Neurodevelopmental outcome following cerebellar tumour sustained in early childhood

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Abstract

Mounting evidence from imaging studies, developmental disorders and typically-developing children suggests that different domains of functioning are more closely related than previously considered. This is reflected in theories of development which are increasingly recognising that developmental progression should be considered as an integrated process, with associations between domains. The extent of the interrelation between cognitive and motor skills remains unclear despite previous investigations. Examination of this relationship in typically-developing children is important to clarify the nature of this link, thereby informing theories of development for both typical and atypical populations. This thesis investigated the underlying nature of the association between cognitive and motor domains to establish the extent of interrelation and whether this link alters across development. As the cerebellum has been hypothesised to be instrumental in this relationship (Diamond, 2000), the role of the cerebellum was investigated by examining cognitive and motor development in children treated for cerebellar tumour in the preschool years (N=15). The impact of cerebellar injury on development of scholastic and attentional skills was also investigated, together with the influence of factors affecting prognosis.

The interrelation of cognitive and motor skills in typically-developing children (N=248; 4-11 years) was found to be underpinned by a link between visual processing abilities and fine manual motor skills. Despite fluctuations in correlations between other aspects of cognitive and motor functioning, this core relationship remained constant, furthering evidence that cognitive and motor development are linked from an early age.

A similar pattern of correlations was seen for the patient sample, suggesting that development in these domains remains tightly linked despite damage to an underlying component of the anatomical network. This suggests that the patients are demonstrating a developmental delay, rather than deviation; their trajectory does not appear to be qualitatively different from that

of typically-developing children, rather development appears to be more constrained than suggested by some hypotheses (e.g. Karmiloff-Smith, 1992). Cerebellar damage was therefore found to impact on the two domains similarly, offering support to a 'universal cerebellar transform' (Schmahmann, 2000b) conceptualisation of cerebellar functioning. Both cognitive and motor skills were found to be compromised following a cerebellar tumour, although no specific impact of cerebellar damage was reported on scholastic skills, above and beyond general cognitive deficit. Attention was found to be impaired in the patient sample, with sustained attention most closely related to functioning in cognitive, academic and motor skills, suggesting that a deficit in this basic underlying process underlies difficulties in other domains. In addition, sustained attention was implicated in the association between visual processing and fine manual control in the patient sample, suggesting that this core link may be further underpinned by more basic cognitive processes. Effective rehabilitation may therefore target sustained attention, as this appears to be related to functioning in the other domains assessed in this study, as well as recognising that an integrated approach across domains is likely to yield maximum benefits.

Of the potential moderating factors investigated, age at diagnosis and tumour type/treatment were found to be the most reliable predictors of outcome. This research highlights the importance of a case-study approach, and the clinical importance of individual investigation of each child's needs for rehabilitation.

Published articles

The following articles appear as chapters in this thesis:

Chapter 2

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Chapter 3

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Chapter 7

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Conference presentations

Work from this thesis was presented at the following conferences:

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The International Society of Paediatric Oncology, Boston (October, 2010) – Neuropsychological outcome following cerebellar tumour sustained in early childhood

ISPNO, Vienna (June, 2010) – Interrelation of cognitive and motor functioning following cerebellar tumour injury sustained in early childhood; Academic attainment in relation to IQ following injury from cerebellar tumour sustained in early childhood; Impact of cerebellar tumour injury sustained in early childhood on motor and cognitive development: a longitudinal study

BPS Developmental Psychology Section Conference, Nottingham Trent University (September, 2009) – Development of cognitive and motor function following cerebellar tumour injury sustained in early childhood

SRCD Biennial Meeting, Denver (April, 2009) – Exploring the interrelation of cognitive and motor development in typically developing children aged 4-11 years

BPS Developmental Psychology Section Conference, University of Plymouth (September, 2008) – Exploring the interrelation of cognitive and motor development in typically developing children aged 4-11 years

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1 Thesis overview

1.1 Introduction

The study of human development attempts to unravel progression across childhood, including how and why children's abilities change. Traditionally this has been achieved by considering development across separate domains of ability, such as cognitive, language and motor skills. Consequently, theories of development have historically focused on progression in one area of functioning. This differentiation has in turn been incorporated into neuropsychology, resulting in classifications and diagnoses based on separate ability domains. Recently, research has shifted towards a more comprehensive view of development which considers multiple aspects of a child's functioning as an integrated whole. Indeed, some researchers have gone so far as to suggest that the historical distinctions drawn between different skill domains are invalid and have highlighted that abilities are interrelated and depend largely on more basic processes, such as attention, processing speed and working memory (Dyck, Piek, Kane, & Patrick, 2009).

Imaging studies, evidence from developmental disorders and research with typically-developing children may be combined to suggest that different domains interact throughout development. Of particular interest for this thesis is how closely cognitive and motor development are associated and the role that the cerebellum may play in facilitating this link. In particular, this thesis examines the impact of a cerebellar tumour in the preschool years on functioning in several domains, and examines the possible function of the cerebellum in both cognitive and motor abilities. It is presented as a series of studies and whilst the full literatures supporting each study are included as an introduction to each chapter, together with specific hypotheses relating to each chapter, this overview will consider the wider background concerning theories of cerebellar

functioning, cerebellar tumours and mechanisms of development relevant to this research.

1.1.1 Models of development

Motor development is a child's increasingly skilled control of their body movements, from spontaneous actions such as kicking towards more complex sequences such as reaching and walking. The developmental trajectory of motor control in typically-developing children has been the focus of many studies and has been demonstrated to generally follow a pattern of larger muscles developing prior to smaller ones, with a general progression from top to bottom (e.g. Sheridan, 1988). Early theories posited that motor development was a result of neuromuscular maturation (e.g. Gesell, 1939) and increasing cortical control over lower reflexes, although this has since been proven inaccurate (Bartlett, 1997). McGraw (1945) also supported a maturational view, although conceded that the environment and experience were important in supporting the process.

More recently, researchers have suggested that additional features may be essential for motor development with recognition that development is a dynamic process with a reciprocal influence between experience and development necessary for many domains (e.g. Gottlieb, 1997). The action-perception hypothesis suggests that action and perception are inherently bound and that perceptual information from the environment must be continually integrated for successful execution and refinement of actions (Gibson, 1988). This theory reflects that the relationship between perception and action is mutual and bidirectional; perception guides action whilst infants' movements influence their perception of their environment. It argues that perception provides information on the current status of the body and the surrounding environment enabling knowledge concerning the current constraints on action and thus allowing for prospective planning of actions (Gibson, 1979). This hypothesis also

highlights the distinction between movements and actions, the latter implying intentionality of a goal that requires planning (Pick, 1989).

Building on this theory of a reciprocal relationship between action and perception, the dynamic systems approach proposes that movement is an emergent property of the interaction of multiple systems; many domains are hypothesised to contribute to functioning with no single element having causal priority (Thelen, 1993). In contrast to development resulting from predetermined movement patterns specified by the central nervous system (i.e. maturation), the dynamic systems perspective suggests that new movements are the result of an interaction of many factors, such as body weight, arousal, gravity and the neuromuscular system, and that development is not the result of an executive plan at either the biological or environmental level. Motor development is therefore conceptualised as self-organising, with the continuously changing nature of the component parts of the system, the environment and the task resulting in discontinuous transitions in behaviours, termed phase shifts. The behaviour that uses the least energy and is the most efficient use of the component parts is preferred. If this functional synergy (Bernstein, 1967) is the most beneficial strategy then the behaviour of the system is said to be limited and the behaviour can be described as hard wired.

Linking this concept together with evidence demonstrating postnatal loss of synapses within the cerebral cortex (e.g. Huttenlocher, 1990), some authors have proposed that development occurs through a selective loss of synaptic connections (e.g. Changeux & Dehaene, 1989). Sporns and Edelman (1993) for example, proposed that integration of new motor strategies occurs through neuronal selection; if a particular neuronal connection produces the most efficient movement pattern, it is consolidated through repeated use. This is known as the neuronal group selection theory (NGST). Unlike the neuromuscular maturation theory, NGST can account for the variation in the range of movements that may be observed in motor development (Piek, 2002).

According to this hypothesis, development starts with primary neuronal repertoires which are variable because of factors such as cell division, migration and death. As the infant explores the range of possible movements specified by this initial repertoire, afferent information is used to select the most efficient movement patterns. Thus, as in the action-perception hypothesis, sensory information serves an important function in motor development. Once the initial selection is complete, NGST proposes that there is a stage of 'secondary variability' in which secondary neuronal repertoires are selected to form the basis of mature variable behaviour which is able to adapt to environmental demands (Hadders-Algra, 2000). Similarly to the dynamic systems approach, NGST argues that movements are the result of an interaction between the neuromuscular system and the environment, although the approach is taken one step further by articulating the specific neural mechanisms that account for development. Some authors (e.g. Forssberg, 1999) have posited that this theory effectively ends the 'nature versus nurture' debate as it emphasises that development is the result of a complex interaction between genes and environment. Others have criticised such selectionist theories and have instead suggested that specificity in neural connections may arise from directed dendritic growth, rather than synaptic loss (e.g. Quartz & Sejnowski, 1997), although it has been argued that there is little evidence to support this theory (Johnson, 2005).

Unlike motor skills, cognitive capacity is intuitively more difficult to define and can be taken to encompass a wide range of abilities that do not easily condense into a single definition. In general it may be conceptualised as the construction of thought processes such as reasoning, language development and how an individual perceives and comes to understand the world. Cognitive control may be thought of as the ability to regulate many competing thoughts and actions (Durston & Casey, 2006) and the ability to hold information in mind for mental manipulation that may then be acted upon (Davidson, Amso, Cruess

Anderson, & Diamond, 2006). The study of cognitive development therefore aims to detail development in terms of what happens when, in addition to explaining why these changes occur. Many theories of cognitive development have been forwarded without considering evidence from imaging and anatomical study of the brain, however with improvements in imaging techniques, cognition and brain development may be considered in conjunction. Theories which aim to address relationships between brain structures and cognitive functions are especially useful for elucidating the effects of brain injury on cognitive development (Johnson, 2005).

Theories of development may be broadly divided into two main areas; nativism/maturational approaches and constructivism. An important aspect of the debate between nativism and constructivism is the idea of modularity (Fodor, 1983). The concept of modularity is linked to the hypothesis proposed by Marr (1976), that evolutionarily, cognitive processes may have become composed of mutually independent subcomponents allowing for alteration in one part without corresponding consequences throughout the system. Fodor (1983) argued that modules are domain specific, that is, they are only able to accept one type of input, that they are innate and are not under voluntary control. From a developmental prospective therefore, Fodor suggested that development begins with innate, pre-specified modules. Others, such as Piaget, upheld that development was the result of domain-general change (Piaget & Inhelder, 1959). Current proponents of modularity have adopted a more flexible interpretation of the concept of modularity, allowing for some degree of communication between modules and applying modularity to processes that are subject to a degree of voluntary control (e.g. Ellis & Young, 1988; Temple, 1991; 1997; Temple, Carney, & Mullarkey, 1996).

Nativists believe that development is the expression of abilities that are innate to the individual, leaving no place for the environment as a factor in development. Neo-nativists have since acknowledged that the environment and

learning are important, although these factors only build upon an infant's inherent knowledge and abilities (Samuels, 2002). These preformist approaches suggest that infants' minds are simply diminished versions of adult minds, and that development occurs as brain pathways or structures mature. In this way, pathways supporting various aspects of the adult system are thought to become operational at certain ages. In addition, maturational theory assumes there is a close mapping between functions and particular brain areas. Critics of this approach have suggested that this theory may provide an adequate approximation to the process of development but that it may fail to account for all evidence (Johnson, 2005). Some authors have suggested that it may be incorrect to assume that particular functions may be localised to a specific brain region (e.g. Friston & Price, 2001) and that cognitive skills may be underpinned by extensive networks encompassing spatially separate components (Carpenter et al., 2001).

In contrast to the maturational view, the constructivist approach posits that development is the result of dynamic relations between many domains, in which potential routes for development are progressively limited and the proportion of feasible end phenotypes is restricted. In this way, constructivists follow Piagetian thinking and suggest that infants construct new knowledge from their experiences. Piagetian stage theory proposed that development is discontinuous, occurring via an invariant series of stages (Piaget & Inhelder, 1969). Whilst many of Piaget's hypotheses have since been questioned, developments of Piagetian stage theory have modified many aspects of the original theory, such as the timing of skill acquisition and the restrictive specification of exclusive and sequential stages (Temple, 1997). For example, Karmiloff-Smith's neuroconstructivist theory of representational redescription suggests that development goes through stages which can be achieved in any order and at any age (Karmiloff- Smith, 1992). With respect to modularity, this theory proposes that a domain-specific end state may arise from more domain-

general beginnings. The constructionist view aims to understand the development of new structures and functions which arise through complex interactions between genes and an infant's environment. This hypothesis of development as a process of gradual modularisation suggests that developmental cognitive neuropsychology aims to examine how disrupted development affects the process of gradual modularisation (Temple, 1997). From this view, developmental disorders and development following early brain insult represent possible developmental trajectories that arise due to a varying set of constraints than those which lead to typical development. The implication of this hypothesis suggests that when development deviates from a typical trajectory, a variety of new factors and adaptations will be activated, most likely resulting in some re-organisation of brain functioning. An example of this is provided by research into children with Williams syndrome, who behaviourally have been demonstrated to have typical face processing abilities whilst their functioning in other domains is severely impaired (e.g. Annaz, Karmiloff-Smith & Thomas, 2008). Further investigation has lead some researchers to posit that the cognitive processes behind the face processing abilities of the children with Williams syndrome is qualitatively different from that of typically-developing controls (e.g. Deruelle, Mancini, Livet, Casse-Perrot, & de Schonen, 1999), although this is not universally accepted (e.g. Tager-Flusberg, Pless-Skewer, Faja, & Joseph, 2003). Evidence of a processing difference however, may highlight that atypical development and cognitive functioning could result in behaviour that is nevertheless classified in the normal range.

Whilst the roots of constructivism may lie in stage models, such as that of Piaget, it has been argued that these models are limited and do not consider the possibility of parallel routes of acquisition, that is, they are able to explain delayed development but not a pattern of disordered atypical development. More recently, connectionist models, or artificial neural networks, composed of nodes with links that can vary in strength, have become increasingly prevalent in

the literature (Johnson, 2005). Nodes and links may be loosely translated as a biological parallel to neurons and synapses. These models are postulated to store information gained from experience either through altering the basic architecture or through adjusting the strength of the connection between nodes. The latter is usually assumed to be the case in most connectionist models, reflecting that there may be innate models which constrain development. Johnson (2005) suggests that only under extreme atypical environmental conditions or genetic abnormalities will the basic architecture be altered.

This departure from traditional developmental descriptions in which stages are outlined in a fixed and invariant sequence gives rise to the hypothesis that there may be parallel routes to achieving certain skills, leading to significant individual variation.

The dynamic systems approach outlined above is a constructivist theory that is not constrained to the motor domain and may also be applied to cognitive development. Indeed, one of the basic tenets of the theory is that many domains contribute to individual functioning and that the cognitive system is not merely the brain, but also the whole nervous system, body and environment (van Gelder & Port, 1995). Taking the dynamic systems hypothesis a step further, the embodiment hypothesis states that an individual's sensory-motor activity, through interaction with an environment, leads to the emergence of intelligence (Smith, 2005). Smith highlights that the cognitive system is non-stationary, a fact she proposes is often neglected in other theories which suggest that the mind is equipped with constant concepts to provide stability during experiences in a variable world. Instead, it is hypothesised that cognition, like motor skills, emerges as a property of a multifaceted system that is connected to the world in real time, and that development is therefore the result of real time changes.

A further constructivist theory, forwarded by Johnson (2001; 2005), is interactive specialisation, which posits that response properties of anatomical

regions in the brain are influenced by their connections to other areas of the brain. Interactive specialization suggests that the onset of skills during development will be linked to changes in activity in several regions. In this way, cognitive abilities emerge due to interactions between different brain areas and between the whole brain and the external environment. Johnson suggests that the study of these interactions should examine alterations in inter-regional connectivity, as opposed to the maturation of intra-regional connections. This hypothesis proposes that the acquisition of a new skill results in a reorganisation between different brain regions and that this process may alter previously existing mappings between cortical areas. Consequently, the same behaviour may be subserved by different neural substrates at different ages during development (e.g. Grossmann, Striano, & Friederici, 2007).

Constructivist approaches to development, especially embodied cognition, forge an explicit link between cognitive processes, perception and action (e.g. Barsalou, 1999) and argue for a central role of perception and action in cognition, as effective cognition must be coupled to the external world in real-time (Smith, 2005). Following from this theory, Diamond (2000) has posited that motor and cognitive development are inextricably linked and that the close co-activation of the cerebellum and the prefrontal cortex is an indication of a cerebellar role in cognitive functioning. Several investigatory studies have examined the link between cognitive and motor functioning (e.g. Ahnert, Bos & Schneider, 2003; Wassenberg et al., 2005); this literature is explored in detail in Chapter 2. These previous studies have often yielded contradictory results, perhaps through inconsistencies in test selection and age groups tested, and have failed to address the underlying structure of any association found between the domains. In addition, cognitive and motor tests have not always been administered concurrently with only a small proportion of the sample having a complete dataset (e.g. Ahnert et al., 2003). Some studies have grouped the children into broad age bands, potentially masking important age differences and

have administered tests to children younger than the normative sample (e.g. Dyck et al., 2009). It is therefore difficult to draw firm conclusions concerning the strength, consistency and nature of the interrelation between cognitive and motor skills across development.

For the interrelation of cognitive and motor skills to be better understood, a systematic investigation is needed to assess cognitive and motor functioning across a wide age range of children using appropriate standardised measures which are administered concurrently. This should enable direct comparisons to be drawn across age and gender and may help to further elucidate the underlying nature of the association between domains by examining specific relationships between particular sub-skills of cognitive and motor functioning. Chapter 2 examines the relationship between motor and cognition in a sample of typically-developing children aged 4-11 years. The interrelation of cognitive and motor skills is also investigated in children who have suffered a cerebellar tumour using the same tests as with the typically-developing children (Chapters 3, 4, & 5), to explore Diamond's suggestion that the cerebellum is instrumental in facilitating a link between these domains. This consistent use of standardised measures again allows for direct comparison between the patient and a typically-developing group. Relating to the hypothesis of Dyck et al. (2009), that distinctions between functional domains are arbitrary, it may be that any association found between different abilities could be accounted for by an underlying basic process for which the cerebellum is important. Possible hypotheses for cerebellar function which may have an overarching influence are discussed below. In addition, Chapter 6 aims to investigate potential underlying processes for cognitive and motor skills in the patient sample who have suffered a cerebellar tumour.

1.1.2 Plasticity

Of particular relevance to this thesis is the concept of plasticity, that is, the capacity of the brain for continuous structural change and function across the life span, allowing the brain to respond to environmental changes or changes within the human. In the context of neuropsychology, plasticity may be thought of as the ability of the developing brain to reorganise following injury. The maturational perspective on development posits that plasticity is a mechanism that is only activated following brain injury, enabling new areas of the brain to take over functions that would typically be subserved by the damaged regions, thus facilitating compensation. In contrast, constructivist approaches suggest that plasticity is a state which describes all regions that have not been fully specified. The maturational perspective on plasticity argues that the existence of developmental disorders, in which plasticity has apparently failed to produce typical functioning, is indicative that some cognitive systems may be constrained by a preformed architecture which limits the potential for variation within development (Temple, 1997). In this way, it may be suggested that there is an important distinction between developmental and acquired disorders, although some studies have suggested that 'developmental disorders' such as dyslexia may have an explicit neurological cause (e.g. Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Alternatively, constructivist theories argue that development is an interaction between the basic organisation of the nervous system which is gene-driven and impervious to experience to protect the brain from minor external disruptions, and neural plasticity systems in specialised brain structures that are capable of adapting to the environment and incorporating information it provides (Greenough, Black, Klintsova, Bates, & Weiler, 1999). In this way, the interaction between these processes links directly to the dynamic systems theory described above.

These two different approaches would therefore appear to offer contradictory hypotheses concerning the outcome of children who have suffered

a brain insult. The maturational approach suggests that the developmental end state of the patients may differ from that of typically-developing children as progression is conceived as a fixed and invariable process. Constructivist theories on the other hand, may predict that functional outcome in children who have suffered a brain insult may not differ greatly from typically-developing children, although a varying pathway may have produced the same outcome.

Following early insult, there are several possibilities for how development may proceed. It is possible that an impairment caused by the injury may persist throughout childhood, with the child failing to progress in any affected domains. Alternatively, development may occur, either at a slower pace than usual, at the same pace as in typically-developing children, or at a faster rate, with patients demonstrating 'catch-up'. Another possibility is that development following injury is qualitatively different from that seen in typically-developing children, with a deviation from the typical pattern of development. These different models for the potential developmental trajectory following early insult are explored in Chapter 4 which investigates the longitudinal outcome in the patient sample studied in this thesis using consistent standardised measures at each assessment point to enable comparisons to be made across time in this sample. Previous studies which have explored longitudinal outcome do not allow for differentiation of these hypotheses as the use of standardised scores alone in previous studies, rather than also considering raw scores of standardised measures, has not allowed exploration of the possibility that children with cerebellar damage do demonstrate developmental progression, albeit at a different rate to typically-developing children. In addition, without comparison to a typically-developing sample, it is difficult to assess whether development in this patient sample is qualitatively different. These difficulties are addressed in Chapter 4.

1.1.3 Cerebellar functioning

The role of the cerebellum has historically been attributed to coordinating gait and voluntary movements. Early work with the cerebellum demonstrated that removal of the cerebellum results in disturbances to posture and movements (e.g. Greenough et al. 1999). These studies were supported by subsequent clinical reports which highlighted that patients with cerebellar degeneration showed difficulties with voluntary movement of extremities, gait, posture and speech (e.g. Holmes, 1907). Holmes also investigated the precise nature of motor deficits following focal cerebellar damage (Holmes, 1939) and understanding of the cerebellar contribution to movement has been advanced by exploring the role of cerebellar functioning in motor control (e.g. Stein & Glickstein, 1992) and motor learning (e.g. Ito, 1982). More recently, investigations using imaging techniques to study cerebellar functioning have suggested that this structure is involved in cognitive processes such as language (e.g. Petersen, Fox, Posner, Mintum, & Raichle, 1988), attention (Allen, Buxton, Wong, & Courchesne, 1997) and affective processes (e.g. George et al., 1995). Schmahmann however has highlighted that this focus on non-motor contributions of the cerebellum to functioning is not a modern concept with a whole body of clinical reports detailing cognitive difficulties following cerebellar damage (see Schmahmann, 1997 for review).

Despite this, the impact of cerebellar damage on motor functioning, which is perhaps more easily assessed than more subtle cognitive impairments, has taken precedence until relatively recently. Bloedel and Bracha (1997) suggested that investigations into patients with cerebellar damage may be classified into five main areas of functioning, namely motor control, proprioceptive reflexes, adaptive modifications of postural reflexes, classically conditioned withdrawal reflexes and cognitive processes. The evolution of these ideas over time has resulted in multiple theories being proposed to account for cerebellar contribution to functioning.

