate, i.e. SRM vs Comparison and LGCA vs Comparison, a series of *t* tests were conducted.

**Analytic strategy child-report of PedsQL over time**

The PedsQL Total score data were normally distributed for each group at each time point and so a repeated measures one-way ANOVA was conducted to test for changes in overall QoL scores within each of the three groups over time followed by repeated-measures contrasts. Further tests were conducted to establish which of the two summary scores, Physical Health or Psychosocial Health, accounted for the improvements in overall QoL between T1 and T3 and between T2 and T3 in the SRM group and between T1 and T3 and between T1 and T2 in the Comparison group. For the Physical Health Summary score the data in the SRM group were not normally distributed at T3 and in the Comparison group they were not normally distributed at T1. For the Psychosocial Health Summary score the data in the SRM group were normally distributed at T1, T2 and T3 and the data in the Comparison group were normally distributed at T1 but not at T2 or T3. Thus, for the Physical Health Summary score Wilcoxon signed-rank tests were conducted for both groups and for the Psychosocial Health Summary score dependent *t* tests were conducted for the SRM group and Wilcoxon signed-rank tests were conducted for the Comparison group. Further tests were conducted to establish which of the three subscale scores, Emotional, Social or School functioning, accounted for the improvements in psychosocial health between T1 and T3 in both the SRM and Comparison groups. The Emotional functioning scores were normally distributed at T1 and T3 in the SRM group but not in the Comparison group. The Social functioning scores were not normally distributed in either group and nor were the School functioning scores. Therefore, for the Emotional functioning subscale scores the dependent *t* test was used for the SRM group and Wilcoxon signed-rank tests were conducted for all other analyses.

**Analytic strategy parent-report of PedsQL over time**

The PedsQL Total score data were normally distributed in the SRM group at T1 and T2 but not at T3 and in the LGCA and Comparison groups at T3 only and so Friedman's ANOVA was conducted to test for differences in overall QoL scores within each of the three groups over time. Further tests were conducted to establish which of the two summary scores, Physical Health or Psychosocial Health, accounted for changes over time in overall QoL in the SRM group. For the Physical Health Summary score the data were not normally distributed at T1 and T3 and for the Psychosocial Health Summary score the data were not normally distributed at T3. Thus, for both summary scores Friedman's ANOVA was conducted to test for changes within the group over time. Further tests were conducted to establish which of the three subscale scores, Emotional, Social or School functioning, accounted for the improvements in Psychosocial Health between T1 and T3 and between

T1 and T2 in the SRM group. The Emotional functioning scores were normally distributed at T1 and T2 but not at T3. The Social functioning scores were normally distributed at T1 and T3 but not at T2 and the School functioning scores were normally distributed at each time point. Therefore, for the Emotional functioning subscale scores the Wilcoxon test was used to test for a difference between T1 and T3, and the dependent *t* test was used to test for a difference between T1 and T2. For the Social functioning subscale scores the dependent *t* test was used to test for a difference between T1 and T3 and the Wilcoxon test was used to test for a difference between T1 and T2. For the School functioning subscale scores the dependent *t* test was used for all the analyses.

**Analytic strategy child-report of HUI over time**

The HUI3 overall HRQoL score data were highly negatively skewed for each group at each time point and so Friedman's ANOVA was conducted to test for differences in HUI3 overall HRQoL scores within each of the three groups over time.

**Analytic strategy parent-report of HUI over time**

The HUI3 overall HRQoL score data were highly negatively skewed for each group at each time point and so Friedman's ANOVA was conducted to test for differences in HUI3 overall HRQoL scores within each of the three groups over time. Further analyses using Wilcoxon signed-rank tests were conducted to see which of the single attribute utility scores (vision, hearing, speech, ambulation, dexterity, emotion, cognition or pain) accounted for the difference in HUI3 overall HRQoL scores between T1 and T3 and between T2 and T3 in the SRM group.