As highlighted above, early motor studies lead to the suggestion that the cerebellum is involved with coordination of spontaneous and goal-directed movements and postural control (Holmes, 1939). Considering the findings from lesion studies that the cerebellum was involved in modification of postural reflexes and that the cerebellum is connected to other brain areas (e.g. Brodal, 1972), explanation for the role of the cerebellum was subsequently revised to include more than a role in motor performance. It was posited that the cerebellum was also implicated in error detection, motor learning and modification of existing behaviours (e.g. Ito, 1984). Demonstration of cerebellar involvement in classically conditioned reflexes, such as eyeblink conditioning, suggested a further role of the cerebellum for creating and accessing associations between stimuli and for developing novel responses in an adaptive, context-dependent manner (Thompson, 1986). In addition to this cerebellar link to procedural learning, cerebellar patients have also been shown to have difficulty with prism adaptation tasks (Weiner, Hallett, & Funkenstein, 1983) and motor tracing tasks (Sanes, Dimitrov, & Hallett, 1990). Taken together, these results suggest that the cerebellum is likely to be involved in both acquisition of motor skills and the integration of sensory input with motor demands. The cerebellum is known to receive input from both the motor cortex and the spinal cord (see below), and it is believed that the cerebellum is able to monitor and modulate movements so as to ensure they are performed in a smooth and coordinated output. The premotor cortex is postulated to provide information concerning intended movement (Fitzgerald, 2002), which is then compared with actual physical movement. The cerebellum is proposed to act as a comparator between these two sources of information and make adjustments to the sequencing and firing of motor neurons where a discrepancy is found (Ito, 1993). A cerebellar role in motor cognition has also been proposed in which the cerebellum predicts movement outcomes, which is believed to be important in

distinguishing whether sensory signals are due to external or internal sources (Bower, 1997; Fuentes & Bastian, 2007).

The cerebellum has also been implicated in timing mechanisms (Ivry & Keele, 1989) as cerebellar patients have demonstrated deficits in tasks requiring rhythmic tapping or judgment of time intervals (Ivry & Baldo, 1992; Ivry & Diener, 1991). Ivry and colleagues have linked this apparent deficit in timing mechanism to the deficits in classical conditioning also described (Ivry, Keele, & Diener, 1988). Other studies have also highlighted a deficit in duration-discrimination tasks in patient with cerebellar lesions suggesting a role of the cerebellum in representing temporal information (Hetherington, Dennis, & Spiegler, 2000; Nichelli, Always, & Grafman, 1996; Spencer, Verstynen, Brett & Ivry, 2007). This conclusion is confounded by findings from an imaging study with healthy adults performing timing tasks, as results demonstrated inconsistent cerebellar activation that was minimal in comparison to the fronto-striatal circuit involved in neural timing (Stevens, Kiehl, Pearlson, & Calhoun, 2007). The authors posit that the cerebellum may be involved in timing tasks, but that it is not a major substrate of mental timing.

These theories of cerebellar functioning, together with the earlier hypotheses outlined, raise the possibility that the cerebellum is involved in learning, plasticity and memory storage and suggest that cerebellar lesions may be responsible for deficits in cognitive performance. Linking with the development of theories concerning separate cognitive and motor domains described above, Bloedel and Bracha (1997) posit that the cognitive and motor deficits seen following cerebellar injury are not indicative of separate cerebellar functions, rather that the distinction drawn between cognitive and motor abilities may be an inaccurate premise for investigation. Instead, it has been suggested that the precise role of the cerebellum is dependent on the nature of the task (Thach, 1996) and context dependent. For example, a cerebellar lesion may disrupt the acquisition of a classically conditioned eyeblink reflex, whilst the

same lesion reduces an unconditioned eyeblink reflex and does not affect spontaneous naturally occurring eyeblinks (Bracha, Webster, Winters, Irwin, & Bloedel, 1994). Bloedel and Bracha (1997) concluded that cerebellar participation in any behaviour consists of both regulating its performance and optimising performance through modification to a specific context.

Schmahmann has proposed that the cerebellum contributes to functioning by maintaining behaviours around a homeostatic baseline (Schmahmann, 1998; Schmahmann, Anderson, Newton & Ellis, 2001). It is argued that the uniform structure of the cerebellum allows it to consistently modulate the neural information it receives, and that this can be achieved in a topographically determined fashion. Schmahmann has termed this functioning of the cerebellum the 'universal cerebellar transform' (Schmahmann, 2000b). The cerebellum may therefore regulate aspects of movement such at rate, force, rhythm and accuracy and in the same way regulate the speed, capacity, consistency and appropriateness of cognitive and emotional processes. Schmahmann extends the error detection role of the cerebellum described above by suggesting that the universal cerebellar transform allows the cerebellum to detect and also prevent and correct mismatches between intended and perceived outcome, thereby incorporating functions previously prescribed to the cerebellum in this complex processing. According to this theory, damage to the cerebellum may result in impairment in the cerebellar modulation of functioning, with different manifestations depending upon the location of the damage (Schmahmann et al., 2002). This hypothesis therefore predicts an association between deficits in different domains that are influenced by the cerebellum.

Many clinical studies within the last decade have reported cognitive consequences following a cerebellar infarct, in both adults and children. Schmahmann and Sherman (1998) have described a cerebellar cognitive affective syndrome (CCAS) for the profile of cognitive difficulties in adults that have been observed following cerebellar damage, including difficulties with

executive functioning, impaired visuo-spatial functioning, personality change and language difficulties, which combine to produce an overall decrease in intellectual ability. In particular, it has been suggested that damage to the vermis results in the most prominent behavioural changes, whilst lesions of the anterior lobe produce minor alterations in executive and visuo-spatial functions.

The overall constellation of difficulties as a consequence of cerebellar damage appears to encompass a wide range of abilities, with specific profiles of functioning often appearing to be related to the age at insult, the precise location and nature of the damage and the subsequent treatment. It is unclear whether the CCAS is applicable to children who have suffered a cerebellar insult, with previous investigations reporting a variety of deficits in this patient group. The finding of vermis involvement in the modulation of aggression and mood has been replicated in children (Riva & Giorgi, 2000), with mutism also presenting following vermis damage (e.g. Levisohn, Cronin-Golomb, & Schmahmann, 2000). In addition, long-term outcome appears to differ for adults and children, with some adult studies reporting that the disruption is to some degree transitory (e.g. Schmahmann & Sherman, 1998). Studies with children offer a mixed prognosis for developmental progression, which is confused by different studies examining a variety of skills across a range of ages. Thus, it is difficult to draw firm conclusions concerning developmental outcome following a cerebellar tumour sustained during childhood and a systematic study examining multiple aspects of functioning is needed to ascertain the prognosis for this population. The functional impact of a cerebellar tumour during childhood and the supporting literature are explored in detail in Chapter 3. This chapter aims to clarify the nature of deficit following treatment for a cerebellar tumour in a sample of 15 patients by using consistent measures across all participants, enabling direct comparisons to be drawn across patients varying in age, tumour type and treatment and tumour histology, in addition to a comparison with the typically-developing children studied in Chapter 2. In addition, Chapter 4

examines the longitudinal outcome in this sample to help clarify if any deficit in functioning or delayed development becomes worse with time, or whether a developmental 'catch-up' is seen in these patients.

Whilst the motor contribution of cerebellar functioning to speech has been recognised (e.g. Darley, Aronson, & Brown, 1975), further anatomical evidence has implicated the cerebellum in higher language functioning (Thach, Goodkin, & Keating, 1992). The dentate nucleus has been shown to project to the frontal lobe, including prefrontal association areas and regions of Broca's language area. Leiner and colleagues have proposed that there may be an association between the size of the dentate nucleus and language capacity (Leiner, Leiner, & Dow, 1993). These authors posit that the feedback portion of this loop, from Broca's area via the red nucleus and inferior olive to the cerebellum adds weight to a cerebellar involvement in language, in addition to language-learning mechanisms. In addition, both clinical (Fiez, Petersen, Cheney, & Raichle, 1992; Leggio, Silveri, Petrosini, & Molinari, 2000) and imaging (Papathanassiou et al., 2000) studies have revealed lateral cerebellar activation during language tasks, more particularly in the right hemisphere. Evidence for a cerebellar involvement in linguistic processing has lead to the implication of the cerebellum in dyslexia (Nicolson, Fawcett & Dean, 2001). Whilst deficits in language processing have been recorded following a cerebellar tumour (e.g. Riva & Giorgi, 2000), little research has focused specifically on reading abilities in children with cerebellar damage. Investigating reading and other academic skills in children who have suffered a cerebellar tumour, in the context of any general cognitive impairment, may help to further elucidate the role of the cerebellum in these skills in addition to directly addressing the cerebellar deficit hypothesis for dyslexia. Again, the use of standardised measures across the sample allows for comparison with a typically-developing standardising sample and enables comparisons across the different tumour types, treatments and tumour histologies encompassed by this sample. The literature concerning a cerebellar role in language development and

the impact of a tumour in childhood on language skills are further explored in Chapter 5.

1.1.4 Cerebellar anatomy and development

Anatomically, it might be unsurprising that the cerebellum may play a role in non-motor brain functioning as it constitutes 10% of the total brain weight and contains more than half of all the neurons in the brain (Ghez & Fahn, 1985). The cerebellum is comprised of two hemispheres joined by the vermis in the midline and can be divided into three lobes; the anterior lobe, the posterior lobe and the flocculonodular lobe. In contrast to the cerebral hemispheres, it has been demonstrated that the cerebellar hemispheres relate to the ipsilateral side of the body for motor control. The posterior lobe, which encompasses the neocerebellum, is likely to be involved in higher order functioning due to its connections with the cerebrum. In addition, it has been noted that the neocerebellum has emerged phylogenetically most recently in the cerebellum, and that its expansion during primate evolution mirrors that of the dorsolateral prefrontal cortex (Diamond, 2000). Diamond postulates that, given the complex composition of the cerebellum, it would be logical to assume that existing structures have been recruited to encompass cognitive functions and that the parallel evolution of these two brain areas implies that they may be used in similar capacities. In this way, Diamond posits that the cerebellum is not only necessary for cognitive functioning, but that it is employed in the same aspects of control as the dorsolateral prefrontal cortex, namely when a task is difficult, novel, when conditions are altered, if a fast response is needed or if concentration is required. A recent imaging study with typically-developing children offers further support for a cerebellar role in cognitive functioning by reporting significant relationships between general cognitive ability and cerebellar volume and suggesting that developmental changes in cerebellar

volume are likely to be an important substrate supporting cognitive development throughout childhood (Pangelinan et al., 2011).

A meta-analysis of activations within the cerebellum for different cognitive tasks has suggested that the cerebellum is functionally organised into distinct regions (Schmahmann, 2000a, b). Motor functions are believed to be represented in the anterior lobe whereas cognitive operations, as discussed, are located in the lateral hemispheres of the posterior lobes. Emotional regulation is influenced by the vermis region, suggesting that the vermis and flocculonodular lobe, which are phylogenetically older than other cerebellar regions, form the 'limbic cerebellum' (Schmahmann, 2000b).

The cerebellum is connected to other brain regions via afferent and efferent fibres that are grouped together into peduncles. Efferent output via the superior peduncles connects the cerebellum to the midbrain and the inferior peduncles connect the cerebellum to the medulla oblongata and afferent input enters through the middle peduncles. The cerebellum contains four intracerebellar nuclei, the fastigial, globose, emboliform and the dentate nucleus, whose axons form the cerebellar outflow in the superior and inferior cerebellar peduncles and gain input through the middle peduncle. The afferent pathways of the cerebellum are summarised in Table 1.1 (from Snell, 2006).

Table 1.1 Afferent pathways of the cerebellum

		Pathway	Origin
Afferent Pathways	**Cerebral cortex**	Corticopontocerebellar pathway	Frontal, parietal, temporal and occipital lobes
		Cerebro-olivocerebellar pathway	Frontal, parietal, temporal and occipital lobes
		Cerebroreticulocerebellar pathway	Cerebral cortex, particularly sensorimotor areas
	Spinal cord	Anterior spinocerebellar tract	Muscles, tendons and joint receptors of upper and lower limbs, skin and superficial fascia
		Posterior spinocerebellar tract	Muscles, tendons and joint receptors in trunk and lower limbs
		Cuneocerebellar tract	Muscles, tendons and joint receptors in upper limbs and upper thorax

The corticopontocerebellar pathway is believed to be the predominant link which conveys information from the cerebral cortex to the cerebellum (Schmahmann, 1991). It has been previously established that this pathway is involved in motor coordination as the pre-motor and supplementary motor areas send their efferent projections to the cerebellum via this corticopontine route. There is increasing evidence that the association areas of the parietal, temporal and frontal lobes and the paralimbic areas of the parahippocampal gyrus also contribute to the corticopontocerebellar pathway (Middleton & Strick, 1994; Schmahmann, 1991, 1996; Schmahmann & Pandya, 1995, 1997). These areas are known to be responsible for complex cognitive functions and findings that these areas communicate with the cerebellum contributes to evidence for a cerebellar involvement in cognition. It has been suggested that the feedforward and feedback links between the association and paralimbic cerebral cortices implies a regulatory and modulatory role of the cerebellum in cognition and affect, rather than one of generation (Malm et al., 1998; Schmahmann & Pandya, 1997).

The main structure of the cerebellum is formed two months after conception, however cerebellar development is prolonged with neurogenesis continuing postnatally until 18 months (Spreen, Tupper, Risser, Tuokko, & Edgell, 1995). Although the cerebellum demonstrates postnatal neurogenesis, its functional development has been demonstrated to be the same as other sensorimotor regions such as the thalamus, brain stem and sensorimotor cortex, showing high glucose metabolic activity as early as 5 days old (Chugani, 1994). The cerebellar vermis is believed to reach adult proportions between six and nine years whilst the hemispheres reach maturity by two years (Hayakawa et al., 1989). The prolonged development of the cerebellum postnatally means that it is vulnerable to developmental aberrations and tumours (Wang & Zoghbi, 2001). Indeed, the cerebellum is a primary site for paediatric brain tumours as an estimated 20-25% of paediatric brain tumours occur in the cerebellum (Duffner, Cohen, Myers, & Heise, 1986; Stiller & Bunch, 1992) with a higher incidence in preschool than school-aged children, particularly in boys. Despite adult proportions of cells constituting the cerebellum at an early age, synaptic connections are modified during development (Brown, Keynes, & Lumsden, 2001) and injury during this period is therefore likely to have a long-term impact.

1.1.5 Cerebellar tumours, treatment, and neurodevelopmental outcome

1.1.5.1 Tumour histology

Three types of tumour are commonly found in the cerebellum in childhood, namely medulloblastoma, ependymoma and astrocytoma. Medulloblastomas constitute 16-29% of all childhood brain tumours (Mueller & Gurney, 1992) and 30-40% of tumours at this site (Jaspan, 2004). These are malignant tumours believed to arise from residual neuroectodermal cells originating from embryonic cells of the cerebellum (Lena & Gentet, 1999). They grow rapidly and invasively with metastases (secondary tumours that have

spread to an area of the body remote from the primary tumour) and primarily arise in the vermis region of the cerebellum. Due to the highly infiltrative nature of this tumour type full surgical resection is not always possible and surgery is therefore followed with chemotherapy and radiotherapy. Survival rates for this tumour type are estimated to be between 50-80% following surgery, chemotherapy and radiotherapy (Modha et al., 2000; Pollack, 1999). The mean age for patients with medulloblastoma is between five to seven years, over half occur before ten years and very few before one year of age, with a higher proportion of boys diagnosed than girls (1.8:1) (Taylor & Rutka, 2007).

Ependymomas are malignant tumours arising from ependymal cells which line the ventricles and account for 6-17% of all paediatric brain tumours (Mueller & Gurney, 1992) and approximately 10% of cerebellar tumours (Jaspan, 2004). This tumour type is also invasive and therefore poses difficulty for achieving a complete surgical resection, meaning surgery is usually accompanied by chemotherapy and radiotherapy. The 5 year survival rate for this tumour type is approximately 50-60% (Merchant & Fouladi, 2005; Sanford & Gajjar, 1997). Ependymomas generally occur earlier than medulloblastomas, at around three years of age, with no sex differences in diagnosis rates (Taylor & Rutka, 2007).

The third common tumour type associated with this region is pilocytic (grade I) astrocytomas, which are benign tumours with non-invasive and non-metastatic growth. They account for 20-49% of all childhood brain tumours (Mueller & Gurney, 1992) and account for approximately one third of all cerebellar tumours. Fibrillary astrocytomas (grade II) and more malignant gliomas (anaplastic astrocytoma, grade III; glioblastoma multiforme, grade IV) are also observed in this site, although they are rare. Astrocytomas usually originate in the vermis however they may also be located within the lateral cerebellar hemispheres (Jaspan, 2004). The prognosis for low-grade astrocytomas is better than for medulloblastomas and ependymomas, with a 10 year survival rate of around 90% in cases where a complete surgical resection is

achieved (Pencalet et al., 1999; Pollack, 1999). Compared to those with total resections, children with subtotal resections have a poorer prognosis with a 60-80% survival rate over a 5 year period.

1.1.5.2 Treatment

The treatment a patient receives is inherently linked to the histology of the tumour and is often multimodal. For all tumour types, the initial approach is to perform a surgical resection to excise the largest volume of tumour as possible. For low-grade astrocytomas it is typical that treatment consists of surgery alone. There is increasing evidence to suggest that surgery alone may result in a moderate level of cognitive difficulties (e.g. Carpentieri et al., 2003). This is in contrast to earlier findings which indicated that cognitive performance remained stable or improved following surgery prior to any adjuvant therapy (Ellenberg et al., 1987). The decline following surgery may reflect perioperative factors such as bacterial meningitis, shunt infections or the effects of multiple surgeries (Kao et al., 1994). Many studies have now demonstrated that children who have undergone surgical resection alone for astrocytoma have cognitive difficulties that persist into adulthood (Aarsen, Van Dongen, Paquier, Van Mourik, Catsman-Berrevoets, 2004; Beebe et al., 2005; Rønning, Sundet, Due-Tonnessen, Lundar & Helseth, 2005; Steinlin et al., 2003). This outcome following insult to the cerebellum suggests a role for the cerebellum in non-motor processes, although previous studies offer differing conclusions concerning the precise nature of the deficits in this population, partly through patchy and inconsistent use of standardised measures. These are discussed in greater detail in Chapter 3. Total surgical resection is not always feasible due to the involvement of critical structures such as the cerebellar peduncles, especially for malignant tumour histologies, and in these instances adjuvant chemotherapy and radiotherapy are administered.

Establishing the impact of chemotherapy on long term developmental outcome has proven challenging as few treatment protocols are restricted to chemotherapy alone, and those that are often use multiple agents. In addition, the majority of the research conducted into the effects of chemotherapy has been done with children treated for acute lymphoblastic leukaemia (ALL) because children with brain tumours who receive chemotherapy are highly likely to also be treated with radiotherapy. The results from studies examining outcome in children with ALL mainly concern the effects of methotrexate, an antimetabolite drug commonly used in chemotherapy, and have revealed an IQ decline of up to 3-4 years following treatment (Brown, Sawyer, Antoniou, Toogood & Rice, 1999; Mahoney et al., 1998). A meta-analysis of children with leukaemia who received chemotherapy alone had difficulties with several areas of cognitive processing, including processing speed, perceptual reasoning and working memory as well as academic problems with reading and maths (Peterson et al., 2008). In contrast, a subsequent literature review found that attention and executive function were affected in this population whilst global cognitive skills were more preserved (Buizer, de Sonnerville & Veerman, 2009). Additional research with children with ALL has suggested that the combination of radiation and methotrexate may result in severe developmental disruption, with some suggesting that the blood-brain barrier is altered when chemotherapy is given at the same time as radiotherapy, allowing more methotrexate to enter the central nervous system (Bleyer & Poplack, 1985).

Far fewer studies have investigated the impact of chemotherapy in children with brain tumours, as many also receive radiotherapy. One study compared developmental outcome in patients who received intrathecal methotrexate, radiation and intravenous methotrexate to outcome in patients who received radiation and intravenous methotrexate only (Riva et al., 2002). The results on neuropsychological measures indicated that those who received intrathecal methotrexate were more severely impaired than those who did not.

Studies which have investigated the effect of chemotherapy with other agents (e.g. vincristine, cisplatinum) have not found that they increased the incidence of intellectual dysfunction (Copeland, deMoor, Moore & Ater, 1999; Ellenberg, McComb, Siegel & Stowe, 1987; Packer et al, 1989; Palmer et al., 2003) suggesting that these agents may not produce neuropsychological effects.

In contrast to chemotherapy, radiotherapy has been consistently linked to neuropsychological deterioration following treatment (e.g. Hoppe-Hirsch et al., 1990; Maddrey et al., 2005; Palmer et al., 2001), with larger and higher doses being associated with poorer outcome (Grill et al., 1999). This decline following treatment is believed to be due to vascular and demyelinating neuropathology (e.g. Mulhern et al., 1999; Palmer et al., 2002) and it has been demonstrated that a younger age at treatment results in a poorer outcome (Packer et al., 1989). For some patients, radiotherapy may be directed towards the region of interest, in this case the posterior fossa, however for others it is also necessary to give full brain radiotherapy. The larger volume affected by radiation in the latter group has been shown to produce a greater deficit in cognitive functioning than in patients with more targeted radiotherapy (Silber et al., 1992). The impact of radiotherapy in relation to cognitive, academic and attention abilities is explored further in subsequent chapters.

1.1.5.3 Other prognostic factors

In addition to tumour type and treatment, other factors are known to impact on neurodevelopmental outcome in children diagnosed with cerebellar tumour. These include the precise location of the tumour within the cerebellum (e.g. Levisohn et al., 2000; Riva & Giorgi, 2000), age at diagnosis (e.g. Dennis, Spiegler, Hetherington, & Greenberg, 1996; George et al., 2003) and the presence of hydrocephalus (e.g. Stargatt, Rosenfeld, Maixner, & Ashley, 2007). The time that has elapsed between treatment and assessment is also known to impact on performance, especially in patients where deterioration over time is

expected (e.g. Hoppe-Hirsch et al., 1995), although others have report no change over time (e.g. von Hoff et al. 2008). The longitudinal investigation in Chapter 4 aims to address this discrepancy. There is currently debate within the literature concerning functional outcome as related to each of these factors, with differences in results which may be accounted for by measurement of varying cognitive abilities in children with different tumour types, this is further discussed in Chapter 3. The impact of each of these factors is examined in detail throughout the following chapters in relation to the various skills assessed. Chapter 7 focuses entirely on the effect of hydrocephalus on the outcome measures included in this study. The pattern of strengths and weaknesses reported in Chapters 3, 4, 5 & 6 led to a case-study approach when considering hydrocephalus in this sample, and highlighted that trends in datasets may emerge as the result of one or two individuals that are not representative of the whole sample. This factor was considered more closely as there is particular controversy in the literature concerning the severity and nature of intellectual impairment following hydrocephalus in children. In addition, the hydrocephalus literature is applicable to a wider range of patient groups due to its occurrence in multiple clinical situations. As medical practice takes hydrocephalus severity into account when considering prognosis, it is important to establish which aspects of functioning may be affected by hydrocephalus.