**Analytic strategy child-report of SDQ over time**

The SDQ Total Difficulties score data were normally distributed for each group at each time point and so a repeated measures one-way ANOVA was conducted to test for differences in overall behavioural functioning scores within each of the three groups over time. In the LGCA group Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(2) = 8.202$, $p = .017$) and so the Greenhouse-Geisser correction was applied. Further tests were conducted to establish which of the four subscales, Emotional Symptoms, Conduct Problems, Hyperactivity/inattention or Peer Problems, accounted for changes in overall QoL between T1 and T3 and between T2 and T3 in the Comparison group. The data were not normally distributed in any of the subscales at any of the time points. Thus, the Wilcoxon signed-rank test was conducted to test for changes between T1

and T3 and between T2 and T3 in each of the subscales.

**Analytic strategy parent-report of SDQ over time**

The SDQ Total Difficulties score data were normally distributed for each of the tumour groups at each time point but non normally distributed at T1 in the Comparison group. Thus, a repeated measures one-way ANOVA was conducted to test for differences in overall behavioural functioning scores within the two tumour groups over time, and Friedman's ANOVA was used for the Comparison group. Further tests were conducted to establish which of the four subscales, Emotional symptoms, Conduct problems, Hyperactivity/inattention or Peer problems, accounted for changes in overall QoL between T1 and T3 in the Comparison group. The data were not normally distributed in any of the subscales at T1 nor at T3 and so the Wilcoxon signed-rank test was used to test for changes in scores between the two time points.

**Analytic strategy teacher-report of SDQ over time**

The SDQ Total Difficulties score data were normally distributed for the SRM group at each time point but non normally distributed at each of the three time points in the LGCA and Comparison groups. Thus, a repeated measures one-way ANOVA was conducted to test for differences in overall behavioural functioning scores within the SRM group over time, and Friedman's ANOVA was used for the LGCA and Comparison groups. No further tests were conducted.

**Analytic strategy parent-report of BRIEF over time**

The BRIEF GEC score data were normally distributed in the LGCA group but not in the SRM or Comparison groups. Friedman's ANOVA was conducted to test for differences in GEC scores within these two groups over time and a repeated-measures ANOVA was used in the SRM group. No further tests were conducted.

**Analytic strategy teacher-report of BRIEF over time**

The BRIEF GEC score data were not normally distributed in any of the groups at T1 therefore Friedman's ANOVA was conducted to test for differences in GEC scores over time in each group. No further tests were conducted.

**Analytic strategy WISC®-IV UK over time**

The WISC FSIQ score data were not normally distributed in the SRM and LGCA groups at

T1 therefore Friedman's ANOVA was conducted to test for differences in FSIQ scores over time in each group of these groups. The data were normally distributed at each time point in the Comparison group and so a repeated measures ANOVA was used for this group. No further tests were conducted.

**Analytic strategy predictors of child-report PedsQL**

At T1, T2 and T3 the first step in the multiple regression analyses was to include SES, child's gender, and child's age at the time of assessment. In the next step at T1 and T2 the child's gender and age were removed and at T3 just gender was removed and replaced with the five domains of function and Caregiver Mental Health. In the next and final step at T1 and T2 SES, Behaviour, Social function, Cognition and Caregiver Mental Health were removed. At T3 SES, child's age, Behaviour, Social function, and Caregiver mental health were removed. For T1 predictors of T3 QoL the first step in the multiple regression analyses was to include SES, child's gender, and child's age at the first assessment. In the next step the child's gender was removed and replaced by the five domains of function and Caregiver Mental Health. In the next and final step SES, Behaviour, Social function, Motor and Sensory function and the Caregiver Mental Health were removed.