1.1.6 Summary

Theories of development are increasingly recognising that developmental progression should be considered as an integrated process, with associations between different domains of functioning. Several studies with typically-developing children have provided evidence for a link between domains, however this is not a universal finding and no underlying mechanism has been elucidated. Diamond (2000) has posited that this interrelation, particularly between motor and cognitive functioning, may be underpinned by cerebellar contribution to

functioning in both areas. Linking in with this hypothesis are studies demonstrating that children with cerebellar tumours are known to have motor difficulties and concurrent cognitive deficits, however the precise nature and severity of these deficits is unclear. Examining a sample of children treated for cerebellar tumour in comparison to a sample of typically-developing children will allow the underpinning of the cerebellum in the association between cognitive and motor skills to be examined further. In addition, comparing the nature of the link between domains across the patient and typically-developing samples should speak to the developmental theories outlined above and establish whether any deficits in the patient sample result from delayed or deviated development. To this end, a highly detailed investigation into this sample of patients was conducted, which included measures of cognitive, motor, language and attention skills, so as to shed further light on the nature of deficits following cerebellar insult and to help to clarify the impact of different prognostic factors.

In order to establish precisely if and how motor and cognitive skills are linked, Chapter 2 reports an investigation into the interrelation of the two domains in typically-developing children. The children in Chapter 2 provide a control comparison group for the results from the interrelation of cognitive and motor skills in children who have suffered a brain tumour in the preschool years which are reported in Chapter 3. Chapters 4 considers the longitudinal change in patients' scores over time and the impact on the correlation between these domains. Chapter 5 investigates the potential role of the cerebellum on academic attainment by examining patients' scores in the light of their cognitive abilities. Chapter 6 explores the impact of a cerebellar tumour on attention scores in these patients and the relationship between attention skills and performance on the previous domains examined. Chapter 7 focuses on the impact of hydrocephalus on performance in all the measures undertaken by the patient sample in this study. Chapter 8 provides a summary of the findings from this study, how they fit into current research concerning development and the

cerebellum, the implications for clinical rehabilitation studies with children who have suffered a cerebellar tumour, and directions for future research. The main objectives for this study are summarised below. Individual hypotheses are presented per chapter.

1.1.7 Objectives

1. To establish the underlying nature of any association between cognitive and motor skills in typically-developing children using standardised measures (Chapter 2).

2. To examine the interrelation of cognitive and motor ability in children that have sustained a cerebellar tumour in the preschool years and to investigate if and how progress varies from a typical trajectory (Chapter 3).

3. To study longitudinal development in the patient sample to address previous conflicting reports concerning increasing developmental delay versus developmental 'catch-up' in this patient group (Chapter 4).

4. To investigate individual profiles of deficit following treatment for a cerebellar tumour, including academic skills in the context of cognitive capacity, (Chapter 5) the impact on attention skills, and the link between attention and performance in other areas (Chapter 6).

5. To investigate potential prognostic factors which may impact upon functional outcome in the patient group, including the location of the tumour, tumour histology and treatment, age at diagnosis, time post treatment and hydrocephalus (Chapter 7).

2 Visual processing and fine manual control underpin the interrelation between cognitive and motor development in typically-developing children aged 4 to 11 years

2.1 Background literature

Cognitive and motor development was traditionally thought to occur across separate domains, along distinct timescales, and be subserved by different regions of the brain. Recently, evidence has mounted from imaging studies, developmental disorders, and typically-developing children to suggest that cognitive and motor development are more closely related than previously assumed and have similarly protracted developmental trajectories (see Diamond, 2000, for a review). Imaging studies have shown an overlap of activation between areas initially thought to subserve just one function, suggesting an underlying neural network that serves both cognitive and motor functioning. For example, the dorsolateral prefrontal cortex (governing cognitive control) has been shown to connect with motor areas, such as the cerebellum (e.g. Schmahmann & Pandya, 1997b), supplementary motor area (e.g. Tanji, 1994) and premotor cortex (e.g. Dum & Strick, 1991). Conversely, the cerebellum is known to receive input from brain areas thought to be involved in cognition, including parietal cortex (Schmahmann & Pandya, 2008) and superior temporal cortex (Schmahmann & Pandya, 1991). Even the dorsal premotor area, considered to be solely a motor area, has recently been shown to participate in non-motor cognitive operations, such as visual-spatial processing for mental calculations (e.g. Abe & Hanakawa, 2009). Given this underlying neural architecture and similarly protracted developmental timescales of maturation it is likely that cognitive and motor development will be linked consistently across childhood, although this has yet to be determined.

2.1.1 Typically-developing studies

The aim of this chapter was to investigate the consistency of interrelation across cognitive and motor development as a function of age and sex in typically-developing children. Previous studies investigating this relationship in typically-developing children have produced inconsistent findings regarding the strength and nature of association. For example, Wassenberg and colleagues (2005) reported no correlation between overall cognitive and motor scores in 5-6 year olds but specific sub-skills were related. In particular, working memory (in girls) and verbal fluency (in boys) were related to motor control. Other studies have also found associations between specific cognitive and motor skills, but these vary across studies and gender. For example, Pangelinan and colleagues (2011) reported that cognitive abilities (Full Scale IQ) and visuomotor performance, as measured by pegboard performance, were strongly associated in a sample of 6-13 year olds, although the correlations were not reported for each age group. Planinsec (2002) reported cognitive ability most strongly correlated with balance and coordination in 5-6 year old boys, whilst in girls of the same age cognitive ability was most highly correlated with speed and explosive strength. Balance has also been shown to correlate with reading and maths scores in children aged 7-11 years (Knight & Rizzuto, 1993) although Livesey, Keen, Rouse and White (2006) found fine motor ability and ball skills, not balance, were related to cognitive control in 5-6 year olds. Furthermore, Roebers and Kauer (2009) reported no significant correlation between composite cognitive and motor scores at 7 years although significant correlations were found for several subtests (e.g. flanker task and jumping) few of which remained significant after controlling for age and processing speed.

Predictive studies also suggest that cognitive and motor development are linked and show that movement experiences in early childhood which facilitate interaction with the environment are necessary for cognitive development (e.g. Campos et al., 2000). For example, the age of attainment of gross motor

milestones, such as learning to stand, is predictive of adult executive functioning (Murray, et al., 2006; Murray, Jones, Kuh & Richards, 2007) and working memory and processing speed in children aged 6-11 years (Piek, Dawson, Smith & Gasson, 2008). Other studies have shown an association between fine motor skills and cognitive ability. For example, Dellatolas and colleagues (2003) found that early manual skill was more strongly associated with cognitive tasks than later acquired manual skill and they recorded correlations between hand skill and visual-spatial and vocabulary tasks, but not speech and phonological memory tasks. As this study did not include measures for gross motor ability it is not possible to determine the differential contribution of gross and fine motor development to later acquired cognitive skills.

These studies suggest that specific cognitive and motor skills may be related during development, although which skills are related vary across studies, age, and gender. It is possible that the nature of interrelation between cognitive and motor ability changes with age, as different skills mature at different rates. Indeed, Ackerman (1988) proposed that any correlation between cognitive and motor functioning would decrease with age, as some motor skills require less attention with practice. Consistent with this, Reilly, van Donkelaar, Saavedra and Woollacott (2008) found that postural interference affected visual working memory in 4-6 year olds, but not in 7-12 year olds and adults. In contrast, Ahnert et al. (2003) found the strength of correlation between cognitive and motor domains for specific sub-skills either increased towards the end of the school years or remained stable across time. Furthermore, a recent cross-sectional study by Dyck et al. (2009) showed that the strength of correlation between cognitive and motor skills varied non-linearly across age. Motor ability was found to correlate significantly with a broad range of measures including language, motor, theory of mind and emotional understanding (15 comparisons) in 3-6 year olds, but only one correlation reached significance in 6-8 year olds, whilst four reached significance in 9-11 year olds and seven were

significant in 12-14 year olds. The authors suggested this reflected differences in the timescale for maturation of different brain regions as the anterior brain regions thought to subserve sensory and motor abilities mature by 5 years whereas those areas serving cognitive skills have a more protracted developmental timescale. The authors suggested that this initial strong interrelation, then subsequent decrease in 6-8 year olds and ensuing increase with age were due to the differences in the timescale for maturation of different brain regions. The anterior brain regions thought to subserve sensory and motor abilities mature by 5 years whereas those areas serving more cognitive skills have a more protracted developmental timescale. The authors posited that as brain regions subserving more cognitive functions mature with time, the different domains become increasingly associated again. Clearly this contradicts claims that the developmental trajectory of motor and cognitive skills are similarly protracted and that the interrelation between these domains is due to an underlying anatomical network involved in both cognitive and motor processing (Diamond, 2000).

Thus, it is difficult to draw firm conclusions about the strength, consistency, and nature of the interrelation between cognitive and motor skills across development because of methodological differences between studies, both in the age of the samples tested and the measures used to assess functioning in each domain. Comparisons across previous studies are confounded due to the use of different standardised or experimental tests given at different ages. In addition, cognitive and motor tests are not always administered concurrently, with an interval of up to six months in some studies, and often only a small proportion of participants have a complete dataset (e.g. Ahnert et al., 2003), which may attenuate the strength of correlations found. Furthermore, some studies administered tests to children younger than the normative sample (e.g. Dyck et al., (2009) gave four subtests of the WISC-III to children aged less than 6 years) and grouping children into broad age bands can

mask potentially important differences (for example, Dyck et al., (2009) grouped 3-5 year olds whilst looking at theory of mind skills yet this age range coincides with major changes in the development of theory of mind skills – see Wellman, Cross & Watson, 2001).

Hence, for the interrelation of cognitive and motor development to be better understood, systematic investigations are needed to assess cognitive and motor functioning across a wide age range of children, using the same standardised tests, administered concurrently, that are appropriate for the age range tested. The choice of standardised tests should reflect those considered to be 'gold standard' so as to assess in detail the development of different cognitive and motor skills. This will enable specific relationships between particular sub-skills of cognitive and motor functioning to be examined in relation to age and gender and the extent to which they contribute to the overall relationship to be determined.

This study sought to overcome some of the methodological problems associated with previous studies by selecting comprehensive standardised tests of cognitive and motor skill that overlapped the age range 4-11 years. This age range was chosen because it covers the period when many cognitive and motor skills develop and are able to be measured reliably using the same tasks. In doing so, each child was given the same set of cognitive and motor subtests, which were administered at the same point in time. It was predicted that, if, as Diamond (2000) suggests, cognitive and motor functioning are subserved by a common anatomical network that matures at a similar timescale, a consistent relationship between domains across age and gender should be observed.

2.2 Method

2.2.1 Participants

Ethical approval for the study was granted from the School of Psychology, University of Nottingham, which accords with the British Psychological Society

ethical guidelines. In total, 248 typically-developing children aged 4 to 11 years were recruited from local primary schools within Nottinghamshire following permission from the head teachers. Children were divided into eight age groups of approximately equal size, each spanning one chronological year. Within each age group care was taken to balance, as far as possible, the number of males and females. Table 2.1 reports the distribution of children across the different age and sex groups. Prior informed consent was obtained from parents/guardians for each child that participated in the study. Parents/guardians were asked to give details of any known or suspected developmental problems. None of the children in this sample presented with identified developmental difficulties.

Table 2.1 Descriptive statistics of participant characteristics across the different age groups

Age group (years)	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Overall**
N	30	30	32	31	30	31	34	30	-
Sex ratio M:F	15:15	15:15	16:16	15:16	15:15	15:16	17:17	15:15	
Mean age (months) (SD)	54 (3.79)	65 (3.12)	80 (2.95)	90 (3.51)	102 (3.89)	114 (3.36)	126 (3.36)	135 (2.18)	-
Mean Fluid Crystallised Index (cognitive index) (SD)	114.50 (13.24)	108.80 (15.54)	102.78 (14.24)	105.71 (13.02)	104.00 (11.28)	95.16 (13.06)	101.85 (13.14)	101.77 (17.38)	104.24 (14.73)
Mean Total Motor Composite (motor index) (SD)	58.57 (10.75)	54.13 (9.33)	53.19 (8.93)	51.23 (6.89)	49.13 (8.65)	49.61 (10.33)	45.62 (6.74)	47.10 (9.05)	51.00 (9.61)

2.2.2 Assessments

To assess cognitive and motor development across this sample the standardised tests described below were administered. These tests were chosen as they are comprehensive measures of each domain and provide standard scores for the chronological age range of the sample.

2.2.2.1 Cognitive ability

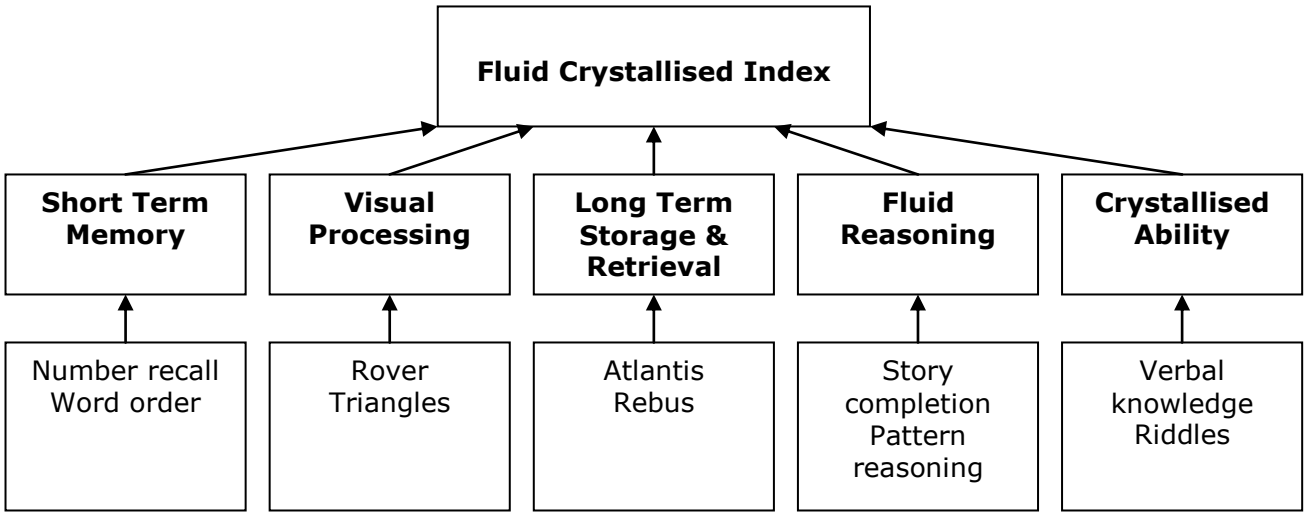
The Kaufman Assessment Battery for Children – 2nd Edition (KABC-II: Kaufman & Kaufman, 2004) was used to assess cognitive and processing abilities. It is an age-adjusted measure for 3 to 19 years and consists of 10 core subtests presented as a series of tasks. Scores on individual subtests are grouped to produce scores for broader processing areas, namely Short Term Memory, Visual Processing, Long Term Storage & Retrieval, Fluid Reasoning and Crystallised Ability (as illustrated in Figure 2.1a). Scores on these broad abilities are then combined to produce the Fluid Crystallised Index (FCI) which is the general measure of cognitive ability ($\mu = 100$, $\sigma = 15$).

2.2.2.2 Motor ability

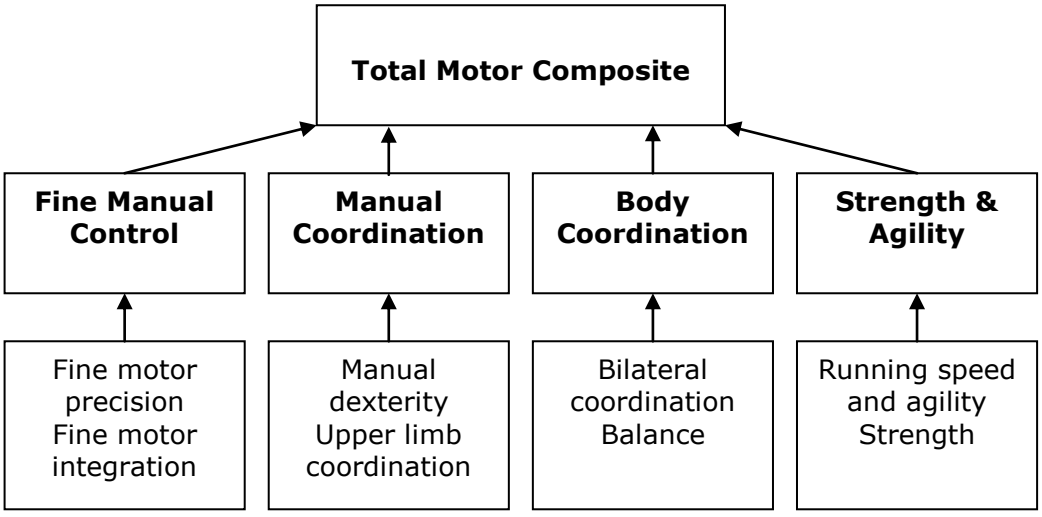
The Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition (BOT-2: Bruininks & Bruininks, 2005) was chosen to measure motor ability as it covers a range of gross and fine motor skills and is considered a gold standard in motor assessment (Gwynne & Blick, 2004). It is an age-adjusted measure for 4 to 21 year olds and consists of 8 subtests. Scores on these subtests are grouped into broader abilities, namely Fine Manual Control, Manual Coordination, Body Coordination and Strength & Agility (see Figure 2.1b). These are combined to produce the Total Motor Composite (TMC) score which provides a general measure of motor ability ($\mu = 50$, $\sigma = 10$).

Figure 2.1 Hierarchical organisations of the standardised measures of cognitive (KABC-II) and motor (BOT-2) ability. Individual subtests load onto broad areas of ability that combine to form the overall general measure of ability

(a) Test organisation of the KABC-II



(b) Test organisation of the BOT-2



2.2.3 Procedure

Each child was assessed individually in a quiet area free from distraction using the standardised measures described above, either within their primary school or in the School of Psychology, University of Nottingham. For those children who were assessed in their primary school, the tests were administered in five sessions, each lasting 20-25 minutes with all tests completed within one to two weeks. Children tested in the School of Psychology were given the tests in one session lasting approximately two hours. All participants were given breaks as and when necessary. The order of test administration was randomised across participants but within each test the same order of subtest presentation was used throughout. For the KABC-II the subtests were arranged into suitable 25-minute blocks and the BOT-2 subtests were conducted in test order.

2.2.4 Statistical analyses

For each participant, standard scores were generated for the five cognitive indices of the KABC-II and the main measure of cognitive functioning (FCI) and the four motor indices of the BOT-2 and the overall score for motor skill (TMC). Scores for all participants were included in the analyses (i.e. no outliers were excluded) to ensure a fair representation of the range of variation within mainstream schooling. Data were inspected for normality and linearity and assumptions for parametric statistics were met. Scores were used to examine 1) if an association exists between these two domains at various points in development (age groups) for each sex and 2) if and how the nature of association differs in strength between broad levels of ability for each domain, as measured by the different indices of the standardised tests.

1) To investigate the relationship between the overall index of cognitive (FCI) and motor (TMC) functioning, a series of Pearson correlations (with Bonferroni correction applied for multiple comparisons) was conducted using

standard scores, both across the entire sample, and for each age and/or sex group. To test for significant differences in strength of correlation for each of the comparisons made Fisher's r to z was applied.

2) To investigate in more detail the nature of association between cognitive and motor ability Pearson correlations (Bonferroni corrected for multiple comparisons) were conducted across the different indices of the KABC-II and the BOT-2 using standard scores of the entire sample, so as to enable areas of ability within each domain that are more or less strongly related to be identified. This was followed up with a principal component analysis to explore if there was a common underlying structure that unifies the broad areas of ability across these two domains.

2.3 Results

2.3.1 Overall measure of cognitive and motor ability

Across the entire sample (N = 248) there was a significant positive correlation (r=.515, p<.0001) between the overall cognitive score (FCI) and overall motor score (TMC). In addition, a discrepancy analysis based on scores for individual children was conducted. For each child the overall score on the cognitive (FCI) and motor (FMC) indices was classified according to proximity (in terms of standard deviations (SD); 15 for FCI and 10 for TMC) to the test norm mean, so the degree of discrepancy between the two indices could be assessed. This enabled the number of children with no discrepancy between domains (e.g. FCI -2SD and TMC -2SD from the mean), and the number of children with a discrepancy of ±1 (e.g. FCI -2SD and TMC -1SD from the mean) or ±2 or more (e.g. FCI -2SD and TMC +1SD from the mean) standard deviations between their cognitive and motor scores, to be determined. This analysis revealed that 97.2% of children showed a discrepancy no greater than ±1 standard deviation between the two measures (of which 64.9% of children demonstrated no discrepancy between their overall cognitive and motor scores and 32.3%

demonstrated a discrepancy of ±1 standard deviations) and only 2.8% of children showed a discrepancy that was ±2 or more standard deviations apart on their FCI and TMC scores.

When the sample was divided across the different age groups a significant positive correlation was found between FCI and TMC for each age group, except for the 7 and 8 year old children (see Table 2.2). Consistent with the other age groups, the 7 and 8 year old groups produced positive correlations between FCI and TMC, but the strength of association did not reach significance (N.B. The p value for the 8 year olds was .068, indicating a trend that just missed significance). The low correlation of the 7 year old children differed significantly from the high correlation found for 6 year olds (z=2.52, p=.012); no other differences between age groups were significant. Furthermore, collapsed across age groups, a significant positive correlation between overall cognitive and motor ability was found for both male (N=123) and female (N=125) participants (females r=.602, p<.001; males r=.410, p< .001) although the strength of association differed significantly across sex (z=2.03, p=.042) as the correlation was weaker for males than females. When effects of sex were investigated per age group, results (see Table 2.2) showed no significant differences in strength of association between FCI and TMC for each age group, except for the group of 4 year olds where females produced a stronger correlation than males (z=2.44, p=.014).

Table 2.2 Correlation coefficients for each age group (collapsed across sex), and for each sex by age, between overall cognitive (FCI) and motor scores (TMC)

Age group	Overall		Male		Female	
(years)	r	p	r	p	r	p
4	.605	<.001	.237	.396	.845	<.001
5	.407	.026	.227	.416	.534	.040
6	.689	<.001	.682	.004	.668	.005
7	.177	.342	.167	.552	.164	.544
8	.343	.068	.388	.153	.267	.337
9	.516	.003	.448	.094	.636	.008
10	.390	.023	.453	.068	.307	.231
11	.570	.001	.483	.068	.621	.013

2.3.1.1 Follow-up investigation

The finding that the strength of correlation dropped significantly between 6 and 7 years warranted further investigation. It is possible that the introduction of additional core subtests at age 7 to assess Fluid Reasoning in the KABC-II, which also contribute to the overall cognitive score (FCI), could have impacted on the correlation strength, although the standardisation procedures of the KABC-II should guard against this. Alternatively, the low correlation found at 7 years could have resulted from group specific factors, but the 7 year old children did not differ significantly in mean FCI and TMC score or socio-economic status (based on their school postal code index) relative to the other age groups tested. To test these hypotheses, we reassessed the 5-6 and 7 year old children on the same standardised measures after a minimum period of 10 months (range 10 – 28 months). This meant that the children originally tested at 5-6 years were aged 7 at follow-up and the children originally tested at 7 years were between 8-10 years at follow-up. Not all of the original sample consented to participate in the follow-up study (some participant attrition was inevitable due to children moving out of the area), so the final sample at follow-up consisted of 14 children (6 male, 8 female) aged 7 years (mean age = 91 months, range 86 - 95 months) and 27 children (12 male, 15 female) aged 8-10 years (mean age = 108 months, range 97-120 months).

Results revealed an increase in correlation strength for the children originally tested at age 7 that were aged 8-10 years at follow-up (1st assessment r=.025, p=.9; 2nd assessment r=.516, p<.01)[1], a difference that approached significance (z=1.89, p=.059). In contrast, the children originally tested at 5-6 years that were retested at age 7 showed a decrease in correlation strength (1st assessment r=.648, p<.05; 2nd assessment r=.537, p<.05), although this

[1] This correlation refers specifically to children included in the follow-up study and thus differs from the correlation of .177 reported in Table 2 for the first assessment based on the original sample.

difference was not significant (z=.4, p=.69). The implications of these data will be considered later in the Discussion.

2.3.2 Broad areas of cognitive and motor ability

Table 2.3 reports the correlations between the different indices of the standardised cognitive and motor tests. Significant positive correlations were found across each of the cognitive and motor indices, except for Manual Control (from the BOT-2) with Long Term Storage & Retrieval, Fluid Reasoning and Crystallised Ability (from the KABC-II) for which positive correlations were found that did not reach statistical significance. Similarly, non-significant positive correlations were found between Strength & Agility (from the BOT-2) and Fluid Reasoning (from the KABC-II). These index correlations were also calculated for each age group separately. The only significant positive correlations that were found consistently across all age groups were between Visual Processing and Fine Manual Control (before Bonferroni correction). Indeed, subtest comparisons including either Visual Processing or Fine Manual control accounted for 67% of all significant correlations found across all age groups.

Table 2.3 Correlation coefficients between each measure of broad ability, as assessed by the KABC-II and BOT-2, collapsed across the entire sample (N = 248). After Bonferroni correction p<.0025. For Fluid reasoning N = 156 because the younger children (aged 4-6 years) are not given these subtests

		BOT-2			
		Fine Manual Control	**Manual Coordination**	**Body Coordination**	**Strength & Agility**
KABC-II	**Short Term Memory**	.362	.194	.232	.268
	Visual Processing	.542	.336	.468	.315
	Long Term Storage & Retrieval	.265	.110 ns	.220	.219
	Fluid Reasoning	.399	.230 ns	.385	.233 ns
	Crystallised Ability	.398	.167 ns	.338	.239

To understand further how these broad areas of ability are associated, an exploratory principal component analysis was conducted in which the indices from each standardised measure were entered as items. The initial sample of 248 children was used in this analysis; no additional data from the retest period was included. As the test developers provide justification for the structure of each test using factor analysis, we considered it admissible to use the index scores generated for each participant in the principal component analysis. However, it was not possible to include the Fluid Reasoning index score from the KABC-II because the subtests used to generate this score are not given to children aged 4-6 years. We thus conducted the principal component analysis without entering Fluid Reasoning.

Initially the factorability of the eight items (indices) was examined using several criteria for the factorability of a correlation, all of which were met (all correlations below .6; Kaiser-Meyer-Olkin measure of sampling adequacy > .8; Bartlett's test of sphericity $p<.001$; communalities < .5). The K1 extraction method (Kaiser, 1960), confirmed by the scree plot, produced a two-factor solution. The initial eigenvalues showed that the first factor explained 44% of the variance and the second factor explained 16% of the variance. As there were reasonable grounds to suggest that the two factors may be related the two-factor solution was examined first using an oblique rotation. All the items had primary loadings .5 or above and two items had a cross-loading above .3. The factor loadings for both the pattern and structure matrices are presented in Table 4. This approach revealed that the two factors are correlated ($r=.370$, $p<.001$), thus justifying the use of direct oblimin rotation.

Table 2.4 shows that the two factors revealed by this analysis map directly onto cognitive (factor 1) and motor (factor 2) skills. This suggests that although these domains are linked across age and gender (as shown in Table 2.3), they appear to be reasonably independent. Some degree of overlap across the two factors is however apparent between Visual Processing and Fine Manual

Control (see Table 2.4). When controlling for scores on the Visual Processing and Fine Manual Control indices using a partial correlation, the association between overall cognitive (FCI) and motor (TMC) scores was no longer significant (r=.078, p=.22). This suggests that visual processing skills and fine manual abilities are largely responsible for the overall correlation observed between the two domains.

Table 2.4 Factor loadings for the pattern matrix and structure matrix for a two-factor solution

	Test / Broad Ability Index	Pattern Matrix		Structure Matrix	
		Factor 1 Cognitive	**Factor 2 Motor**	**Factor 1 Cognitive**	**Factor 2 Motor**
KABC-II	**Crystallised Ability**	.838		.838	
	Long Term Storage & Retrieval	.783		.745	
	Short Term Memory	.734		.741	
	Visual Processing	.565	.373	.703	.582
BOT-2	**Manual Coordination**		.817		.780
	Strength & Agility		.788		.757
	Body Coordination		.703		.749
	Fine Manual Control	.324	.575	.536	.692

The link between Visual Processing and Fine Manual Control was further investigated by calculating correlation coefficients for these scores when the sample was divided by age and gender, using results only from the original sample (see Table 2.5)[2]. Consistent with the correlation coefficient for the entire sample, significant positive correlations were found across age groups, with no significant differences found between groups. Interestingly the decrease in the strength of correlation for the 7 and 8 year old groups observed for the previous correlation between gross cognitive and motor measures was not seen between these indices. In contrast, the decrease in correlation coefficient for the 4 year old boys seen in the overall correlation between cognitive and motor ability was preserved in this analysis.

Table 2.5 Correlation coefficients for each age group (collapsed across sex), and for each sex by age, between Visual Processing (VP) and Fine Manual Control (FMC) scores

Age group	Overall		Male		Female	
(years)	r	p	r	p	r	p
4	.432	.017	.067	.811	.635	.011
5	.480	.007	.312	.257	.571	.026
6	.709	<.001	.714	.002	.671	.004
7	.481	.006	.486	.066	.561	.073
8	.581	.001	.508	.053	.666	.007
9	.573	.001	.395	.145	.730	.001
10	.546	.001	.631	.007	.447	.072
11	.602	<.001	.743	.001	.393	.148

[2] These correlation coefficients are based on the original sample results only, and do not include the results that were collected in the follow-up study.

As some previous work in this area has highlighted processing speed as a potential common factor (Roebers & Kauer, 2009), partial correlations were conducted to examine this using standardised subtest scores from five tasks from the BOT-2, namely making dots in circles, transferring pennies, pegboard, sorting cards and threading beads, as these are timed tasks and thus constitute a basic measure of processing speed. Results showed that the correlation between Visual Processing and Fine Manual Control was relatively unaffected by measures of processing speed and remained highly significant (controlling for: making dots in circles performance, r=.544, p<.001; transferring pennies performance, r=.548, p<.001; pegboard performance, r=.549, p<.001; card sorting performance, r=.546, p<.001; bead threading performance, r=.545, p<.001).

The individual subtests which constitute the Visual Processing and Fine Manual Control indices were also studied in closer detail. The Visual Processing index comprises two measures. 'Triangles' requires the child to use 3D shapes to construct a copy of a picture of an abstract design. There is a time disqualification if the child takes too long and for older children there is a time bonus where faster performance scores more highly. For 'Rover' the child uses a toy dog to traverse a grid avoiding obstacles to find the fastest route, and for this measure there is a time disqualification if the child takes too long. Children under 6 years do not complete this measure. Fine Manual Control includes 'Fine Motor Precision', which includes tasks such as colouring-in, drawing, folding and cutting-out, whilst 'Fine Motor Integration' involves copying geometric shapes. Both of these motor measures are untimed. Likewise, across all participants significant positive correlations were found between all of these subtests (min; r=.286, p<.001, max: r=.539, p<.001) with the strongest association found between 'Fine Motor Precision' and 'Triangles'. Across all ages positive correlations were found between 'Triangles' and both measures of Fine Manual Control (min; r=.279 p=.111, max; r=.695, p<.001), with 81% (13/16

correlations) reaching significance following Bonferroni correction. In contrast 'Fine Motor Precision' was only found to correlate with 'Rover' for the 11 year old participants (r=.659, p<.001) and 'Fine Motor Integration' was significantly related to 'Rover' in 9 year olds only following Bonferroni correction (r=.567, p=.001).

In addition, a discrepancy analysis was conducted based on individual participants (similar to that detailed above for FCI and TMC) for Visual Processing and Fine Manual Control scores. This demonstrated a similar distribution of discrepancies to the FCI and TMC analysis; 97.6% of children showed a discrepancy no greater than ±1 standard deviation between the two measures (of which 58.9% of children demonstrated no discrepancy between their overall cognitive and motor scores and 38.7% demonstrated a discrepancy of ±1 standard deviations) and only 2.4% of children showed a discrepancy that was ±2 or more standard deviations apart on their Visual Processing and Fine Manual Control scores.

2.4 Discussion

This study examined the strength and nature of the interrelation between cognitive and motor development across age and sex by measuring performance in each of these domains in a group of 4-11 year old children using two standardised tests. Across the entire sample, a significant positive correlation of moderate strength was found between the overall cognitive (FCI) and motor (TMC) indices generated by the standardised measures, indicating that these domains are developmentally linked.

To investigate further the nature of this relationship, scores from the broad areas of ability on each standardised test were correlated for the entire sample. The data showed that across all index correlations the strongest association was between Visual Processing and Fine Manual Control. Significant positive correlations were found between most of the cognitive and motor indices

however and were generally stronger than has been reported in previous studies (e.g. Wassenberg et al., 2005; Ahnert et al., 2003). The increased strength in correlations found here compared to previous studies most likely arises from the use of two comprehensive standardised tests in this study (for which there is a high degree of internal consistency across individual subtests), administered across all age groups rather than a range of measures drawn from different tests for different ages. In addition, the data showed that Manual Coordination (from the BOT-2) was the motor component with the weakest correlation with the cognitive indices (from the KABC-II) with Long Term Storage & Retrieval, Fluid Reasoning and Crystallised Ability failing to reach significance following Bonferroni correction. In contrast, Fine Manual Control and Body Coordination (comprising subtests measuring balance and bilateral coordination) were the motor components with the strongest correlations with all cognitive indices. These results are consistent with some previous research that has also shown fine motor skill (e.g. Dellatolas et al., 2003; Livesey et al., 2006) and balance (e.g. Knight & Rizzuto, 1993) to be associated with cognitive ability, although Livesey et al. (2006) found balance was not related to cognitive skill in 5-6 year olds. The discrepant findings with regard to balance across studies may arise from differences in the measures used to assess cognitive skill. Knight and Rizzuto (1993) used a standardised test (Iowa Test of Basic Skills) to measure reading and mathematics ability, whereas Livesey at al. (2006) specifically assessed cognitive control using the day-night Stroop test (Berlin & Bohlin, 2002) and the Rowe behaviour rating inventory (Rowe & Rowe, 1992), the latter of which relies on teacher report. For the cognitive indices, Visual Processing correlated most strongly of all the motor indices, which may be expected, as visual processing abilities are essential for both cognitive and motor skills.

The nature of this association was explored in more detail using an exploratory principal component analysis in which the indices from each standardised measure were entered as items. This process revealed two factors,

Cognitive and Motor, with two items cross loading onto both factors. These overlapping skills were Fine Manual Control and Visual Processing, one index from each of the standardised measures. These results, combined with the index correlations, not only suggest a close connection between Visual Processing and Fine Manual Control, but also that this relationship may underpin the association found between the overall cognitive and motor indices. This hypothesis was given further weight by the partial correlation between FCI and TMC controlling for Visual Processing and Fine Manual Control. As the correlation between FCI and TMC was no longer present when controlling for Visual Processing and Fine Manual Control, this suggests that the association between these two indices may be largely responsible for the overall correlation found across domains.

Further support for the pivotal role of Visual Processing and Fine Manual Control in the interrelation of these domains can be taken from the similarity between the discrepancy analyses for both the overall scores across domains (FCI and TMC) and the Visual Processing and Fine Manual Control indices. These analyses highlight that most (97.6%) children demonstrate a discrepancy no greater than ±1 standard deviation indicating these skills are tightly linked. A small number of children (2.4%) however demonstrated differences of ±2 standard deviations or more between their scores in each domain. The moderate strength of the correlation found in this study thus allows scope for individual variation, such as those who demonstrate a large discrepancy between domains, as some children may develop particular strengths and weaknesses, possibly as a result of environmental influences.

To investigate the relationship between Visual Processing and Fine Manual Control, the individual correlations between the subtests of Visual Processing and Fine Manual Control illustrated that 'Triangles' from the Visual Processing index is most closely associated with the Fine Manual Control subtests. As the 'Triangles' subtest has a time bonus, and is therefore more discriminatory of

manual skill by rewarding children with better precision of their movements, it is perhaps unsurprising that this subtest more closely relates to measures of fine motor skills than the 'Rover' subtest for which timing is less discriminative. It is possible that these factors may be linked by another process not investigated here, such as attentional capacity or motivation. Unlike some previous studies (Roebers & Kauer, 2009) general processing speed did not impact on the strength of this association in this study however this would need to be confirmed using more explicit, sensitive measures of processing speed, such as the Trail-Making Task (Reitan & Wolfson, 1992).

In general, the data showed consistent correlations across age for both overall cognitive (FCI) and motor (TMC) ability and Visual Processing and Fine Manual Control, suggesting close and stable links throughout childhood. This result accords with previous research that has examined the relationship between cognitive and motor development across childhood (Ahnert et al., 2003), but does not support the prediction by Ackerman (1988) that the strength of this relationship will decrease with age as motor skills require less attention with practice. In addition, the correlations between the separate indices of the tests demonstrate that Visual Processing and Fine Manual Control is the only correlation that is consistently conserved across all age groups, further indicating that these specific skills underpin the overall gross correlation between domains at all ages tested.

This finding is particularly striking given the anomaly in the general pattern of interrelation between FCI and TMC across age, where for 7 year old children the strength of correlation dropped to a level that was no longer significant. Follow-up of these children at least 10 months after the initial assessment showed an increase in correlation strength at the second assessment, when the children were aged 8-10 years, to a level that reached significance. This was accompanied by a decrease in correlation strength in children initially assessed at 5-6 years, who were aged 7 years at follow-up,

although the correlation at follow-up remained significant. Given the preservation of the correlation between Visual Processing and Fine Manual Control in the original sample of 7 year olds, it suggests that this core association is preserved whilst other skills dissociate, impacting on the overall gross correlation between these domains at this age.

Results from the follow-up study indicate that, although not as marked as initially implied, there may be a slight reduction in the strength of correlation between overall cognitive and motor ability for children aged 7 years, with a corresponding decrease in the number of significant index correlations. This finding agrees with some previous research, for example Roebers and Kauer (2009) reported no correlation between these two domains in their sample of 7 year old children. Similarly, Dyck et al., (2009) reported a decline and following increase in correlation between cognitive and motor ability in 6-8 year olds. The findings reported here concord with that of Dyck et al., (2009) as the correlation between overall cognitive and motor scores demonstrated a similar dip and subsequent increase from 7 years. This study extends previous work however, by highlighting that the seemingly core association between these domains, that is between Visual Processing and Fine Manual Control, remains stable, even at 7 years, despite a fluctuating profile of correlations across all indices with age.

There is some suggestion that in the UK children in Year 3 at school (ages 7-8) fail to make any significant academic progress (e.g. Doddington, Flutter & Rudduck, 1999). Whilst the reasons behind this gap are unclear, a de-coupling of these domains may occur if motor skills continue to advance whilst there are no ostensible improvements in cognitive functioning. It could be expected however that any dip in progress would be masked by the use of standardised measures, so this anomaly at 7 years may arise from sample-specific factors. To clarify this finding, a longitudinal study is needed to establish if the observed decrease in correlational strength at 7 years found here is sustained in a larger sample, and if so, whether there is a corresponding

alteration in the nature of the association between domains at this particular age.

The strength of correlation between FCI and TMC was affected by sex, with the relationship being stronger in female than male participants. Subsequent analysis by sex and age indicated that the 4 year olds were primarily driving the sex effect, as this was the only age group in which the correlation was significantly stronger for females than males. Importantly, Visual Processing and Fine Manual Control indicated the same pattern, with a non-significant correlation for the 4 year old males. This result may reflect differences in the developmental trajectory of motor skills between the two sexes in early childhood as girls are thought to develop fine motor skills ahead of boys, whilst boys are considered to develop gross motor skills before girls (e.g. Touwen, 1976; Livesey, Coleman & Piek, 2007).

With the exception of the 4 year old boys, these results showed a consistent relationship across Fine Manual Control and Visual Processing (and overall cognitive and motor development) across age, whereas some previous studies have indicated that early manual skill is more strongly associated with cognitive ability than later manual skill (Dellatolas et al., 2003). The results are also consistent with reports that children's attainment in school depends in part on their handwriting (Sassoon, 1990), which is an important application of fine motor control. However, the results do not support the finding of Piek et al. (2008) who reported that early gross motor trajectory was more predictive of cognitive skills than were fine motor skills. These differences in fine and gross motor development across the sexes may reflect the type of play activities girls and boys typically engage in during the preschool years, as boys have been shown to participate in more physical play than girls (Feingold, 1994), which promotes development of gross motor skills. Differences in play activities across males and females often attenuate with age perhaps because school provides a

more unified environment for both sexes. Interestingly, the data showed no significant effect of sex once children had entered the school system at 5 years.

2.4.1 Broader theoretical implications

The consistent strength of correlation between Visual Processing and Fine Manual Control across development suggests stability throughout childhood rather than discontinuous transitions in behaviour, the latter of which would predicted by the dynamic systems theory of development (e.g. Thelen, 1993). To some extent this data supports the embodied cognitive hypothesis, proposed in recent years, that purports intelligence emerges as a result of a child's interactions with an environment through sensory-motor activity (e.g. Smith, 2005), but see Mahon and Caramazza (2008) for critique of this hypothesis. These results strongly suggest that it is the child's dynamic interaction with the environment that is important for learning, and that this interaction is supported by a close coupling of the primary sense, i.e. visual processing and a physical connection with the environment i.e. fine motor control. However, more direct evidence is needed to support this theory that learning is contingent upon interaction with the environment.

These results provide further support to the mounting evidence that the underlying neural structures recruited for cognitive and motor tasks are connected, even in early childhood. This raises interesting questions for the identification of symptoms used in the clinical diagnosis of developmental disorders. Both cognitive and motor difficulties are often reported in a range of developmental disorders, including attention deficit hyperactivity disorder (ADHD) (e.g. Piek & Dyck, 2004), dyslexia (e.g. Viholainen, Ahonen, Cantell, Lyytinen & Lyytinen, 2002), autism and Asperger's syndrome (e.g. Rinehart et al., 2006; Green et al., 2002), developmental coordination disorder (e.g. Kaplan, Wilson, Dewey & Crawford, 1998; Alloway & Temple, 2007), and extremely low birth weight (e.g. Marlow, Roberts & Cooke, 1993). Whilst motor difficulties are

included in the DSM-IV-TR criteria for some of these conditions, such as ADHD (American Psychiatric Association, 2000), they are not diagnostic of others, such as dyslexia. If, as the data suggest, cognitive and motor skills are interrelated consistently across development, some degree of co-occurrence may be expected, even in children with developmental disorders. However, whether or not co-occurrence is considered to be integral to a particular condition requires further consideration, and perhaps needs support from neuroimaging. For example, boys with ADHD have been shown to have smaller premotor *and* prefrontal volumes (Mostofsky, Cooper, Kates, Denckla & Kaufmann 2002) in addition to basal ganglia dysfunction (Schrimsher, Billingsley, Jackson & Moore, 2002).

Another avenue for investigation to further elucidate the nature of this relationship may be to examine the development of fine manual skills in visually impaired or congenitally blind children. It is possible that this population may show a substitution of haptic and/or auditory processing in the place of visual skills in this association. Conversely, examining the visual processing skills of individuals with a physical disability affecting hand use may also help to establish whether or not a truly causal relationship exists between these two abilities.

2.4.2 Limitations

A possible limitation of this study concerns the cross-sectional design employed, as these findings may reflect sample effects rather than representing the nature of development across childhood. Other studies have also employed a cross-sectional design (e.g., Ahnert et al., 2003; Dyck et al., 2009; Knight & Rizzuto, 1993; Livesey et al., 2006; Planinsec, 2002; Reilly et al., 2008; Roebers & Kauer, 2009; Wassenberg et al., 2005) which may explain some of the differences in results between studies. However, it seems highly unlikely that results reported here arise from sampling effects as the striking consistency of the correlation between visual skills and fine motor abilities found in this study

suggests that this association remains stable across childhood. Indeed, the additional longitudinal component of this study which focused on 7 year olds, found the link between visual skills and fine motor abilities remained constant in the same group of children over time, despite alterations in correlations between other indices. Further studies are needed to investigate the associated brain structures involved with this functional link between visual processing and fine manual skills, and how these develop over childhood. This would address the hypothesis forwarded by Dyck et al. (2009) that variation in white and grey matter maturation rates leads to different abilities being related across developmental stages, and may help to elucidate the neural basis underlying the consistent interrelation between visual processing and fine motor skill found here.

2.4.3 Practical implications

The close developmental association between cognitive and motor development reported here has important implications for the clinical management and education of children with developmental disorders, as it raises the possibility that intervention in one domain may support development of the other. Rehabilitation programmes and intervention studies which focus solely on a single domain might benefit from incorporating elements designed to target the other domain concurrently, for example the multimodal approach to teaching individuals with dyslexia (e.g. Westwood, 1993; Reid, 2005). Similarly, rehabilitation programmes for patients following damage to a brain area traditionally regarded as subserving only one domain might consider targeting both domains in treatment. For example, Schweizer et al. (2008) demonstrated a positive impact of a cognitive rehabilitation programme on a patient with focal cerebellar damage. Similarly, aerobic fitness appears to be related to executive control in children (e.g. Hillman, Buck, Themanson, Pontifex & Castelli, 2009), and exercise following stroke in older populations can be an effective way of

limiting the loss of cognitive health (e.g. Quaney et al., 2009). Such programmes may be particularly effective during childhood when functional and anatomical plasticity is high.

When conducting clinical assessments and experimental studies with children in either the cognitive or motor domain, the impact of the other domain should be considered in terms of task demands that may affect performance. In particular, these results suggest that visual processing and fine motor skills should be carefully considered, and the effects of these processes should be controlled for, either experimentally or statistically, when interpreting test scores designed to tap specific functions that draw on these processes, such as selective attention and executive control. As many aspects of these two broad domains are closely linked across development, child-rearing and educational practices might benefit from providing an environment that is highly stimulating to all aspects of motor and cognitive skill, so as to exploit this association and maximise learning potential.

2.4.4 Conclusion

To conclude, the underlying association between the cognitive and motor domains appears to be underpinned by fundamental connection between visual processing and manipulation of the environment through fine manual control to enable skilled actions which in turn support learning. Future research is needed to investigate the potential causal direction or underlying reciprocity in the development of this relationship.

3 Development of cognitive and motor function following cerebellar tumour injury sustained in early childhood

3.1 Background literature

The role of the cerebellum in motor control has long been recognised (e.g., Holmes, 1939). More recently the cerebellum has also been implicated in higher-level cognition. Evidence for this stems from developmental disorders (e.g., autism, Allen & Courchesne, 2003; dyslexia, Nicolson et al., 2001; Attention Deficit Hyperactivity Disorder, Piek & Dyck, 2004; Developmental Coordination Disorder, Kaplan et al., 1998) and anatomical studies (e.g., Leiner et al., 1993; Allen et al., 2005). Additionally, patients with damage to the cerebellum have been demonstrated not only to have motor deficits (e.g., Duffner et al., 1986a; Konczak, Schoch, Dimitrova, Gizewski, & Timmann, 2005) but also concurrent cognitive impairments across a range of functions, including general IQ (Hoppe-Hirsch et al., 1995; Dennis et al., 1996; Beebe et al., 2005; von Hoff, 2008), attention, memory, processing speed, executive function, visuo-constructive and visual spatial skills, and language (Levisohn et al., 2000; Scott et al., 2001; Steinlin et al., 2003).