**Analytic strategy predictors of parent-report PedsQL**

At T1, T2 and T3 the first step in the multiple regression analyses was to include SES, child's gender, and child's age at the time of assessment. In the next step at T1, T2 and T3 the child's gender and age were removed and replaced with the five domains of function and Caregiver Mental Health. In the next and final step at T1 and T2 SES, Behaviour, Social function, and Caregiver Mental Health were removed. At T3 SES, Emotion, Behaviour, Social function, and Caregiver Mental Health were removed. For T1 predictors of T3 QoL the first step in the multiple regression analyses was to include SES, child's gender, and child's age at the first assessment. In the next step the child's gender and age were removed and replaced by the five domains of function and Caregiver Mental Health. In the next and final step SES, Behaviour, Social function and Caregiver Mental Health were removed.

## Appendix B. Domains of functioning

**Domains of function**

| | | |
|---|---|---|
| **1. Emotional functioning** | 5 subscales | (2 parent, 2 child and 1 teacher) |
| **2. Behavioural functioning** | 6 subscales | (2 parent, 2 child and 2 teacher) |
| **3. Social functioning** | 6 subscales | (2 parent, 2 child and 2 teacher) |
| **4. Motor and sensory functioning** | 12 subscales | (6 parent, 6 child) |
| **5. Cognitive functioning** | 22 subscales | (9 parent, 5 child, 8 teacher) |
| **6. Parental mental health** | 1 scale | (GHQ-12) |

**Strengths and Difficulties Questionnaire (SDQ)** (parent, child, teacher)

A behavioural screening questionnaire comprising 25 psychological attributes.

Total difficulties score comprising 4 subscales:

1. Emotional symptoms
2. Conduct problems
2. Hyperactivity/inattention
3. Peer problems

And:

3. Prosocial behaviour

**Health Utilities Index (HUI)** (parent, child)

A measure of health status and health related quality of life comprising 16 items.

The overall HRQL score comprises 8 single attribute functions:

4. Vision
4. Hearing
4. Speech
4. Ambulation
4. Dexterity
5. Cognition
1. Emotion
4. Pain

**Behavior Rating Inventory of Executive Function (BRIEF)** (parent, teacher)

A measure of executive function in daily life comprising 86 items.

The Global Executive Composite comprises 2 supraordinate scales and 8 subdomains.

Behavioral Regulation Index:

5. Inhibit
5. Shift
5. Emotional Control

Metacognition Index

5. Initiate
5. Working Memory
5. Plan/organise
5. Organization of Materials
5. Monitor

**General Health Questionnaire (GHQ-12)** (parent)

A measure of adult mental health comprising 12 items.

6. Total score only

**Wechsler Intelligence Scale for Children® - 4th UK Edition (WISC)** (child)

It measures neuropsychological functioning.

It provides a composite score representing FSIQ comprising 4 domains of cognitive functioning:

5. verbal comprehension
5. perceptual reasoning
5. working memory
5. processing speed

## Appendix C. Cronbach alpha analyses

Cronbach alpha analyses to examine internal consistency of theoretically derived domains of function including all the subscales at each time point

### 1. Emotional functioning T1

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 101 | 91.8 |
| | Excluded[a] | 9 | 8.2 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .714 | .749 | 5 |

**Item-Total Statistics**

| T1 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent emotional symptoms | 7.9604 | 21.338 | .700 | .545 | .551 |
| SDQ child emotional symptoms | 8.0198 | 25.200 | .653 | .465 | .579 |
| SDQ teacher emotional symptoms | 8.7228 | 25.622 | .513 | .273 | .658 |
| HUI3 parent emotion level | 9.4356 | 40.688 | .446 | .319 | .713 |
| HUI3 child emotion level | 9.4653 | 42.391 | .307 | .191 | .734 |

For the regression model, the mean of the standardized scores for each of these 5 subscales combined will constitute the 'emotion' predictor at T1.

### Emotional functioning T2

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 94 | 85.5 |
| | Excluded[a] | 16 | 14.5 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .703 | .781 | 5 |

**Item-Total Statistics**

| T2 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent emotional symptoms | 7.3936 | 21.553 | .589 | .464 | .598 |
| SDQ child emotional symptoms | 7.4043 | 23.620 | .624 | .460 | .574 |
| SDQ teacher emotional symptoms | 8.0638 | 24.318 | .470 | .246 | .663 |
| HUI3 parent emotion level | 8.6702 | 37.191 | .527 | .377 | .691 |
| HUI3 child emotion level | 8.5957 | 37.512 | .521 | .330 | .695 |

For the regression model, the mean of the standardized scores for each of these 5 subscales combined will constitute the 'emotion' predictor at T2.