Anatomically, the cerebellum is known to project widely to the cerebral cortex, forming part of a cerebro-cerebellar and cerebello-cerebral network (Schmahmann, 1991; Middleton & Strick, 1998). The cerebellum receives input from a variety of brain structures known for their role in cognition, for example the superior temporal cortex (Schmahmann & Pandya, 1991), prefrontal cortex (Schmahmann & Pandya, 1997a), and parietal cortex (Schmahmann & Pandya, 2008). Being part of this anatomical network it is likely that the cerebellum will be involved with both motor and cognitive development, especially as it has a generic role in processing novel (Schmahmann & Sherman, 1998) and timing (Keele & Ivry, 1990) information. The cerebellum is thus likely to be involved with processing novel cognitive and motor tasks and in the acquisition of new

cognitive and motor skills (Ivry, 1993; Dennis et al., 1999; Diamond, 2000), leading to a developmental association between these domains.

Recently, studies have shown that cognitive and motor skills are interrelated in typically-developing children (e.g., Planinsec, 2002; Ahnert et al., 2003; Wassenberg et al., 2005; Murray et al., 2006; Davis, Limback, Pitchford & Walker, 2008; Roebers & Kauer, 2009) although the precise nature of this relationship is not yet known. Chapter 2 suggested that it is visual processing and fine manual control which underpin the association between the gross cognitive and motor scores. Charting the interrelation between cognitive and motor development in typically-developing children is important as once the typical trajectory is established deviations can be identified in atypical populations. Deviations from the normal pathway could arise from developmental delay (which would be shown by a similar extent of interrelation between cognitive and motor skills, but at depressed levels of performance) or developmental deviance (which would be expressed by normal or advanced levels of performance in one domain alongside depressed levels of performance in the other domain). Distinguishing developmental delay from deviance is important for the clinical and educational management of children and also provides insights into the extent to which these domains can dissociate during development.

The primary aim of this study was to build on the previous chapter by examining the interrelation of cognitive and motor skills in children who have suffered a cerebellar tumour in early childhood. Using the results from Chapter 2 as a control for this study, this chapter aimed to establish the possible mediating role of the cerebellum in this relationship by exploring the nature of this relationship in children who have suffered injury to the cerebellum through tumour during the preschool years. Using this approach, contrasting hypotheses can be drawn concerning the functional outcome of the cerebellar patient group. If these domains are closely linked early in development, damage to the

underlying anatomical system through tumour and/or consequences of treatment may result in delayed development. In this case, the extent of association between domains in the patient group would be expected to be similar to that shown by typically-developing children, even though the cerebellar patients may have depressed levels of performance. Conversely, if, as a consequence of early insult to the cerebellum, atypical pathways develop in one and/or the other domain, functioning across domains should dissociate, resulting in impairment in one domain (i.e., motor control) but not the other (i.e., cognitive control). In this case, the extent of interrelation between cognitive and motor development would be expected to be lower in patients with cerebellar injury than in typically-developing children.

3.1.1 Prognostic factors

The second aim of this research was to investigate prognostic factors that might influence performance within the cerebellar patient group, such as age at diagnosis, time post treatment, tumour type, treatment, and location within the cerebellum. Although previous studies have investigated these factors results are often contradictory and difficult to disentangle given that these factors are unlikely to operate in isolation (Dennis et al., 1996) and may also interact with changes that typically occur throughout development. The novel approach taken here enables for the first time the impact of these different prognostic factors on the interrelation between cognitive and motor development to be determined.

3.1.1.1 Age at diagnosis

Whilst some studies suggest neurodevelopmental outcome is poorer in children who sustain injury to the cerebellum through tumour in early childhood, especially if treated with radiation therapy (e.g., Packer et al., 1989; Balestrini, Mischeli, Giordano, Lasio, & Giombini, 1994; Allen & Epstein, 1982; Duffner, Cohen & Thomas, 1986; Dennis et al., 1996; George et al., 2003), others report

that younger children appear least impaired (e.g., Levisohn et al., 2000). Steinlin et al. (2003) noted that the most vulnerable age for insult is between 5 and 10 years but Konczak et al. (2005) found that age at surgery did not correlate with outcome measures of motor function. However, as younger children are less likely to suffer a medulloblastoma, tumour type or consequent treatment may be a confounding factor.

3.1.1.2 Tumour histology/treatment

Cognitive outcome is generally thought to be poorer following medulloblastoma, although this may arise from the high dosage of radiotherapy typically used to treat this type of tumour (Hoppe-Hirsch et al., 1995). However, even with reduced-dose radiation patients have been shown to demonstrate a cognitive decline (Cantelmi, Schweizer, & Cusimano, 2008). Furthermore, patients with astrocytomas, typically considered to be low risk, can show impaired cognitive ability, even in cases without radiotherapy (Beebe et al., 2005).

3.1.1.3 Time post treatment

Performance for children with medulloblastoma has been shown to deteriorate significantly between 5 and 10 years; an effect not seen in children treated for ependymoma (Hoppe-Hirsch et al., 1995). This could be attributed to differences in the use of radiotherapy for treating these different types of tumour, although von Hoff et al. (2008) noted no loss of cognitive ability over time following radiotherapy. Konczak et al. (2005) found no effect of recovery time on the variability in motor outcome, suggesting that once past the initial short-term recovery period of plasticity and reorganisation no further improvement should be expected.

3.1.1.4 Tumour location

Some studies have shown that damage to the right cerebellar hemisphere without concurrent damage to the vermis results in language deficits but spared visual-spatial functioning, whilst left hemisphere injury shows the opposite effect (Levisohn et al., 2000) and damage to the vermis impairs regulation of affect (see also Riva & Giorgi, 2000; Scott et al., 2001; Turkel et al., 2004). In contrast, Steinlin et al. (2003) found that patients with tumours in the left cerebellar hemisphere resulted in poorer outcome on all of the cognitive measures they used compared to patients with right-sided cerebellar tumours. However, their patients with left hemisphere involvement had greater vermis damage than patients with right hemisphere involvement, suggesting that damage to the vermis has a strong impact on subsequent cognitive skill. This is consistent with other findings (Choux, 1982; Dias et al., 2005) that suggest the vermis and paravermis are the most critical sites of injury for subsequent outcome.

Whilst these results may be conflicting, it is possible to pinpoint patients that may be at increased risk given their combination of prognostic factors. In a recent review, Konczak and Timmann (2007) proposed that the strongest predictors of functional outcome for both motor and cognitive abilities are involvement of the deep cerebellar nuclei in conjunction with radiotherapy or chemotherapy treatment. In addition to the prognostic factors discussed above, there is evidence that neurological deficits following a cerebellar tumour may affect cognitive outcome. Children identified with cerebellar syndrome (i.e., ataxia, dysmetria, nystagmus) were found to perform more poorly on IQ measures than those who were not (von Hoff et al., 2008), however Stargatt et al. (2007) suggested post-operative neurological status only contributes to cognitive deficits in the first months following surgery but is not responsible for long-term outcome. Hydrocephalus is also thought to negatively impact upon

cognitive functioning in children without brain tumours (e.g., Anderson, Northam, Hendy, & Wrennall, 2001) as well as in patients with cerebellar tumour (Jacobs, Northam, & Anderson, 2001; Merchant et al., 2004; Stargatt et al., 2007; von Hoff et al., 2008). However, it has yet to be established whether these factors differentially affect cognitive and motor development in children with cerebellar injury.

This chapter reports on a case series of 15 children, each of whom underwent resection of a tumour to the cerebellum during the preschool years (0-5 years). They were administered the same standardised tests of cognitive and motor ability as used in Chapter 2, to assess skills at varying ages post treatment. The results from the typically-developing children were used to compare the relationship between different cognitive and motor sub-skills found within the patient sample to that found in typically-developing children. Finally, the effects of potential moderating variables on outcome in the patient sample were investigated, namely age at diagnosis, time post treatment, sex, tumour type/treatment, tumour location, and hydrocephalus.

3.2 Method

3.2.1 Participant information

Ethical approval for all studies involving cerebellar patients (Chapters 3-7) was granted from the NHS North Nottinghamshire Research Ethics Committee (see Appendix 2) and the School of Psychology, University of Nottingham, which accords with the British Psychological Society ethical guidelines.

NHS records, held from 1998 onwards at Queen's Medical Centre in Nottingham, were consulted to identify patients suitable for participation in the study. From a total of 23 patients who satisfied the inclusion criteria outlined below, 15 children (ranging in age from 4 to 14 years) agreed to take part. The following inclusion criteria were specified: (i) diagnosis at or before 5 years of

age; (ii) chronological age at test of 4 years or above; (iii) MRI scans available for localising the site of tumour by the neuro-radiologist; (iv) not previously treated for any type of malignant disease; (v) no other significant medical condition or developmental disability prior to diagnosis; (vi) identified as suitable for participation in the study by the referring clinician; (vii) English-speaking; (viii) parental consent. Patient details (Age at Diagnosis, Time post Treatment, Sex, Tumour Type/Treatment, Tumour Location/Damage, Hydrocephalus and Neurological Deficits) are given in Table 3.1.

The details for the control children used in this study are described in Chapter 2.

3.2.2 Assessments

Each patient was given a standardised test of cognitive ability and a standardised test of motor development. Tests were chosen that provide standard scores that span the chronological age range of the patient sample (4 to 14 years).

3.2.2.1 Cognitive ability

The Kaufman Assessment Battery for Children – 2nd Edition (KABC-II: Kaufman & Kaufman, 2004) was used to assess cognitive and processing abilities. Details of this test are included in Chapter 2.

3.2.2.2 Motor ability

The Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition (BOT-2: Bruininks & Bruininks, 2005) was chosen to measure gross and fine motor abilities. Details of this test are included in Chapter 2.

3.2.3 Procedure

The KABC-II was administered before the BOT-2, and subtests within each of these standardised tests were administered in the order specified by the test manual. Each child was assessed individually within their homes, in a quiet area free from distraction using the standardised measures of cognitive and motor ability described below. Tests were completed over one session lasting approximately two hours with regular breaks.

Table 3.1 Case details of each of the 15 patients with cerebellar injury studied. MB = medulloblastoma, EPD = ependymoma, P AST = pilocytic astrocytoma, F AST = fibrillary astrocytoma, RH = right cerebellar hemisphere, LH = left cerebellar hemisphere, CT – chemotherapy, RT = radiotherapy, MR = macroscopic resection, NTR = near total resection, STR = subtotal resection, NTV = neuroendoscopic third ventriculostomy, VP Shunt = Ventriculoperitoneal shunt, EVD = external ventricular drain

Case	Age at diagnosis (months)	Time post treatment (months)	Sex	Tumour		Treatment			Hydrocephalus		PF Syndrome/ neurological deficits	Mutism
				Type	Location[3]	Treatment	Extent resected	Structures damaged	Pre-op /post-op	Treatment		
P01	53	77	M	MB	Midline inferior vermis/4th ventricle	CT, PF radiation/ CSI	MR	Surgical approach: vermis divided using fixed retraction	Pre-op: mild	NTV	Pre-op: ataxic gait, nystagmus Post-op: ataxic gait, nystagmus	32 days of mutism
P02	42	68	M	P AST	Vermis/ RH	None	STR	Vermis split	Pre-op: moderate Post-op: pseudomen-ingocele	Cystoperitoneal shunt	None recorded	
P03	18	126	M	MB	Vermis/ medial RH	CT, PF radiation	MR	Right lateral approach to R cerebellar hemisphere; damage to right paravermian area	Pre-op: severe		Pre-op: ataxic gat, truncal ataxia, right hemiparesis Post-op:: nystagmus, ataxia	

[3] According to clinical protocol, post-op scans were either done early, i.e. within 72 h of surgery, or late, i.e. more than six weeks later to minimise risk of post-op enhancement confounding tumour observations

P04	53	119	M	P AST	Inferior vermis extending into foramen magnum, obstruction 4th ventricle foraminae	None	MR	Surgical approach: inferior vermis	Pre-op: moderate Post-op: pseudomen-ingocele	Bilateral VP shunt	Pre-op: mild ataxia Post-op: mild ataxia	
P05	59	34	F	P AST	Paravermis	None	STR	Midline approach, vermis split; possible damage to right superior aspect. Possible dentate damage	Post-op: moderate	NTV (frontal approach)	Post-op: mild left sided ataxia	
P06	57	33	M	MB	(Scan unavailable)[4]	PF radiation/ CSI	STR		Post-op: moderate	EVD; left parietal VP shunt	Post-op: nystagmus, left sided ataxia	34 days of mutism
P07	31	24	F	P AST	Vermis	CT	STR	Midline approach; possible vermian damage	Post-op; severe	VP shunt	None recorded	
P08	60	114	M	P AST	RH (displacing LH to left)	None	MR	Peripheral approach, RH	Pre-op; moderate		Post-op; ataxic gait	
P09	52	5	F	P AST	Vermis/LH	None	MR	Midline approach	Pre-op; moderate	VP shunt	Post-op; left sided Dysmetria, mild ataxia	
P10	29	85	M	EPD	Inferior vermis/ RH	CT	NTR	Right paramedian approach to right cerebello-pontine angle; possible vascular damage to right side of medulla				

[4] Although appropriate scans were completed for P06, they were unavailable for analysis

P11	21	110	M	MB	Vermis	CT, PF radiation	MR	Midline approach to vermis	Pre-op: severe Post-op: severe	NTV (frontal approach)	Post-op: limb ataxia, nystagmus, hypotonia, slight left-sided hemiparesis
P12	60	69	M	P AST	Vermis/ medial inferior RH/right tonsil	None	NTR	Cyst near surface of cerebellar; possible paravermian damage on right	Pre-op: severe		Pre-op: truncal ataxia, heel-toe walk difficulty, right finger-nose difficulty Post-op: heel-toe walk difficulty, right sided dysmetria
P13	42	27	F	EPD	4^{th} ventricle	CT	MR	Inferior vermian split, into both Foramina of Luschka	Pre-op: severe	NTV	None recorded
P14	60	93	M	F AST	LH	None	STR	Residuum near cerebellar peduncles	Pre-op: moderate Post-op: pseudomen-ingocele	Lumber peritoneal shunt	None recorded
P15	49	73	F	MB	LH	PF radiation/ CSI	STR	Midline approach	Pre-op: moderate		None recorded

3.2.4 Statistical analyses

For each participant, standard scores were generated for the five cognitive indices and the main FCI of the KABC-II and the four motor indices and the main TMC of the BOT-2. These were used in the following three sets of analyses, to examine 1) the impact of cerebellar injury sustained through tumour during the preschool years on cognitive and motor development, 2) the nature of the relationship between cognitive and motor development in the sample of typically-developing children and cerebellar patients, and 3) the influence of potential moderator variables (i.e., Age at Diagnosis, Time post Treatment, Sex, Tumour Type/Treatment, Tumour Location/Damage, and Hydrocephalus) on cognitive and motor development in children with early acquired cerebellar tumours. All analyses were conducted using parametric statistics, where $p \leq .05$ (unless specified) at a two-tailed level of probability.

1) To examine the impact of sustaining a tumour to the cerebellum during the preschool years on the development of cognitive and motor function standard scores were inspected for each patient. In addition, group means were calculated for each of the indices of the KABC-II and BOT-2. Standard scores (for individual patients and group means) that were ≤ 2 standard deviations (sd) from the test norms were taken as clinical impairments in functioning.

2) To investigate the interrelation between cognitive and motor development a series of correlations with Bonferroni correction was conducted on the data from the typically-developing children and patient group. Pearson correlations were conducted across each of the five indices from the KABC-II and the four indices from the BOT-2, as well as the overall index of cognitive (FCI) and motor (TMC) functioning. As group sizes differed across the patient and control samples Fisher's z was applied to test for significant differences in the strength of correlation for each of the comparisons made.

3) To explore the influence of the potential moderator variables on cognitive and motor test performance within the patient group several analyses

were conducted. Age at diagnosis and Time post treatment were correlated with tests scores and Bonferroni correction applied. As tumour type and treatment are closely linked, the effect of these prognostic factors was investigated by generating five sub-groups. Group 1 (N=7) were children with astrocytoma and surgery alone, group 2 (N=1) were those with astrocytoma and chemotherapy, group 3 (N=2) were children with ependymoma and chemotherapy, group 4 (N=2) were those with medulloblastoma, chemotherapy and posterior fossa radiotherapy, and group 5 (N=3) were children with medulloblastoma, chemotherapy and craniospinal radiation (CSI). The impact of these different tumour types and treatments on outcome was investigated using a series of chi square tests for each of the cognitive and motor indices to explore differences in performance between the five sub-groups. To explore the possibility that damage to the vermis would result in poorer outcome, as shown by some previous studies (e.g., Choux, 1982; Dias et al., 2005), a series of one-group chi square tests was conducted for the different cognitive and motor indices, in which the sum frequency of the sub-group of children with (N=10) and without (N=4) vermis involvement was compared to the expected frequency based on chance. The differential impact of damage to the Left and Right hemisphere of the cerebellum, reported in some previous studies (e.g., Steinlin et al., 2003; Riva & Giorgi, 2000; Scott et al., 2001), was investigated using chi square tests for each of the cognitive and motor indices to explore differences in performance between the subgroup of children with Left (N=3) or Right (N=5) hemisphere involvement (note there was also vermis involvement for 1 child with Left and 4 children with Right hemisphere damage). The impact of hydrocephalus was also investigated using a series of one-group chi square tests for each of the cognitive and motor indices. The sample was divided into four groups: no hydrocephalus (N=1), mild (N=1), moderate (N=7), and severe (N=5) hydrocephalus, based on the presence and severity pre- and/or post-operatively,

as judged by senior surgeons and neuroradiologists involved in the patient's clinical assessment.

3.3 Results

3.3.1 Patient results

This section explores the impact of treatment for a cerebellar tumour on cognitive and motor development within the patient group. As can be seen from Table 3.1 there was a high level of heterogeneity amongst the patient group. Ten of the 15 patients were male and age at diagnosis ranged from 18 to 60 months. Five had been treated for medulloblastoma, of whom three had craniospinal irradiation (CSI) with chemotherapy and two had involved field radiotherapy (RT) with chemotherapy. Two had been treated for ependymoma, both of whom received chemotherapy. The remaining eight were treated for astrocytoma, one of whom received chemotherapy. Six patients were reported to have a macroscopic resection, two a near-total resection (95-100%), and six a subtotal resection (<95%). All but one patient were reported to have hydrocephalus, of which one was mild, six were moderate and five were severe. Nine patients were recorded to have pre- and/or post-operative ataxia.

3.3.1.1 Cognitive scores

Table 3.2 reports the standard scores for the five cognitive indices and general cognitive index (FCI) of the KABC-II achieved by each of the children who sustained injury to the cerebellum through tumour during the preschool years. Sample means and standard deviations are also given. Inspection of Table 2 shows much variation in test performance across patients and indices: 7/15 (47%) children were significantly impaired on at least one of the five cognitive indices and 5/15 (33%) showed a significant impairment on the general cognitive index (FCI). Across the five indices significant impairments in functioning were found for 6/12 (50%) children for Fluid Reasoning, 5/15 (33%)

children for Visual Processing, 1/15 (7%) children for Long Term Storage & Retrieval and also Crystallised Ability, and 1/15 (7%) children for Short Term Memory. Although all sample means were above the clinical criteria for significant impairment (i.e., -2sd of the test norms), all were less than the test norm of 100 (min. = 77.0, max. = 88.2). All standard deviations were close to the test norm of 15 (min. = 10, max. = 18.8).

Table 3.2 Standard scores for cognitive development as measured by the KABC-II (test norm μ= 100, σ = 15). Standard scores for Fluid Reasoning could not be calculated for MS, EH, and TE because of their young age at test

Child	Short Term Memory	Visual Processing	Long Term Storage & Retrieval	Fluid Reasoning	Crystallised Ability	Fluid Crystallised Index
P01	97	71	75	96	72	76
P02	97	87	92	93	100	91
P03	83	71	75	62*	75	65*
P04	77	80	78	85	90	78
P05	106	84	92	96	111	96
P06	100	64*	89	62*	69*	70*
P07	97	61*	86	-	90	79
P08	74	89	84	64*	80	73
P09	88	88	89	-	93	87
P10	68*	50*	92	57*	92	65*
P11	91	64*	75	67*	80	68*
P12	83	91	89	105	102	92
P13	91	80	75	-	74	75
P14	97	111	97	108	102	104
P15	74	64*	58*	67*	77	60*
μ	*88.20*	*77.00*	*83.07*	*80.17*	*87.13*	*78.60*
σ	*11.25*	*15.46*	*10.22*	*18.80*	*12.91*	*12.83*

* - 2sd, $p \leq .05$, at least

3.3.1.2 Motor scores

Standard scores achieved by each of the cerebellar patients, sample mean scores and standard deviations across the four motor indices, and general measure of motor skill (TMC) on the BOT-2 are given in Table 3.3. As can be seen, there was considerable variation in performance across patients and indices: 7/15 (47%) children had a significant impairment in at least one of the four broad areas (indices) of motor skill and 6/15 (40%) children were significantly impaired on the general measure of motor ability (TMC). Across the four motor indices significant impairments were found in 6/16 (40%) children for Manual Coordination, 4/15 (27%) children for Body Coordination, and 3/15 (20%) children for Fine Manual Control and also Strength & Agility. All of the sample means were above -2sd of the test norm of 50, but all very depressed and were close to the criteria for clinical impairment (min. = 31.33, max. = 38.27). All sample standard deviations were similar to the test norm of 10 (min. = 6.14, max. = 9.11).

Table 3.3 Standard scores for motor development as measured by the BOT-2 (test norm μ= 50, σ = 10)

Child	Fine Manual Control	Manual Coordination	Body Coordination	Strength & Agility	Total Motor Composite
P01	32	29*	26*	27*	26*
P02	40	39	34	45	37
P03	30*	28*	26*	39	29*
P04	46	35	30*	38	35
P05	39	32	34	44	33
P06	34	26*	32	31	27*
P07	35	34	40	44	34
P08	45	38	49	45	41
P09	52	39	41	48	42
P10	23*	20*	20*	20*	20*
P11	34	33	31	38	32
P12	39	36	45	53	39
P13	38	20*	32	37	28*
P14	40	38	36	40	36
P15	30*	23*	35	25*	28*
μ	*37.13*	*31.33*	*34.07*	*38.27*	*32.47*
σ	*7.26*	*6.67*	*7.53*	*9.11*	*6.14*

* - 2sd, $p \leq .05$, at least

3.3.2 Interrelation of cognitive and motor skills

Table 3.4 reports the correlations between the different indices of the standardised cognitive and motor tasks for the samples of cerebellar patients and control children. As can be seen, significant correlations were found for the sample of typically-developing children (N=242) across each of the cognitive and motor indices, except for Manual Coordination from the BOT-2, which did not correlate significantly with either Long Term Storage & Retrieval or Crystallised Ability from the KABC-II. In contrast, significant correlations were found with the case sample (N=15) only for Visual Processing from the KABC-II and each index from the BOT-2, except Body Coordination. However, it is apparent from Table 3.4 that the magnitude of correlations found for the patient sample was stronger than those of the control sample for 14/20 (70%) comparisons, even though only 3 of the patient sample correlations were significant. To test if the difference in significance pattern across the cognitive and motor test correlations was due to differences in N between the patient (N=15) and control (N=242) samples Fisher's z was applied to each pair of correlations (i.e., patient r compared to control r per correlation). Results revealed no significant difference for each pair of correlations, illustrating that the pattern of strength of correlation did not differ significantly across the patient and control samples for each of the cognitive and motor indices.

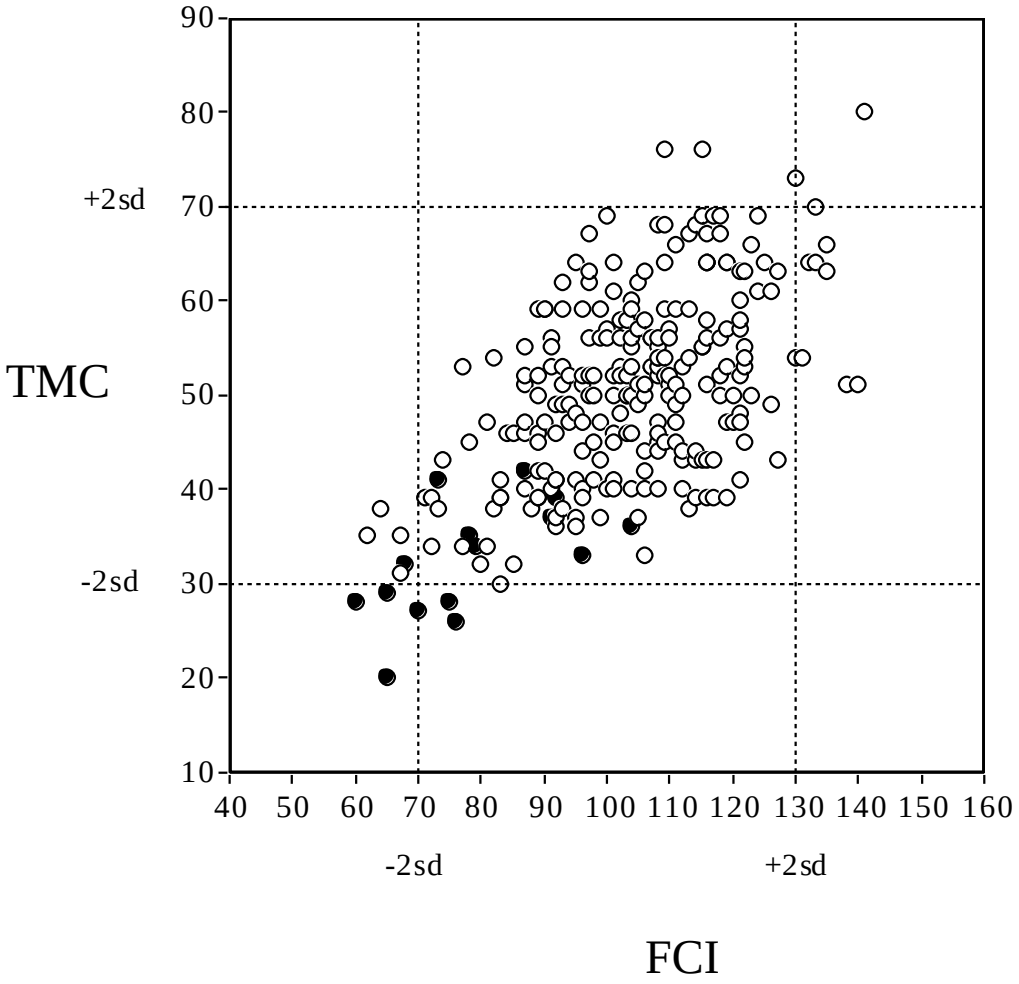
Table 3.4 Correlations (*r*) and difference in magnitude of correlations (Fisher's z) across cognitive and motor indices for the sample of typically-developing control children (N=242) and cerebellar patients (N=15)

Index			Motor Ability (BOT-2)			
			Fine Manual Control	**Manual Coordination**	**Body Coordination**	**Strength & Agility**
Cognitive Ability (KABC-II)	**Short Term Memory**	Patient r	.154	.242	.039	.293
		Control r	.360*	.206*	.224*	.273*
		z	.74	-.13	.64	-.07
	Visual Processing	Patient r	.710*	.670*	.547	.654*
		Control r	.541*	.342*	.458*	.316*
		z	-.95	-1.54	-.4	-1.54
	Long Term Storage & Retrieval	Patient r	.278	.456	.180	.405
		Control r	.272*	.109	.213*	.226*
		z	-.02	-1.29	-0.12	-.07
	Fluid Reasoning	Patient[1] r	.487	.613	.287	.515
		Control r	.403*	.225*	.367*	.226*
		z	-.35	-1.64	.3	-1.15
	Crystallised Ability	Patient r	.334	.528	.262	.516
		Control r	.398*	.161	.316*	.237*
		z	.25	-1.44	.2	-1.11

* $p \leq .01$ at least (Bonferroni corrected .05/5), [1]N=12 because standard scores for Fluid Reasoning could not be calculated for 3 of the cerebellar patients because of their age at test.

Likewise, similar correlations were found across the general index of cognitive (FCI) and motor (TMC) ability for the patient (r=.597, p=.017) and control (r=.508, p=.001) samples, the strength of which did not differ significantly (z=.045). This suggests that the standard scores for cognitive (FCI) and motor (TMC) ability produced by the cerebellar patients and control children fall within the same distribution, as is clearly illustrated in Figure 3.1.

Figure 3.1 Relationship between cognitive (FCI) and motor (TMC) functioning in the sample of typically-developing control children (N=242) and patients (N=15) with cerebellar tumour sustained during the preschool years. Open circles=control children; filled circles=cerebellar patients



3.3.3 Prognostic factors

The influence of potential moderator variables was also investigated. Results are reported in Table 3.5. As can be seen, a range of positive correlations were found between Age at Diagnosis and test performance across the different cognitive and motor indices that varied in strength, from weak (min. *r*=.15) to medium (max. *r*=.6), although none was found to be significant after Bonferroni correction[5]. Time post Treatment produced mostly weak negative correlations across the different test indices (min. *r*=.024, max. *r*=-.501), none of which was found to be significant. Likewise, no significant effect of Sex was found for any of the cognitive and motor indices (min. t=-.105, max. t=-.840).

The effect of Tumour Type was explored in conjunction with Treatment. A significant effect of Tumour Type/Treatment was found for both the overall measures of cognitive and motor ability. In addition, significant effects were found for Visual Processing, Fluid Reasoning and Crystallised Ability of the cognitive indices and for all the motor indices measured. Further analysis revealed that for the cognitive and motor indices (except Strength & Agility) children with astrocytoma and surgery only performed most highly (Figure 3.2).

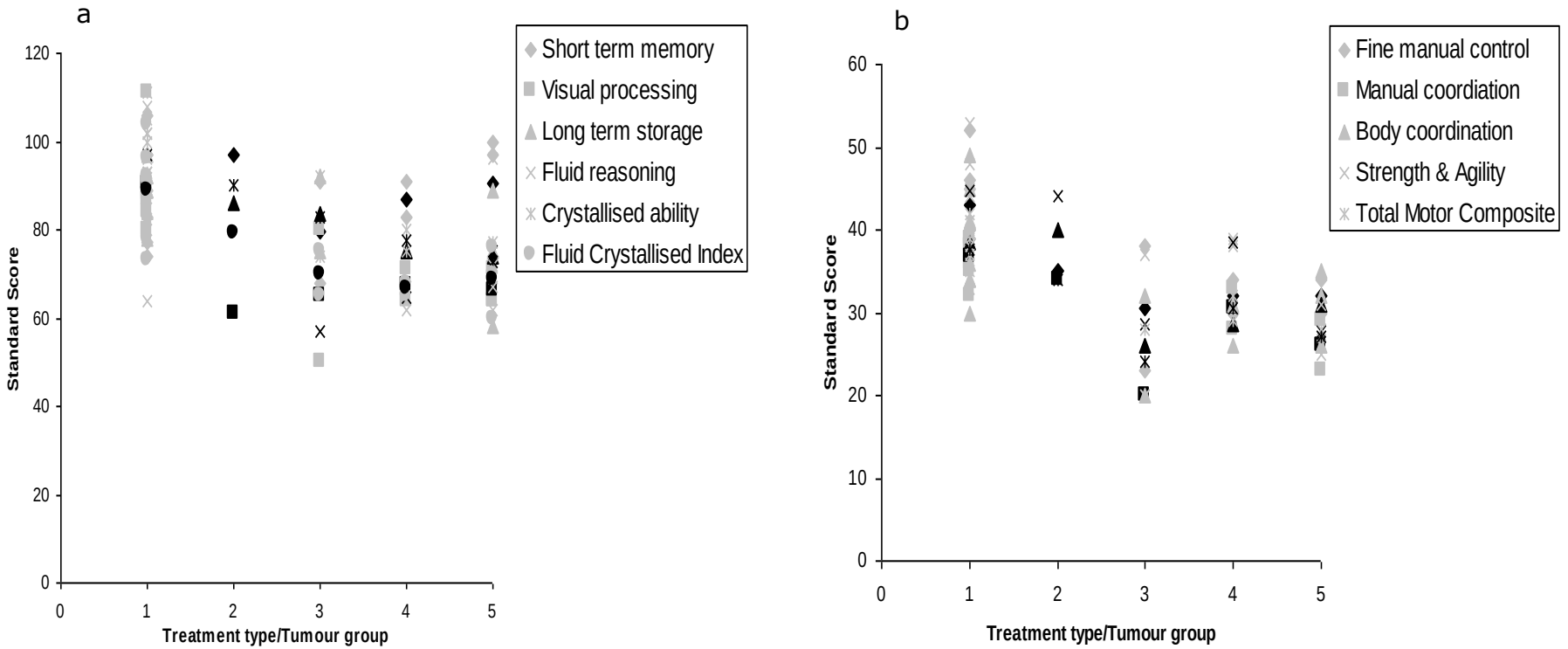
[5] The correlations between age at diagnosis and VP (r=.6) and FCI (r=.515) from the KABC-II were significant at $p \leq .05$, two-tailed.

Table 3.5 Correlations (*r*) and difference in mean performance (t, χ2) across cognitive and motor indices in relation to the different potential moderator variables

	Index	Potential Moderator Variable					
		Age at Diagnosis (r)	Time post Treatment (r)	Sex (t)	Tumour Type/ Treatment (χ2)	Tumour Location (χ2)	Hydrocephalus (χ2)
Cognitive Ability (KABC-II)	Short Term Memory	.150	-.501	-.717	2.816	.678	5.945
	Visual Processing	.600	.024	.274	29.206**	4.597*	15.088*
	Long Term Storage & Retrieval	.254	-.254	.811	7.330	1.223	2.931
	Fluid Reasoning	.552	-.252	-.105	24.004**	1.765	63.284**
	Crystallised Ability	.255	-.149	-.386	17.420**	1.745	4.195
	Fluid Crystallised Index	.515	-.276	-.165	18.486**	.110	5.017
Motor Ability (BOT-2)	Fine Manual Control	.492	-.208	-.615	12.532*	.150	8.129*
	Manual Coordination	.307	.088	.698	17.666**	.706	5.612
	Body Coordination	.497	-.233	-.840	11.408*	2.300	9.811*
	Strength & Agility	.211	-.172	-.388	22.257**	.578	14.439**
	Total Motor Composite	.383	-.063	-.230	13.103*	.043	7.339

* p ≤ .05 (chi square analyses); **p ≤ .01 at least (Bonferroni corrected .05/5, for correlation and t-test analyses)

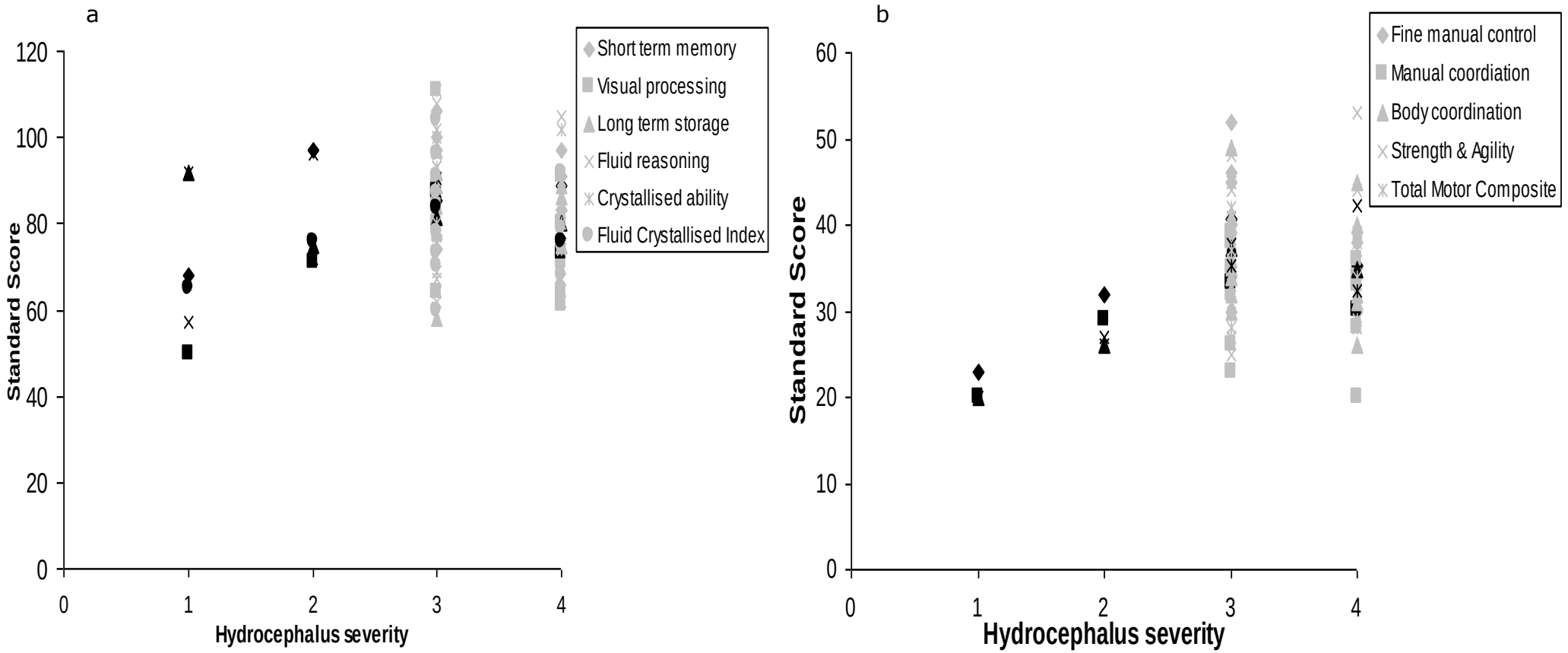
Figure 3.2 Effect of tumour type/treatment group on standard scores achieved on the (a) cognitive and (b) motor indices (1=astrocytoma, surgery; 2=astrocytoma, chemotherapy; 3=ependymoma, chemotherapy; 4=medulloblastoma, chemotherapy, PF radiotherapy; 5=medulloblastoma, chemotherapy, PF radiation/CSI), bold points represent group means



A significant effect of vermis involvement was found for one sub-skill only: children with vermis involvement performed significantly lower (mean 74.7) on the Visual Processing cognitive index compared to those without damage to the vermis (mean 86.0). In addition, results showed no significant effect of hemispheric damage across all indices (max. χ^2=2.255, p=.133), except for the overall measure of motor ability (TMC) for which children with Right hemisphere damage (mean 23.20) performed less well than those with damage to the Left hemisphere (mean 35.33).

A significant effect of hydrocephalus (see Table 3.5) was found for the cognitive indices Visual Processing and Fluid Reasoning and the motor indices Fine Manual Control, Body Coordination and Strength & Agility. In keeping with previous literature, for Fluid Reasoning results showed that children with the most severe hydrocephalus performed significantly lower than expected. However, contrary to previous reports, the data showed that the child who did not suffer hydrocephalus performed most poorly on Visual Processing, Fine Manual Control, Body Coordination and Strength & Agility (Figure 3.3).

Figure 3.3 Effect of hydrocephalus on mean standard scores achieved on the (a) cognitive and (b) motor indices (1=None; 2=Mild; 3=Moderate; 4=Severe), bold points represent group means



3.4 Discussion

This study examined the interrelation between cognitive and motor development and the role of the cerebellum in this relationship by measuring performance across these domains in 15 children, each of whom sustained injury to the cerebellum through tumour during the preschool years, and comparing their performance to that of a large group of typically-developing controls. Within the patient group, depressed group mean levels of performance were found for each domain on the overall measures of ability. Although at the group level the mean standard scores of the overall cognitive (FCI) and motor (TMC) index did not indicate significant clinical impairment (≤ -2 SD), the cognitive index (FCI) mean was 1.4 SD below the test norm mean, and the motor index (TMC) mean was 1.7 SD below the test norm mean. A similar pattern of results was found at the group level across the broad cognitive and motor indices. These results suggest that both cognitive and motor development can be seriously compromised following treatment for a cerebellar tumour acquired early in life, before five years of age.

3.4.1 Impact of cerebellar tumour on functioning

At an individual level, considerable variation in cognitive and motor scores was found. For each domain 7/15 patients were significantly impaired on at least one of the broad abilities measured, but only four showed a consistent deficit across both domains. Furthermore, a high degree of variation was found both within and across domains for individual children, and across individual patients. For example, P10 demonstrated a large range of scores across the five cognitive indices (50-92), two of which were significantly impaired (Visual Processing and Fluid Reasoning) whilst the others were close to the test norm. In contrast, P10 showed much less variation in scores across the four motor indices (20-23), all of which were significantly impaired. In addition, there were patients within this sample who did not show significant deviations from test

norms across each of the domains. For example, P14 produced a range of scores on the cognitive test (97-111) that was close to the control mean of 100, with some scores above the norm mean, and his range of scores generated on the motor test (36-40), whilst all lower than the norm mean of 50, were also not significantly impaired. These results illustrate how reporting group mean performance can mask significant differences in individual profiles for children with cerebellar tumours, and demonstrate the power of a case series approach.

3.4.2 Interrelation of domains

To investigate further the interrelation between cognitive and motor development following treatment for a cerebellar tumour acquired in early childhood, a large sample of typically-developing control children were given the standardised assessments used with the patient sample and performance across domains was correlated. A similar profile of results was found for the patient sample in comparison to the control participants, with the strongest correlations shown between the Visual Processing index and the different motor indices. Even though the overall pattern of correlations between the cognitive and motor indices was similar across the patient and control samples, most of the correlations for the patient group failed to reach significance, because of the relatively small number of cases studied. Case to control comparisons, using Fisher's z scores, did not highlight any significant differences in magnitude of the correlations across groups for the different measures of broad ability and the overall cognitive and motor index. This shows that the interrelation between cognitive and motor development found for the patient group is highly similar to that of typically-developing children, even though the patient scores tended to fall at the lower end of the distribution, as is clearly shown in Figure 3.1. This is particularly striking given the heterogeneity of prognostic factors within the patient sample.

These results demonstrate that a strong, positive association exists between cognitive and motor skill from early to middle childhood. The magnitude of correlations found between indices across domains means there is scope for individual variation, both within and across individuals, as observed in the patient sample, but overall cognitive and motor skills seem to develop in parallel. Furthermore, the results from the patient participants suggest that the strength of this relationship appears impervious to early neurological insult from tumour in the cerebellum during the preschool years. Seemingly, development of cognitive and motor function is tightly bound and these domains do not appear to dissociate despite early insult to a major component of the anatomical network subserving cognitive and motor control. Rather, a clear pattern of developmental delay characterised the impact of early cerebellar injury on subsequent development across these domains and implies that the cerebellum is involved with the development of both domains, perhaps due to its generic role in processing novel and timing information, important for both motor and cognitive skills.

These findings have clear clinical and educational implications, as the data suggest that treatment for a cerebellar tumour in the preschool years may not be well compensated and is likely to affect subsequent development of both cognitive and motor skills. Early intervention in both domains seems necessary so as to minimise downstream effects on development. As Cantelmi et al. (2008) highlight, a specific cognitive rehabilitation programme has been shown to be effective in remediating executive functions in a single non-irradiated cerebellar patient (Schweizer et al., 2008). The results reported here suggest that cognitive rehabilitation targeting broad areas of ability should be applied to most children following resection of a cerebellar tumour. In addition, it is possible that given the linear relationship found between the two domains across development, remediating effects of therapy in one domain might improve

functioning in the other. Intervention studies are clearly needed to explore this possibility.

3.4.3 Impact of prognostic factors

As the group of cerebellar patients varied in several factors thought to be associated with outcome, the impact of these prognostic factors was explored. Few of the predictor variables that are thought to influence neurodevelopmental outcome following cerebellar tumour in childhood reached significance in this sample. Positive correlations between age at diagnosis and the cognitive and motor sub-skills tested indicated a consistent relationship across measures. Although none was significant once corrected for multiple comparisons (note for Visual Processing and FCI, $p \leq .05$), this trend further supports the finding that development of cognitive and motor skills are linked from a very early age. Even within the first 5 years of life, early onset of symptoms tends to result in a poorer outcome for both domains. This finding confirms most previous studies (e.g., Packer et al., 1989; Balestrini et al., 1994) but contradicts others (e.g., Konczak et al., 2005). It is possible that by limiting the age at diagnosis in this study to the preschool years, the predictive value of this prognostic factor has been attenuated. It is also difficult to ascertain if there are 'windows of vulnerability' (Scott et al., 2001) for children following cerebellar tumour, although the general trend found here would suggest that this is not the case.

The correlations between time post treatment and the different skills measured indicated a weak negative tendency, although there was considerable variation and none reached significance. This negative trend suggests that there is little evidence of 'catch-up' within the patient group but rather that delay may even increase with time. Again these results support some previous work (Hoppe-Hirsch et al., 1995) but contradict others. For example Konczak et al., (2005) reported no effect of time post treatment on motor skills, although they reported generally stronger correlations for the cognitive subtests (mean

r=.243) compared to the motor tests (mean *r*=.152) administered, which is similar to the results reported here. No difference in outcome between girls and boys was found in the current study, which is consistent with other studies, although the imbalance in this sample makes it difficult to draw firm conclusions.

In contrast, a significant effect of tumour type /treatment was found to operate across both cognitive and motor skills. Children were grouped into five tumour/treatment groups and performance on the cognitive and motor tasks was investigated. Results showed that the effect of the different tumour/treatment groups on performance was significant for all cognitive indices except the measures of memory (Short Term Memory and Long term Storage & Retrieval) and for all motor indices. In general, there was a tendency for children with medulloblastoma treated with CSI and chemotherapy (group 5) to perform less well than those with astrocytoma and no chemotherapy (group 1), but the two children with ependymoma and chemotherapy (group 3) also fared poorly. These results are largely consistent with previous studies examining the effect of tumour and treatment type on developmental outcome (e.g., Hoppe-Hirsch et al., 1995; Cantelmi et al., 2008) and indicate that tumour type/treatment is a significant predictor of the extent for developmental delay to be expected post-operatively.