## Emotional functioning T3

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 90 | 81.8 |
| | Excluded[a] | 20 | 18.2 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .732 | .787 | 5 |

**Item-Total Statistics**

| T3 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent emotional symptoms | 7.2111 | 21.045 | .668 | .537 | .613 |
| SDQ child emotional symptoms | 7.6333 | 24.055 | .695 | .497 | .595 |
| SDQ teacher emotional symptoms | 7.7444 | 26.911 | .453 | .271 | .714 |
| HUI3 parent emotion level | 8.3444 | 38.341 | .512 | .406 | .726 |
| HUI3 child emotion level | 8.3111 | 37.947 | .473 | .370 | .725 |

For the regression model, the mean of the standardized scores for each of these 5 subscales combined will constitute the 'emotion' predictor at T3.

## 2. Behavioural functioning T1

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 101 | 91.8 |
| | Excluded[a] | 9 | 8.2 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .753 | .768 | 6 |

**Item-Total Statistics**

| T1 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent conduct problems | 11.6040 | 47.162 | .475 | .407 | .722 |
| SDQ teacher conduct problems | 12.5248 | 50.792 | .494 | .355 | .727 |
| SDQ child conduct problems | 11.2772 | 45.762 | .583 | .436 | .698 |
| SDQ parent hyperactivity/inattention | 9.5941 | 38.684 | .620 | .482 | .678 |
| SDQ teacher hyperactivity/inattention | 10.5644 | 43.368 | .418 | .295 | .744 |
| SDQ child hyperactivity/inattention | 9.8317 | 43.121 | .460 | .395 | .729 |

For the regression model, the mean of the standardized scores for each of these 6 subscales combined will constitute the 'behaviour' predictor at T1.

## Behavioural functioning T2

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 95 | 86.4 |
| | Excluded[a] | 15 | 13.6 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .731 | .753 | 6 |

**Item-Total Statistics**

| T2 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent conduct problems | 10.9474 | 39.880 | .482 | .421 | .694 |
| SDQ teacher conduct problems | 11.8316 | 45.142 | .410 | .251 | .723 |
| SDQ child conduct problems | 10.6421 | 39.147 | .525 | .423 | .684 |
| SDQ parent hyperactivity/inattention | 9.1368 | 32.311 | .524 | .353 | .678 |
| SDQ teacher hyperactivity/inattention | 9.8526 | 31.701 | .506 | .349 | .688 |
| SDQ child hyperactivity/inattention | 8.9579 | 33.637 | .498 | .328 | .686 |

For the regression model, the mean of the standardized scores for each of these 6 subscales combined will constitute the 'behaviour' predictor at T2.

## Behavioural functioning T3

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 90 | 81.8 |
| | Excluded[a] | 20 | 18.2 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .828 | .837 | 6 |

**Item-Total Statistics**

| T3 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent conduct problems | 10.6111 | 48.263 | .705 | .608 | .782 |
| SDQ teacher conduct problems | 11.6778 | 57.165 | .491 | .456 | .825 |
| SDQ child conduct problems | 10.3778 | 48.507 | .675 | .591 | .787 |
| SDQ parent hyperactivity/inattention | 8.9778 | 42.831 | .663 | .506 | .788 |
| SDQ teacher hyperactivity/inattention | 9.9667 | 46.437 | .537 | .502 | .818 |
| SDQ child hyperactivity/inattention | 9.1667 | 45.781 | .607 | .434 | .800 |

For the regression model, the mean of the standardized scores for each of these 6 subscales combined will constitute the 'behaviour' predictor at T3.