Location of tumour within the cerebellum had very little effect on outcome in this sample. Children with damage to the vermis performed significantly more poorly than those without vermis involvement on only one of the cognitive indices (Visual Processing). Likewise, children with Right cerebellar hemisphere damage performed significantly less well than those with Left cerebellar hemisphere damage on only the overall index of motor ability (TMC). The lack of a more pervasive effect of tumour location found here contrasts with some previous studies, but may be expected to some extent given the relatively small sample size and overlapping locations involved for most patients (see Table 3.1). The surgical damage reported in Table 3.1 indicates a high level of variation

across individuals, which may also contribute to the lack of findings in this study. So the results on tumour location should be treated cautiously.

The necessity for an external ventricular drain, a ventriculoperitoneal shunt, or a neuroendoscopic third ventriculostomy to relieve hydrocephalus is an extra surgical procedure undergone by many of these patients. Furthermore, the severity of and treatment for hydrocephalus with this patient sample cannot account for the variation in performance patterns found *within* individual patients.

A significant effect of hydrocephalus was found however contrary to predictions, as the patient without hydrocephalus (P10) was the most severely impaired on many of the cognitive and motor indices, suggesting that other prognostic factors may be more salient and hence masking any potential effect of hydrocephalus in this patient. Stargatt et al. (2007) reported that once hydrocephalus has been resolved, attention span is the only area of deficit in the long-term. None of these patients were being treated for hydrocephalus at the time of testing and the time post treatment was highly variable, thus it is possible that any effects of hydrocephalus were short-lived in this group of patients.

Neurological deficits such as cerebellar mutism syndrome, ataxia and pyramidal symptoms have been shown to have an adverse effect on functional outcome in children treated for ependymoma (e.g., von Hoff et al., 2008). As only two of the patients (P01 and P06) were reported to have cerebellar mutism syndrome it was not possible to investigate this effect further. Similarly, most patients demonstrated a degree of ataxia, but the effects of this will be reflected in the scores on the BOT-2 as it includes typical measures of ataxia. Of particular note is that, despite varying in clinical symptoms, all of the 15 children studied here showed a normal relationship between motor and cognitive skills, even when performance levels were low. Thus, if treatment for cerebellar

tumour during the preschool years results in motor deficits it appears to have a concurrent effect on cognitive processing as well.

It is difficult to draw firm conclusions regarding the effect that each of the potential moderating variables has on cognitive and motor outcome within this patient sample, because these variables are not likely to act independently (Dennis et al., 1996). Of the factors considered in this study, tumour type/treatment and age at diagnosis seem to be the most reliable predictors of outcome for both cognitive and motor skill, however the relatively small sample size for each variable makes it difficult to draw out any interactions between the variables studied.

3.4.4 Conclusion

To conclude, this study suggests that when children receive treatment for a cerebellar tumour in the preschool years, adverse development of both cognitive and motor ability is likely to ensue. Although depressed performance was found at the group level across a wide range of cognitive and motor skills, there was considerable variation within individual profiles. Clearly this type of analysis cannot reveal a causal relationship, but the results suggest cerebellar involvement in the development of both domains. Type of tumour/treatment and age at diagnosis were found to be the most reliable predictors of subsequent outcome, but the interacting effects of other moderating variables limit interpretation of these results. Importantly, this study showed that cognitive and motor skills are intimately linked across development for both typically-developing children and children with cerebellar injury. Although cognitive and motor development may be delayed following treatment for a cerebellar tumour in childhood, the interrelationship between these two domains is typical. Longitudinal follow-up is needed to see if this relationship continues to follow a linear trajectory with increasing time post onset, even if performance levels become further delayed.

4 Longitudinal follow-up of the impact of cerebellar tumour injury sustained in early childhood on motor and cognitive development

4.1 Background literature

Impairment in neurodevelopmental outcome in both the cognitive and motor domains is common following treatment for a cerebellar tumour in early childhood (e.g. Beebe et al., 2005; Davis, Pitchford, Jaspan, Macarthur & Walker, 2010). However, the extent to which recovery of function or attainment of standard developmental milestones can occur is unclear due to a paucity of longitudinal investigations in this population. Children with posterior fossa tumours have been found to demonstrate higher levels of unemployment in adulthood than their siblings (Mostow, Byrne, Connelly & Mulvihill, 1991) which may be accounted for by a continuing decline in cognitive skills following treatment (Mulhern & Palmer, 2003). If this is the case, early rehabilitation focussing on appropriate areas of functioning may help to reduce this discrepancy. Although many previous studies have examined the long-term outcome of children with cerebellar injury, whilst long-term studies are potentially useful for predicting developmental outcome, they offer little information concerning the process by which development of functioning occurs in this population. To achieve this end longitudinal studies are required, mapping any changes in ability in individual patients over time.

An important consideration for longitudinal studies is the widespread use of standardised assessments to measure developmental progression, as a decline in standardised IQ score does not automatically demonstrate a decrease in ability but may instead reflect acquisition of skills at a slower rate than peers. Also, the magnitude of standard score loss which reflects a genuine decrease in ability is likely to vary according to individual standardised tests making it difficult to compare across studies that have used different measures. Longitudinal studies should therefore consider both standardised and raw scores

when examining change in performance in any sample where a delay or deficit in typical development is expected.

4.1.1 Models of developmental progression

To establish the developmental progression of children with injury to the cerebellum any increase or decline in scores should be measured over time and any developmental change may be examined from two approaches. Qualitative examination may be used to establish whether a deviation from a typical pattern of development is seen and the nature of any such difference. This may be established by investigating the interrelation of the development of different domains across childhood in typically-developing children and comparing the results to those found for children with cerebellar tumour. Alternatively quantitative investigation may be used to explore the nature of any developmental delay present in this population. Based on this distinction several models may be proposed for the possible developmental progression post treatment in children who have suffered a cerebellar tumour. These, and predictions based on the models, are detailed below and considered with reference to previous studies in the area. It should be noted that many different models could be forwarded and that those described here are aimed to be the simplest models to provide a useful framework in which developmental progression may be considered. In reality the development of these children may reflect a combination of the different models proposed here and examination of the data should help to determine which models (or combination of models) might be most applicable for the basis of future research.

4.1.1.1 Model 1 – Deviation from typical pattern of development

This model posits a more qualitative change in development than the subsequent models proposed and suggests that the relationship between development in different domains may be altered due to the impact of a tumour

and treatment, resulting in atypical development. One major theory of developmental change in infants, probabilistic epigenesis, suggests that development occurs through complex bidirectional interactions between genes, structural brain changes and functional development (e.g. Johnson, 2005). According to this view, deviation from a typical trajectory forces reciprocal change in genetic, structural and functional interactions; adaptations are implemented which in turn cause additional factors to influence development thus causing further adaptation. The end result is likely to be some degree of reorganisation of brain function, which may result in different associations between developmental domains than are seen in typically-developing children.

The results explored in Chapter 3 suggest that this model may not be an appropriate explanation for the scores in these children as the correlation between their cognitive and motor scores was similar to that seen in typically-developing children, despite including patients with varying time since treatment. Investigating any changes in correlation longitudinally may help to further distinguish whether any qualitative differences are present in the developmental progression of patients compared to that of typically-developing children.

This model predicts that the associations between skills for patients may be expected to differ longitudinally from the correlations reported for typically-developing children across time. The similarity between the cognitive and motor correlations found in Chapter 3 for the patient and typically-developing groups therefore would be predicted not to be maintained in the longitudinal follow-up.

4.1.1.2 Model 2 – Persistent impairment or declining performance

This model proposes that development is persistently affected in this population resulting in a persistent impairment or a decline in scores over time. This model may be divided into three broad outcomes to further clarify the developmental trajectory of the patient sample. These hypotheses are highlighted in Figure 4.1,

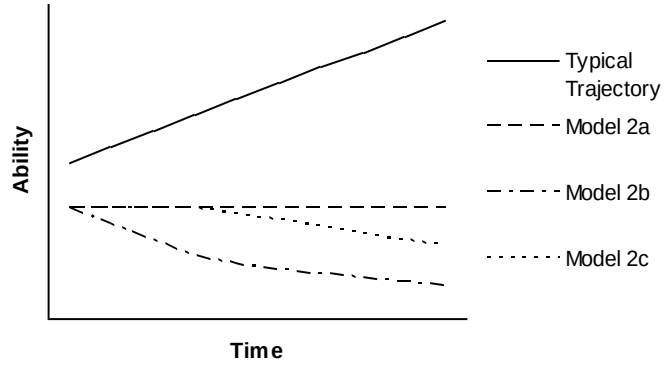
which illustrates predictions for changes in raw scores over time. For the purposes of illustration the typical trajectory is depicted as a linear increase, although it is acknowledged that this may not be the case for many cognitive or motor abilities it serves to highlight the different models predicted here.

Model 2a. For the children who were significantly impaired in Chapter 3, it would seem that they have failed to acquire the appropriate skills with development and are continuing to function at a diminished level compared to peers. It should be noted that this model would result in a decreasing standardised score over time as the increase of a typical trajectory is translated into a stable standardised score over time. This model predicts that the standard scores would decrease whilst no difference would be found in the raw scores

Model 2b. This hypothesis suggests that patients may actually decline in ability level across development, with a loss of skills relative to earlier functioning. This may then result in a plateauing of decline at a level below that first recorded after treatment. This model predicts that both the standard and raw scores would decrease with time.

Model 2c. Patients may continue to function at the same level for some time following treatment and a subsequent decline may become apparent some years later. This model predicts that the standard and raw scores would both decrease before reaching a plateau. This model also suggests that those patients with a longer time since treatment may be expected to exhibit a smaller decline between subsequent sessions than patients who have received treatment more recently.

Figure 4.1 Models 2a, b & c for developmental progression



4.1.1.3 Model 3 – Delayed performance with developmental progression

This model suggests that patients continue to develop along a typical trajectory, although many may be starting from a diminished baseline and may not gain skills at the same rate as peers. Again, this model may be divided into three sections for clarification (see Figure 4.2).

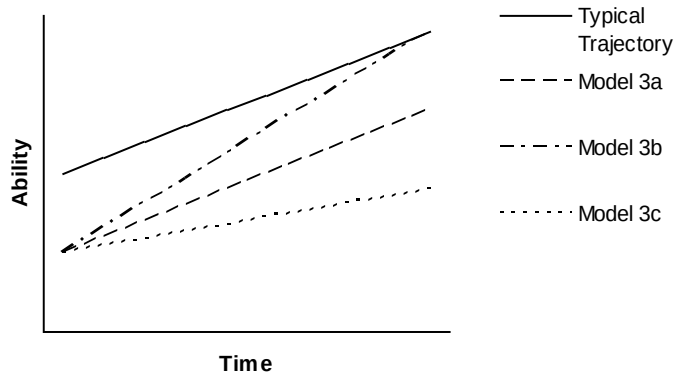
Model 3a. Children treated for cerebellar tumour may develop at the same rate as typically-developing children. For those patients who exhibit a lower performance, this suggests that the gap between them and their typically-developing peers may be expected to remain fairly constant with time. In addition, their standard scores may be expected to remain similar across development despite increases in their raw scores. For this model, it is unclear whether the end state reached is equivalent to that of typically-developing children, with development therefore continuing for longer, or whether the final level of functioning attained is correspondingly lower. Longitudinal studies spanning all childhood would be necessary to satisfy this question. This model predicts no change in standard scores across time although an increase would be seen in raw scores.

Model 3b. The developmental progression in children with cerebellar damage may occur at a faster rate than in typically-developing children, with

patients demonstrating 'catch-up' to their typically-developing peers. This model predicts that both standard and raw scores would increase with time.

Model 3c. The rate of progression in patients may be slower than in typically-developing children suggesting that their developmental delay may increase across childhood. This model suggests that standard scores would decline despite increasing in raw scores.

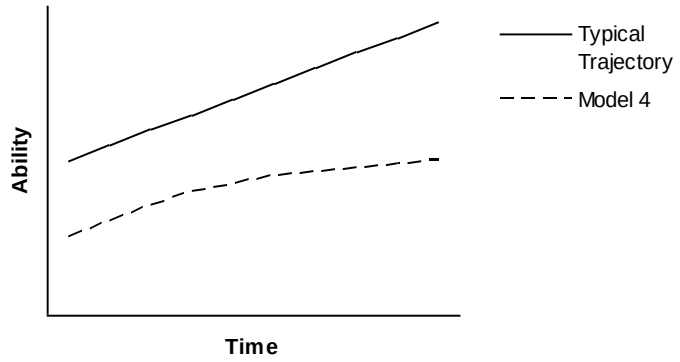
Figure 4.2 Models 3a, b & c for developmental progression



4.1.1.4 Model 4 – Developmental progression with plateau

As with Model 3, this model proposes that patients may demonstrate development, either at the same rate, an increased or decreased rate as in typically-developing children. However this model suggests that potential for skill acquisition has been limited by the damage caused by the tumour and/or treatment so that a developmental plateau is reached at a level below that achieved in typical development. Model 4 predicts that the standard scores should remain constant before decreasing whereas the raw scores would demonstrate an increase before reaching a plateau (Figure 4.3).

Figure 4.3 Model 4 for developmental progression



It is possible that these models may not be mutually exclusive in the population as developmental progression also depends on other prognostic factors that have been demonstrated to impact upon outcome, including the age at diagnosis, the location of the tumour within the cerebellum and tumour type/treatment received. Chapter 3 indicated that these factors affected scores in the initial assessment and it may therefore be expected that these factors will similarly impact the developmental progression in each individual.

4.1.2 Background literature

Previous studies which have examined either the long-term outcome or longitudinal progression of development in this population are reviewed below to establish whether any evidence can be found to support or refute the proposed models.

As stated above, cognitive ability in typically-developing children as measured by standardised IQ tests is thought to remain stable across development. In contrast, many studies have reported that time post treatment is negatively associated with outcome in a variety of cognitive, attentional and adaptive measures in children treated for cerebellar tumour (e.g. Dennis et al., 1996; Poggi et al., 2005). For example, in a seven-year follow-up study on children with medulloblastoma treated with craniospinal irradiation (CSI),

participants demonstrated a decline in intellectual functioning (Palmer et al., 2003). This study found a linear rate of decline of 2.05 points a year, slightly lower than the rate reported in previous studies of between 2.55 and 4.30 points per year (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Palmer et al., 2001; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001; Walter et al., 1999). The additional impact of factors such as age at diagnosis and differences in treatment regimes may account for these apparent differences. The decrease in standardised scores reported for the children in these studies does not allow for differentiation of the models outlined above and may constitute support for several of the models (all parts of Model 2, Model 3c and Model 4) as a decline in standard scores may not automatically reflect a decrease or plateauing of ability. In addition, these studies do not investigate any qualitative differences that may exist in the development of these patients as compared to typically-developing children.

The rate of decline in standard scores across time is thought to be related to the age of the patient at diagnosis. Palmer et al. (2003) split their group into older (μ=11.05 years) and younger (μ=5.86 years) subgroups based on median age at diagnosis. Those in the older group maintained baseline performance for approximately two years when there was a slight decline. At around four years post treatment the rate of decline increased. In the younger group their data demonstrated a more immediate decline in ability that continued until a late plateau was reached. Importantly, between 3-5 years post treatment the older and younger groups diverged, demonstrating the need for follow-up over a long time period. All of their sample suffered medulloblastoma and were treated with CSI, and chemotherapy was not found to have an additional impact on longitudinal changes. A similar pattern of decline in younger children (mean 6.08 years at diagnosis) was reported by Spiegler and colleagues, who found that there was an attenuation of the rate of decline with each year post diagnosis, although the authors suggested further study is needed to pinpoint

the stage at which the decline in intelligence reaches a plateau (Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). In their case-by-case study of seven children with cerebellar lesion in the preschool years, Scott et al. (2001) reported a plateauing of reading and verbal skills, as measured by standard scores, in two of their participants respectively. These two children were 5 and 8 years post diagnosis at the time of the final testing session. It may be expected that a differential profile of decline would be seen for abilities with varying typical developmental trajectories. For example, abilities that are acquired early in childhood, such as gross motor function, may be less affected if the insult occurs after skill acquisition. Conversely cognitive skills that are not acquired until later in development may fail to develop appropriately if earlier functions necessary for scaffolding these skills have not been gained. Similarly to above, at face value these results would seen to offer most support for Model 2, in particular Model 2b, however the reporting of standard scores alone limits the conclusions that may be drawn from these studies as increases in raw scores may have been obtained by children in these studies.

A study directly comparing outcome in children treated for ependymoma and medulloblastoma revealed that children with medulloblastoma demonstrated a significant deterioration in cognitive skills between 5 and 10 years post treatment, an effect not found for the ependymoma group (Hoppe-Hirsch et al., 1995). These results offer limited support for Model 2c, although again raw scores were not reported. An important implication of this study however, given that children with ependymoma did not decline over time, is that the decrease in standard scores recorded in studies of cerebellar tumour patients may be due to the effects of CSI in children treated for medulloblastoma. The long-term intellectual and academic decline following treatment with CSI has been well documented in paediatric populations (e.g. Mulhern et al., 1999; Mulhern et al., 2004; Reeves et al., 2006; Ris & Noll, 1994). A younger age at treatment with CSI (e.g. Radcliffe et al., 1994), a higher dose of radiation (e.g. Grill et al.,

1999; Kieffer-Renaux et al., 2000) and increased time since treatment are known to be additional risk factors for a cognitive decline (e.g. Copeland et al., 1999). The precise mechanism of damage caused by CSI is not fully understood. It has been proposed that initial disruption is due to the death of neuronal cells and oligodendrocytes with subsequent microvascular damage (Hopewell & van der Kogel, 1999; Schultheiss, Kun, Ang & Stephens, 1995). Another hypothesis suggests that CSI causes damage to the myelin membrane due to oxidative stress (e.g. Tofilon & Fike, 2000).

It is posited that white matter is more susceptible to damage than grey matter as it has a longer maturation and indeed there is evidence to suggest that changes in white matter are related to changes in cognitive ability (Mulhern et al., 1999). If the change in intellectual processing is due to white matter disruption, this may explain why younger children are consistently found to have a poorer cognitive outcome. Indeed one study indicated that a high proportion of the association between IQ and age at treatment can be accounted for by cerebral white matter volume (Mulhern et al., 2001). In addition, in typically-developing children intellectual abilities are thought to be strongly underpinned by working memory and processing speed (Fry & Hale, 2000) and in turn processing speed is thought to be linked to white matter volume (e.g. Turken et al., 2008). Longitudinal studies have been conducted to establish whether white matter differences seen in children who have undergone radiotherapy are the result of tissue loss, a failure to develop white matter at an appropriate rate, or both mechanisms together. Reddick et al. (1998) reported that children treated for a medulloblastoma demonstrated a decrease in white matter volume compared to age-matched controls treated with surgery alone. In addition, children who received a higher dose demonstrated a greater reduction in white matter volume (Palmer et al., 2002).

A prospective longitudinal investigation examined the impact of conformal radiation therapy (CRT), which limits the impact on surrounding normal tissues,

on the subsequent academic and cognitive performance of children who have suffered ependymoma (Conklin, Li, Xiong, Ogg & Merchant, 2008). At the beginning of CRT, baseline academic scores were found to be within the average range. Subsequent testing sessions over the follow-up period of 8 years demonstrated a significant decline in reading standard scores that was more marked in children who were younger at diagnosis. Maths and spelling were found to remain constant across time suggesting that children were acquiring these skills at a similar rate to their peers. Similarly cognitive ability remained stable across the testing period. The authors therefore warn against using purely IQ as a measure of outcome as children may demonstrate deficits in other areas of functioning. This decoupling of cognitive and academic skills is perhaps surprising given the strong link between these two areas (e.g. Frey & Detterman, 2004) and may highlight a differential effect on the cognitive capacities which underpin the academic abilities. For example the findings of Conklin et al. suggest that these patients may have a difficulty with automatisation of skills, which may be important for reading skills and is thought to have a high cerebellar involvement (e.g. Nicolson et al., 2001, see Chapter 5). This also highlights that the models outlined above may apply differentially to different skills. In this study, the results suggested that for cognitive, maths and spelling abilities Model 3a, b or c may be the most applicable whereas for reading, Models 2a, b or c may better account for the findings. In addition, the differential profile of impairment seen in the participants of this study offers tentative support for Model 1 and suggests that there may be a qualitative difference in the development of this sample.

It should be noted that a finding of deterioration of standard scores over time in children treated with radiotherapy has not been recorded in all studies. For example, von Hoff et al., (2008) reported a sample of nineteen children treated with surgery and posterior fossa irradiation for ependymoma, and found that despite significant impairments in cognitive ability, no change in standard

scores was found over time. These results appear to offer support for Model 3b; development is occurring at the same rate as in typically-developing children, although functioning may remain impaired. Similarly to the study by Conklin et al. (2008) described above, the difference between this study and others reporting a decline in functioning may be explained by differences in treatment. Findings suggest that whilst children with infratentorial tumours who receive CSI show a decrease in IQ, those treated with posterior fossa radiotherapy and those with no radiotherapy tend to display a slight increase in IQ (Fouladi et al., 2005) or no difference over time (Merchant et al., 2004).

Of the few longitudinal studies reported in this population, most have focused on mapping changes in intellectual abilities alone in the time following diagnosis. A few long-term outcome studies have investigated other areas of functioning following treatment for brain tumour or leukaemia with CSI and reduced capacity has been noted in visual-perceptual abilities, memory, attention, learning, information processing speed and adaptive functioning (e.g. Copeland et al., 1999; Spiegler et al., 2004; Stargatt et al., 2007). In addition to cognitive disruption, motor deficits are well-documented sequelae in children treated for a posterior fossa tumour (e.g. Duffner et al., 1986a). One study found no effect of recovery time on the variability in motor outcome in children treated for a range of cerebellar tumours, suggesting that once past the initial short-term recovery period of plasticity and reorganisation no further improvement should be expected (Konczak et al., 2005). This study did not use standardised scores for the motor measures and these results therefore offer reasonable support for Model 4, suggesting a plateauing of developmental progression. In contrast, Spiegler and colleagues (2004) reporting on survivors of medulloblastoma and ependymoma found that fine motor speed and dexterity improved or was unchanged across the follow-up period suggesting that fine motor skills are not sensitive to the long term effects of CSI. Given the postulated impact of CSI on white matter, which is important for processing

speed, it is somewhat surprising that fine motor speed is unaffected in these children. This study employed standardised assessments to measure motor development and does not report raw scores, however the results provide strongest support for Model 3a or b, with improving function across time.

A case study following an individual from diagnosis with medulloblastoma at age four through to adulthood (age 24) reported on the development of the heel-to-toe tandem walk (Dennis, Hetherington, Spiegler & Barnes, 1999). The initial follow-up test indicated a complete loss of this ability resulting from the acute effects of the cerebellar tumour and treatment. At the third testing phase, approximately 2.5 years following resection, skill improvement was recorded; although the curve of learning was much steeper, perhaps reflecting an additive effect of recovery and development, the level achieved was still well below that of peers. At the fourth testing twenty years after diagnosis the individual's performance remained significantly less than expected and the developmental curve was similar to that of peers. The presence of a chronic motor deficit in adulthood suggests that recovery will never reach the same level as that of typically-developing adults. The results from this study support Model 4, with a plateauing of skills despite initial acquisition of skills at a faster rate than peers. In a similar study investigating long-term outcome using the tandem walk measure, Dennis et al. (1999) also reported that five years post diagnosis, survivors of medulloblastoma and astrocytoma both showed deficits in comparison to controls but did not significantly differ from each other, although generally the group with astrocytoma scored more highly. The similarity between these two groups suggests that impairments are present that are not solely due to radiotherapy. It has been proposed that the short-term deficits following cerebellar damage are due to changes in the metabolic activity of the efferent pathways (Ackermann & Hertrich, 2000), which would be present in both groups of patients.