### 3. Social functioning T1

I had to reverse score prosocial behaviour in order to run these analyses as it is negatively correlated with peer problems.

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 101 | 91.8 |
| | Excluded[a] | 9 | 8.2 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .659 | .669 | 6 |

**Item-Total Statistics**

| T1 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent peer problems | 8.3861 | 29.799 | .489 | .310 | .582 |
| SDQ teacher peer problems | 9.0792 | 32.874 | .415 | .243 | .613 |
| SDQ child peer problems | 8.5842 | 34.705 | .296 | .184 | .646 |
| SDQ parent prosocial | 8.3663 | 29.314 | .362 | .297 | .631 |
| SDQ teacher prosocial | 8.2574 | 28.453 | .364 | .190 | .633 |
| SDQ child prosocial | 8.4653 | 29.911 | .452 | .321 | .594 |

For the regression model, the mean of the standardized scores for each of these 6 subscales combined will constitute the 'peer relationships' predictor at T1.

## Social functioning T2

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 95 | 86.4 |
| | Excluded[a] | 15 | 13.6 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .685 | .677 | 6 |

**Item-Total Statistics**

| T2 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent peer problems | 8.1579 | 31.475 | .412 | .365 | .645 |
| SDQ teacher peer problems | 8.5684 | 32.716 | .386 | .243 | .653 |
| SDQ child peer problems | 8.4632 | 36.996 | .260 | .291 | .686 |
| SDQ parent prosocial | 8.4316 | 30.801 | .467 | .488 | .626 |
| SDQ teacher prosocial | 7.9263 | 26.175 | .536 | .382 | .597 |
| SDQ child prosocial | 8.4000 | 31.689 | .423 | .317 | .641 |

For the regression model, the mean of the standardized scores for each of these 6 subscales combined will constitute the 'peer relationships' predictor at T2.

**Social functioning T3**

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 90 | 81.8 |
| | Excluded[a] | 20 | 18.2 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .719 | .720 | 6 |

**Item-Total Statistics**

| T3 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| SDQ parent peer problems | 8.8111 | 40.964 | .489 | .368 | .670 |
| SDQ teacher peer problems | 9.3556 | 39.895 | .517 | .397 | .660 |
| SDQ child peer problems | 9.3000 | 46.078 | .385 | .365 | .700 |
| SDQ parent prosocial | 8.9111 | 39.632 | .493 | .422 | .668 |
| SDQ teacher prosocial | 8.5444 | 38.273 | .462 | .430 | .680 |
| SDQ child prosocial | 9.0222 | 44.022 | .376 | .260 | .702 |

For the regression model, the mean of the standardized scores for each of these 6 subscales combined will constitute the 'peer relationships' predictor at T3.

4. **Motor and sensory functioning T1**

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 107 | 97.3 |
| | Excluded[a] | 3 | 2.7 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .800 | .788 | 12 |

**Item-Total Statistics**

| T1 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| HUI3 parent vision level | 15.3364 | 31.395 | .219 | .574 | .802 |
| HUI3 parent hearing level | 15.3551 | 31.231 | .203 | .374 | .803 |
| HUI3 parent speech level | 15.1869 | 28.719 | .533 | .561 | .781 |
| HUI3 parent ambulation level | 14.7383 | 21.987 | .708 | .755 | .754 |
| HUI3 parent dexterity level | 15.1121 | 26.270 | .637 | .573 | .766 |
| HUI3 parent pain level | 14.7757 | 28.496 | .340 | .542 | .797 |
| HUI3 child vision level | 15.2056 | 28.901 | .376 | .668 | .792 |
| HUI3 child hearing level | 15.3551 | 30.231 | .300 | .482 | .797 |
| HUI3 child speech level | 15.2804 | 29.524 | .460 | .522 | .787 |
| HUI3 child ambulation level | 14.9065 | 22.935 | .723 | .754 | .751 |
| HUI3 child dexterity level | 15.1589 | 27.361 | .496 | .462 | .781 |
| HUI3 child pain level | 14.8318 | 29.877 | .287 | .488 | .799 |

For the regression model, the mean of the standardized scores for each of these 12 subscales combined will constitute the 'motor and sensory functioning' predictor at T1.

## Motor and sensory functioning T2

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 97 | 88.2 |
| | Excluded[a] | 13 | 11.8 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .774 | .756 | 12 |

**Item-Total Statistics**

| T2 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| HUI3 parent vision level | 14.3093 | 21.633 | .256 | .522 | .772 |
| HUI3 parent hearing level | 14.2784 | 20.453 | .277 | .415 | .774 |
| HUI3 parent speech level | 14.3196 | 19.949 | .648 | .700 | .743 |
| HUI3 parent ambulation level | 13.9588 | 14.811 | .772 | .839 | .703 |
| HUI3 parent dexterity level | 14.2474 | 19.334 | .546 | .595 | .745 |
| HUI3 parent pain level | 13.9381 | 19.767 | .395 | .405 | .760 |
| HUI3 child vision level | 14.3299 | 22.390 | .151 | .434 | .778 |
| HUI3 child hearing level | 14.3918 | 22.991 | -.021 | .155 | .795 |
| HUI3 child speech level | 14.2887 | 21.166 | .327 | .569 | .767 |
| HUI3 child ambulation level | 14.1340 | 16.867 | .651 | .812 | .726 |
| HUI3 child dexterity level | 14.2577 | 18.339 | .678 | .830 | .729 |
| HUI3 child pain level | 13.9897 | 21.364 | .216 | .325 | .777 |

For the regression model, the mean of the standardized scores for each of these 12 subscales combined will constitute the 'motor and sensory functioning' predictor at T2.

## Motor and sensory functioning T3

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 92 | 83.6 |
| | Excluded[a] | 18 | 16.4 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .765 | .761 | 12 |

**Item-Total Statistics**

| T3 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| HUI3 parent vision level | 14.0217 | 17.384 | .216 | .514 | .769 |
| HUI3 parent hearing level | 14.1848 | 17.954 | .177 | .260 | .769 |
| HUI3 parent speech level | 14.1087 | 16.538 | .503 | .446 | .740 |
| HUI3 parent ambulation level | 13.8587 | 14.167 | .576 | .691 | .725 |
| HUI3 parent dexterity level | 14.0978 | 16.001 | .575 | .556 | .732 |
| HUI3 parent pain level | 13.6739 | 14.574 | .435 | .493 | .751 |
| HUI3 child vision level | 14.0543 | 17.437 | .364 | .575 | .754 |
| HUI3 child hearing level | 14.2283 | 18.508 | .137 | .251 | .769 |
| HUI3 child speech level | 14.1522 | 17.757 | .276 | .223 | .760 |
| HUI3 child ambulation level | 14.0326 | 14.823 | .626 | .715 | .720 |
| HUI3 child dexterity level | 14.1522 | 16.130 | .518 | .590 | .737 |
| HUI3 child pain level | 13.7826 | 15.820 | .428 | .401 | .746 |

For the regression model, the mean of the standardized scores for each of these 12 subscales combined will constitute the 'motor and sensory functioning' predictor at T3.

5. **Cognitive functioning T1**

I had to reverse score the WISC subscales in order to run these analyses as they were negatively correlated with the other items.

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 97 | 88.2 |
| | Excluded[a] | 13 | 11.8 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .931 | .941 | 22 |

**Item-Total Statistics**

| T1 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| HUI3 parent cognition level | 1093.8454 | 29649.090 | .619 | .633 | .932 |
| HUI3 child cognition level | 1093.3918 | 29672.595 | .559 | .568 | .932 |
| BRIEF parent inhibit T score | 1045.2784 | 27989.682 | .549 | .672 | .929 |
| BRIEF parent shift T score | 1041.3918 | 26783.887 | .668 | .741 | .927 |
| BRIEF parent emotional control T score | 1040.6598 | 27114.310 | .641 | .712 | .927 |
| BRIEF parent initiate T score | 1042.0000 | 27404.917 | .644 | .773 | .927 |
| BRIEF parent working memory T score | 1040.6392 | 26582.629 | .777 | .842 | .925 |
| BRIEF parent plan/organise T score | 1041.7938 | 27122.165 | .711 | .850 | .926 |
| BRIEF parent organisation of materials T score | 1044.5670 | 29219.915 | .183 | .478 | .934 |
| BRIEF parent monitor T score | 1043.3093 | 27227.695 | .687 | .839 | .927 |
| WISC verbal reasoning | 1037.3505 | 27246.459 | .402 | .420 | .934 |
| WISC perceptual reasoning | 1037.8454 | 26804.861 | .571 | .669 | .929 |
| WISC working memory | 1041.2062 | 26819.207 | .574 | .589 | .929 |
| WISC processing speed | 1034.8557 | 26453.479 | .610 | .627 | .928 |
| BRIEF teacher inhibit T score | 1044.6495 | 28230.543 | .532 | .726 | .929 |
| BRIEF teacher shift T score | 1040.1134 | 26882.122 | .706 | .716 | .926 |
| BRIEF teacher emotional control T score | 1041.2268 | 27143.594 | .688 | .758 | .927 |
| BRIEF teacher initiate T score | 1040.4742 | 26386.898 | .811 | .902 | .924 |
| BRIEF teacher working memory T score | 1038.8866 | 25802.727 | .768 | .882 | .925 |
| BRIEF teacher plan/organise T score | 1040.7216 | 26928.682 | .756 | .884 | .925 |
| BRIEF teacher organisation of materials T score | 1043.6392 | 27674.962 | .590 | .744 | .928 |
| BRIEF teacher monitor T score | 1042.0928 | 27032.502 | .758 | .865 | .926 |

For the regression model, the mean of the standardized scores for each of these 22 subscales combined will constitute the 'cognitive functioning' predictor at T1.

## Cognitive functioning T2

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 90 | 81.8 |
| | Excluded[a] | 20 | 18.2 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .921 | .928 | 22 |

| T2 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| HUI3 parent cognition level | 1092.2333 | 27940.496 | .515 | .572 | .922 |
| HUI3 child cognition level | 1091.8333 | 27968.028 | .444 | .557 | .922 |
| BRIEF parent inhibit T score | 1043.2333 | 26292.878 | .561 | .775 | .918 |
| BRIEF parent shift T score | 1040.5000 | 25692.860 | .578 | .665 | .917 |
| BRIEF parent emotional control T score | 1038.3222 | 25747.592 | .594 | .618 | .917 |
| BRIEF parent initiate T score | 1041.0889 | 25638.689 | .678 | .798 | .916 |
| BRIEF parent working memory T score | 1038.8444 | 25385.594 | .700 | .865 | .915 |
| BRIEF parent plan/organise T score | 1041.3444 | 25806.858 | .644 | .858 | .916 |
| BRIEF parent organisation of materials T score | 1043.1222 | 27538.176 | .162 | .473 | .924 |
| BRIEF parent monitor T score | 1042.6444 | 26037.445 | .604 | .784 | .917 |
| WISC verbal reasoning | 1035.6778 | 24761.097 | .615 | .671 | .917 |
| WISC perceptual reasoning | 1037.3111 | 25007.812 | .627 | .697 | .917 |
| WISC working memory | 1041.4444 | 25761.755 | .475 | .609 | .920 |
| WISC processing speed | 1037.0778 | 24987.443 | .529 | .549 | .920 |
| BRIEF teacher inhibit T score | 1042.3556 | 26820.749 | .424 | .757 | .920 |
| BRIEF teacher shift T score | 1036.6778 | 24672.446 | .642 | .889 | .916 |
| BRIEF teacher emotional control T | 1038.6667 | 25313.483 | .598 | .863 | .917 |
| BRIEF teacher initiate T score | 1038.6333 | 24708.257 | .790 | .851 | .913 |
| BRIEF teacher working memory T score | 1035.9000 | 24203.799 | .784 | .868 | .913 |
| BRIEF teacher plan/organise T score | 1039.0667 | 24863.501 | .787 | .890 | .913 |
| BRIEF teacher organisation of materials T score | 1041.7333 | 26293.928 | .429 | .745 | .920 |
| BRIEF teacher monitor T score | 1040.0222 | 25634.044 | .660 | .825 | .916 |

For the regression model, the mean of the standardized scores for each of these 22 subscales combined will constitute the 'cognitive functioning' predictor at T3.

## Cognitive functioning T3

**Case Processing Summary**

| | | N | % |
|---|---|---|---|
| Cases | Valid | 84 | 76.4 |
| | Excluded[a] | 26 | 23.6 |
| | Total | 110 | 100.0 |

a. Listwise deletion based on all variables in the procedure.

**Reliability Statistics**

| Cronbach's Alpha | Cronbach's Alpha Based on Standardized Items | N of Items |
|---|---|---|
| .935 | .943 | 22 |

**Item-Total Statistics**

| T3 | Scale Mean if Item Deleted | Scale Variance if Item Deleted | Corrected Item-Total Correlation | Squared Multiple Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|---|
| HUI3 parent cognition level t | 1110.0119 | 38030.518 | .590 | .753 | .936 |
| BRIEF parent inhibit T score | 1060.7381 | 35544.364 | .691 | .796 | .931 |
| BRIEF parent shift T score | 1058.7381 | 35368.967 | .635 | .674 | .932 |
| BRIEF parent emotional control T score | 1056.4048 | 35046.244 | .667 | .679 | .931 |
| BRIEF parent initiate T score | 1058.3214 | 35328.727 | .669 | .776 | .931 |
| BRIEF parent working memory T score | 1056.1071 | 34511.109 | .715 | .847 | .930 |
| BRIEF parent plan/organise T score | 1058.3810 | 35425.564 | .701 | .832 | .931 |
| BRIEF parent organisation of materials T score | 1060.4762 | 37017.264 | .311 | .466 | .936 |
| BRIEF parent monitor T score | 1059.4167 | 35165.089 | .737 | .864 | .931 |
| HUI3 child cognition level | 1109.7976 | 38124.091 | .426 | .609 | .936 |
| WISC verbal reasoning | 1051.8690 | 35489.296 | .470 | .607 | .935 |
| WISC perceptual reasoning | 1056.4286 | 34206.561 | .643 | .728 | .932 |
| WISC working memory | 1056.7381 | 35244.485 | .531 | .620 | .933 |
| WISC processing speed | 1056.3452 | 33057.482 | .652 | .615 | .932 |
| BRIEF teacher inhibit T score | 1059.1190 | 35914.998 | .511 | .835 | .934 |
| BRIEF teacher shift T score | 1052.1667 | 33558.622 | .671 | .803 | .931 |
| BRIEF teacher emotional control T score | 1053.7976 | 33765.416 | .654 | .829 | .932 |
| BRIEF teacher initiate T score | 1055.7500 | 34002.479 | .808 | .879 | .929 |
| BRIEF teacher working memory T score | 1051.9524 | 32885.877 | .815 | .877 | .928 |
| BRIEF teacher plan/organise T score | 1055.1548 | 34151.626 | .801 | .900 | .929 |
| BRIEF teacher monitor T score | 1056.0357 | 34750.276 | .688 | .810 | .931 |
| BRIEF teacher organisation of materials T score | 1057.7500 | 34941.539 | .544 | .597 | .933 |

For the regression model, the mean of the standardized scores for each of these 22 subscales combined will constitute the 'cognitive functioning' predictor at T3.

**Z-scores**

1. All the Z-scores were created from the means and SDs of the scores in the Comparison group.
2. Each domain of function for the regression analyses was then created from the mean of the sum of the constituent subscales z-scores.

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