Other studies have also reported neurodevelopmental deficits in children with benign cerebellar tumours, i.e. astrocytoma, due to damage associated with the tumour and surgical treatment (e.g. Hoppe-Hirsch, 1993). Far fewer studies have investigated the longitudinal impact of this damage on developmental outcome than in children who have received CSI. One study included 106 children with craniopharyngioma, optic glioma, pilocytic astrocytoma or ependymoma and administered a range of neuropsychological measures three months following surgery, prior to receiving radiotherapy (Carpentieri et al., 2003). Deficits were recorded in several domains including motor output, visuospatial skills and verbal memory. This suggests that the surgery, in addition to perioperative complications (e.g. bacterial meningitis, hydrocephalus) may result in cognitive difficulties, although this outcome study does not inform whether such effects are transient or more lasting as with deficits following radiotherapy. Another study which examined children with astrocytoma at the time of diagnosis prior to treatment found impairments in memory, motor, attention and visuo-spatial skills again suggesting that the tumour itself has an adverse effect, not merely the impact of treatment (Ater, Moore, Francis, Catillo, Slopis, & Copeland, 1996).

Although some studies have suggested that outcome following treatment with surgery alone results in minimal disruption (e.g. Copeland et al., 1999), more detailed studies investigating long-term outcome in children with benign tumours suggest that they may also suffer long term cognitive and behavioural impairments (e.g. Beebe et al., 2005; LeBaron, Zeltzer, Zeltzer, Scott & Marlin, 1988; Rønning et al., 2005; Scott et al., 2001; Steinlin et al., 2003). Aarsen et al. (2004) examined 26 children treated for pilocytic astrocytoma using a range of neuropsychological measures between 1 and 8 years post treatment. All children showed deficit in at least one area of functioning, with 24% requiring special education. These results were confirmed in a later study which reported that all children with cerebellar astrocytoma included in the study had deficits in

language, visuo-spatial memory and executive functioning up to three years post treatment (Aarsen et al., 2009). Similarly to the findings with more aggressive tumours, this study reports that a younger age at diagnosis is a significant risk factor for subsequent development. The authors suggest that the delay before cognitive difficulties become apparent in children with astrocytoma supports the idea that brain damage may have a cumulative effect throughout development as more functions are expected to mature that need to be accommodated by undamaged tissues (Anderson et al., 2001). These findings, and explanation, offer some support for Model 2c although only standard scores are reported limiting any conclusions. This finding contrasts with other studies that report a trend towards a younger age at treatment resulting in a better developmental outcome (e.g. Levisohn et al., 2000; Rønning et al., 2005). Rønning et al. posit that this may be due to better neural plasticity in an immature brain to aid recovery of mechanical trauma in a way that would not be possible for damage resulting from CSI. Therefore, it may be that the follow-up period in studies with children who have suffered an astrocytoma have not considered a sufficiently long time period to establish whether the deficits seen in this group attenuate with time. The study by Rønning et al. (2005) suggested otherwise as the mean age at diagnosis was 7.4 years and the mean age at follow-up was 23 years indicating that deficits continue into adulthood. In addition, few studies with this population have gathered data at multiple time points to track any alterations over time which would enable distinctions to be drawn between the models proposed here in children with more benign tumours.

Slightly conflicting results are reported in a study which examined a range of developmental outcomes at baseline and at one, two and three years post diagnosis in children with medulloblastoma, astrocytoma and ependymoma (Stargatt et al., 2007). Patients were grouped according to whether they had received radiotherapy. Over the follow-up period there was no significant change in IQ score for the group that did not receive CSI, although there was a

general trend suggesting a slight improvement over time suggesting for this group Model 3b may be most applicable. For the children who did receive CSI the overall trend suggests a decline in ability over time, however no significant difference was seen between baseline and the first year post treatment and a significant improvement was seen between the first and second year scores. A subsequent significant decline was recorded between the second and third year to a level below the initial baseline score. As suggested above, a combination of the models proposed may account for this finding; however the overall pattern suggests that Model 2b may be the most relevant for this group. A similar pattern of change was found for digit span, with a trend towards improvement in the group without CSI, although a steady decline was recorded for children who did receive CSI. As the effects of CSI are not believed to have an immediate impact on cognitive function (Heideman, Packer, Albright, Freeman, & Rorke, 1997), the authors suggested the initial decline in the CSI group may be due to other factors operating in the short term, such as the effects of surgery, or perioperative complications. Longitudinal assessment in this population may therefore be particularly pertinent to assess rehabilitation needs across development.

The impact of treatment for a tumour without radiotherapy may also be investigated by examining children with ependymoma or medulloblastoma who have not received CSI, in comparison to those children who have, to establish whether they demonstrate a similar decline in ability. In addition, it should be considered that children who have only received posterior fossa (PF) irradiation may not be a suitable comparison group to compare to patients treated with CSI, as the field affected by radiotherapy in children who have received PF radiotherapy may include a large portion of the supratentorial brain, including inferior portions of the occipital, parietal and temporal lobes, the thalamus and diencephalon (e.g. Benk, Bouhnik, Raquin, Kalifa, & Habrand, 1995; Miralbell et al., 1997). It should also be taken into account that age at diagnosis may be a

confounding factor in this population as the decision to treat with CSI is often linked to the age of the child with younger children less likely to receive CSI, especially in the UK.

The data reported in Chapter 3 indicated a high correlation between cognitive and motor skills in both typically-developing children and those who have suffered a cerebellar tumour. As hypothesised by Grill et al. (2004) the link between motor and cognitive deficit in these patients may either be because damage in one domain affects development of the other, or because they are both affected by the same underlying cause, i.e. cerebellar damage/treatment for tumour. Findings from Grill et al. suggest that the latter explanation may be the case as fine motor skills were found to be related to both non-verbal and verbal skills. Another study however indicated that deficits in attention shifting tasks may be the result of motor difficulties in adult cerebellar patients (Ravizza & Ivry, 2001) and that consequently cognitive impairments may result from impaired motor abilities. Previous work with typically-developing children (see chapter 2) has investigated the underlying link between these two domains. It appears that the link between fine motor skills and visual processing accounts for the apparent global association between the domains. Investigating longitudinal changes in each domain concurrently may help to further establish the impact of a cerebellar tumour on the interrelation of these abilities. This in turn will clarify the validity of Model 1; whether any qualitative differences are present in the development of children with cerebellar injury.

All of the studies detailed above reported on the standard scores of cerebellar patients which limits the conclusions that can be drawn concerning the different development models. One study which has reported raw scores demonstrated that despite a loss of 2.55 IQ points per year, raw scores on standardised measures significantly increased over time just not at a rate comparable with typically-developing peers (Palmer et al., 2001). This study examined the cognitive development of 44 children (aged 1-12 years at

diagnosis) treated for medulloblastoma, with data collected before radiotherapy, at six months following radiotherapy and subsequently at yearly intervals (a maximum of six examinations in one participant only and with a median of three assessments per patient). These results appear to offer support for Model 3c; the rate of development was attenuated in this population but progress was recorded nonetheless.

The majority of previous studies in this area have reported impairments in standardised scores in children who have suffered a cerebellar tumour. In addition, many of the longitudinal studies reviewed here have found a decline in standard IQ scores over the time following treatment. In particular, children who have suffered a more aggressive tumour, i.e. medulloblastoma, and received CSI or PF radiotherapy appear to be at greatest risk of declining standard scores over time. In addition, a younger age at diagnosis is also thought to be a risk factor for a poorer longitudinal outcome. These findings are taken to suggest that children with cerebellar tumours are demonstrating declining skills over time, which would seem to support Model 2, however without the data concerning the raw scores for these children, it is not possible to determine which developmental model may best account for progression in these patients. Indeed, a decline in standard scores may actually represent an increase in abilities over time as illustrated by Model 3c. Children who have suffered a more benign tumour, i.e. astrocytoma, have been found to show a variable pattern of development, with overall IQ remaining constant and reading skills demonstrating a decline. For IQ in these children therefore Model 3b may be the most appropriate, however without raw scores is it again difficult to draw firm conclusions.

It is possible to highlight two main difficulties in interpreting the standard scores from previous studies. The use of standard scores without the complementary raw scores does not allow for the possibility that children with cerebellar tumour are improving, but at a different rate to that seen in typically-

developing children. In addition, the lack of comparison to the alteration in control scores over time means that the developmental trajectory of the patient sample cannot be compared to a typical trajectory of development. This study aims to address both of these limitations by examining standard and raw scores in both control and patient samples.

4.1.3 Current study

This study investigates the longitudinal outcome for cognitive and motor skills in a sample of 12 children who have suffered a cerebellar tumour in the preschool years, to establish the developmental trajectory of skills in each domain with increasing time post treatment. To establish whether any of the models outlined above can explain the developmental progression found in the children included in this study, scores were recorded on the KABC-II and BOT-2 at two further time points from those reported in Chapter 3. In order to make a comparison to a typical developmental trajectory, any alterations in the patient scores were compared to the change in the scores of those typically-developing children reported in Chapter 2 who were assessed twice (N=41). These comparisons aimed to distinguish between the hypothetical models outlined above using both raw and standardised scores.

In addition to the models outlined above, other hypotheses may be forwarded considering evidence from previous studies and Chapter 3, concerning factors that may be predicted to impact on developmental progression in the patients:

- It appears more likely that a decline in cognitive skills (Modes 2a, b or c) may be observed in children who have received treatment with radiotherapy, both those with PF radiotherapy and CSI.
- For the children with more benign tumours who received either surgery or chemotherapy alone, the majority of previous work suggests that these

children will also demonstrate long-term deficits in cognitive skills although they may not be as severe.

- Previous work suggests that whilst deficits in motor functioning may be evident, they may not be so marked as cognitive difficulties and that the deterioration following initial insult may not be as severe for motor abilities as for cognitive skills. Little differentiation in outcome on motor skills between the several tumour/treatment types has been established.
- Age at diagnosis is also predicted to impact upon the longitudinal change, with children younger at diagnosis displaying greater deficits. It may be hypothesised that a younger age at diagnosis could lead to a widening of the gap with typically-developing children as fewer age-appropriate skills are attained. It should be considered however that age at diagnosis may be confounded with both tumour type, and consequently treatment received, with younger children suffering a higher proportion of medulloblastoma and therefore radiotherapy.

4.2 Method

4.2.1 Participant Information

4.2.1.1 Patient Information

When families were approached for this study, parents were asked for their child to participate in three testing sessions at six-month intervals. The 15 children initially recruited to the study, as detailed in Chapter 3, were therefore enrolled for all three sessions, however only 12 children (excluding P08, P12 & P15) completed the second and third sessions. Reasons for withdrawal from the study were family crisis, reoccurrence of a brain tumour and one family moved away from the area.

4.2.1.2 Control Information

The control participants used in this study were the children from the typically-developing study (Chapter 2) who completed an additional testing session to explore the relationship between cognitive and motor development around seven years of age. Each of these children completed two testing sessions and the time gap between the two sessions ranged from 10 – 27 months.

Table 4.1 Sample characteristics of control participants

	Time 1	**Time 2**
Age range (months)	65-96	84-119
N	41	
Sex ratio M:F	18:23	
Mean age (months) (SD)	84.39 (8.69)	102.51 (9.96)
Mean Fluid Crystallised Index (cognitive index) (SD)	108.21 (12.17)	108.02 (14.25)
Mean Total Motor Composite (motor index) (SD)	52.71 (8.13)	50.73 (8.13)

4.2.2 Procedure

Each of the cerebellar patients completed a cognitive (KABC-II) and motor (BOT-2) standardised measure on three separate occasions (Time 1, T1; Time 2, T2; and Time 3; T3), at six-month intervals over an 18-month period. The results from Time 1 are reported in Chapter 3. The tests were both administered in a single session lasting approximately two hours on each occasion. To minimise practice effects, it is usual to leave at least three months between testing sessions (Kline, 2000). For this study six months was chosen as the retest period both to reduce practice effects and to ensure that any developmental changes could be accurately mapped. Standardised scores for the KABC-II and BOT-2 are based on age-banded samples of norm participants. For the KABC-II the width of the norm sample band is either 2 or 3 months

(depending on age) for the subtest scores meaning that an interval of 6 months between testing sessions translated into a shift of at least two age bands for standardisation. For the BOT-2 the width of the norm sample band is either 3 or 6 months (again depending on age) for the subtest scores meaning a shift of at least one age band in the norm sample for this measure.

The procedure followed for the control children is detailed in Chapter 2 and the same standardised measures were used as for the patients (KABC-II; BOT-2). For the children tested in schools, the second assessment was also conducted in the school over consecutive days as described in Chapter 2. Similarly, those children seen in the Nottingham Toddler Lab at Time 1 were also tested there for the second assessment, which was again conducted in one session.

4.2.3 Statistical analyses

Many previous studies have examined the change in scores over a longitudinal design by using random coefficient models (e.g. Palmer et al., 2003; Ris et al., 2001), however these studies included much larger, homogeneous samples, in terms of tumour type/treatment, than measured here (50 and 43 respectively). There appears to be some debate surrounding an appropriate sample size for more complex statistical analyses, for example von Hoff et al. (2008) used description for their longitudinal data due to a small sample (n=23) whereas Copeland et al. (1999) used mixed model regression analyses in their study (n=27). Given the small, highly heterogeneous nature of the sample in this study, multi-factorial designs would be inappropriate, would lack necessary statistical power and may produce unreliable conclusions. Thus, the standardised scores generated for each of the overall cognitive and motor indices as well as the broad levels of ability on each test were used to examine the difference in performance between T1, T2 and T3 for cognitive and motor skills. In addition the raw scores from the subtests of each standardised measure were

used to compare patient and control longitudinal change. The following analyses were conducted:

1) *Individual patient analyses*

   Preliminary data analysis examined individual patient cases to establish whether any changes in scores over time were recorded, and to investigate whether a uniform pattern of development was seen across both participants and indices. To highlight any differences between children two individual comparisons were drawn using patients selected to have similar prognostic factors; the outcomes for P01 and P06 (medulloblastoma, similar age at diagnosis, surgery, chemotherapy, CSI and PF radiotherapy) and P02 and P09 (pilocytic astrocytoma in the vermis and LH, similar age at diagnosis, surgery alone, moderate hydrocephalus) were directly compared as these pairs of children were hypothesised to display similar profiles of change.

2) *Qualitative differences in longitudinal outcome between patients and controls*

   For all comparisons between the control and patient groups, the scores from T1 and T3 alone were used for the patient group as the gap between these two sessions was more comparable to that of the control group.

   - To investigate the validity of Model 1, the correlations between the cognitive and motor indices at each time point for the patient sample were assessed using Pearson correlations. Fisher's z was applied to test for significant differences in strength of correlations across time. These analyses were conducted for both the overall cognitive (FCI) and motor (TMC) indices as well as for each of the indices of the cognitive and motor tests.
   - Model 1 was also examined by comparing the proportion of patients and typically-developing children who demonstrated an increase in both domains, an increase in one domain but not the other, or a decline in

both domains as measured by the overall standardised scores (FCI & TMC). This was achieved using a chi square analysis.

3) *Quantitative differences in longitudinal outcome between patients and controls*

- To investigate the hypotheses made by Models 2, 3 & 4 chi square analyses were conducted to examine the difference in the frequencies of patients and control children who showed an improvement (≥+1 point), no difference or a decline (≤-1 point) in both raw and standard scores for each index (standard scores) and subtest (raw scores) separately. For indices and subtests in which significant differences in frequencies were found, two sample z tests were used to determine where the significant differences lay.
- The differences values between scores at T1 and T2 (T3 for patients) for both the index (standard) and subtest (raw) scores were compared for the patient and control groups using Mann-Whitney U analyses.
- Raw subtest scores from T1 and T2 (T3) were examined graphically for the patient and control groups for comparison to the models outlined previously. The magnitude of change in the patient and control groups was assessed for the raw scores using Mann-Whitney U analyses between the patient and control groups at T1 and separately for T2 (T3 for patients).

4) *Index and subtest score comparisons across time for the patient group*

To establish whether the separate indices of the cognitive and motor measures demonstrated varying profiles of change across time in the patient sample, the subtest raw scores, the standardised index scores and the overall gross scores were assessed with Friedman's ANOVA. This non-parametric measure was used as the sample size for this study is relatively small and tests of normality were not satisfied. Post-hoc tests were conducted for those indices in which a main overall effect of time

was found using Wilcoxon paired rank tests. Bonferroni correction was applied to the pairwise analyses yielding a significance level of .025 (the α value of .05 was divided by the maximum number of analyses a value was entered in to, in this instance 2).

5) *Impact of Prognostic factors*

In Chapter 3 several of the prognostic factors examined were found to have an impact on cognitive and motor functioning. A trend towards a younger age at diagnosis resulting in a poorer outcome was recorded. A trend towards a poorer outcome following a longer time post treatment was found, however this was not significant. No differential effect of sex was found. The patients were grouped according to tumour type and treatment and those children who suffered a medulloblastoma and received surgery, chemotherapy, CSI and PF radiotherapy were found to perform most poorly on many of the cognitive and motor indices. In comparison, those children with astrocytoma who were treated with surgery alone generally performed most highly. These factors were considered here in relation to the longitudinal change found in the patients.

- The impact of Age at Diagnosis and Time Post Treatment were assessed by correlating these factors with any variation in scores between T1 and T3. The gradient (m) from the linear equation calculated between T1, T2 and T3 scores for each participant was used to quantify any change in scores.
- The effect of Treatment Type/Tumour was investigated using rank order non-parametric statistics due to the differences in valence depending on increase or decrease in scores with time. Kruskal-Wallis tests were used to assess any differences in the gradient values between the Tumour Type/Treatment groups. In addition the difference values between T1-T2 and T2-T3 for each group were also

assessed with Kruskal-Wallis tests as using the overall slope may mask any important differences between T1-T2 and T2-T3. Similarly, this design was used to examine the impact of Hydrocephalus and Tumour Location. Pairwise analyses were conducted for any overall main effects using Mann Whitney U tests, with Bonferroni correction as above (α=.025). The impact of Sex upon change in scores over time was assessed using Mann Whitney U tests.

- The relationship between ability at baseline (T1) on the overall cognitive (FCI) and motor (TMC) indices and the magnitude of variation seen across time in the patient group was assessed using Pearson's correlation coefficient as this is an additional baseline factor which may help to predict subsequent decline or improvement in scores.

4.3 Results

4.3.1 Individual patient analyses

Individual scores for the patient sample are presented in Table 4.2 (cognitive) and 4.3 (motor). For the cognitive indices, at Time 1 5/12 children were significantly impaired on at least one index and 4/12 were significantly impaired on the general cognitive index (FCI). At Time 2, 3/12 children were significantly impaired on at least one index and 3/12 were significantly impaired on the FCI. At Time 3, 2/12 children were significantly impaired on at least one index and 2/12 were impaired on the FCI. This is a preliminary suggestion that cognitive scores may be improving with time. For the motor indices, at Time 1 6/12 children had a significant impairment in at least one area and 5/12 were significantly impaired on the general measure of motor ability (TMC). At Time 2, 9/12 were significantly impaired on at least one index and 5/12 were significantly impaired on the TMC. At Time 3, 9/12 had significant impairment in at least one index and 6/12 were impaired on the TMC. These scores suggest that unlike for the cognitive measure, motor skills may be declining with time.

Table 4.2 Standard scores for cognitive development as measured by the KABC-II for Time 1 (T1), Time 2 (T2) and Time 3 (T3) (test norm μ=100, σ=15) * -2SD from test norm mean

Patient	Short-Term Memory				Visual Processing				Long-Term Storage				Fluid Reasoning				Crystallised Ability				Fluid Crystallised Index			
	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1
P01	97	103	100	3	71	91	103	32	75	84	78	3	96	85	90	-6	72	75	77	5	76	82	85	9
P02	97	112	109	12	87	100	85	-2	92	108	105	13	93	105	111	18	100	114	100	0	91	110	102	11
P03	83	85	91	8	71	74	71	0	75	67*	94	19	62*	64*	72	10	75	72	77	2	65*	64*	75	10
P04	77	83	83	6	80	92	100	20	78	86	81	3	85	99	99	14	90	95	95	5	78	88	89	11
P05	106	112	106	0	84	87	72	-12	92	100	114	22	96	102	105	9	111	106	111	0	96	101	102	6
P06	100	100	91	-9	64*	61*	64*	0	89	86	84	-5	62*	62*	51*	-11	69*	72	75	6	70*	70*	66*	-4
P07	97	94	91	-6	61*	71	71	10	86	97	97	11	-	-	-	-	90	85	85	-5	79	82	81	2
P09	88	88	91	3	88	94	98	10	89	105	108	19	-	-	-	-	93	101	98	5	87	97	99	12
P10	68*	80	83	15	50*	64*	61*	11	92	92	97	5	57*	62*	69*	12	92	75	82	-10	65*	68*	66*	1
P11	91	91	85	-6	64*	77	74	10	75	73	75	0	67*	85	82	15	80	80	75	-5	68*	75	71	3
P13	91	77	80	-11	80	86	89	9	75	78	103	28	-	-	-	-	74	77	74	0	75	77	83	8
P14	97	97	112	15	111	124	118	7	97	114	120	23	108	105	114	6	102	104	102	0	104	111	118	14

Table 4.3 Standard scores for motor development as measured by the BOT-2 for Time 1 (T1), Time 2 (T2) and Time 3 (T3) (test norm μ=50, σ=10)

Patient	Fine Manual Control				Manual Coordination				Body Coordination				Strength & Agility				Total Motor Composite			
	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1	T1	T2	T3	T3-T1
P01	32	35	35	3	29*	29*	29*	0	26*	27*	29*	3	27*	29*	26*	-1	26*	28*	28*	2
P02	40	38	38	-2	39	35	35	-4	34	36	33	-1	45	39	38	-7	37	35	34	-3
P03	30*	29*	28*	-2	28*	28*	30*	2	26*	26*	25*	-1	39	35	34	-5	29*	27*	21*	-8
P04	46	41	36	-10	35	41	36	1	30*	38	25*	-5	38	35	24*	-14	35	36	28*	-7
P05	39	43	38	-1	32	28*	28*	-4	34	33	41	7	44	44	45	1	33	33	34	1
P06	34	32	32	-2	26*	26*	22*	-4	32	32	28*	-4	31	24*	20*	-11	27*	24*	21*	-6
P07	35	27*	22*	-13	34	28*	22*	-12	40	33	30*	-10	44	39	37	-7	34	28*	22*	-12
P09	52	39	44	-8	39	44	50	11	41	44	36	-5	48	59	56	8	42	44	44	2
P10	23*	25*	26*	3	20*	24*	22*	2	20*	20*	23*	3	20*	20*	20*	0	20*	20*	20*	0
P11	34	32	32	-2	33	30*	31	-2	31	35	30*	-1	38	38	31	-7	32	31	29*	-3
P13	38	42	38	0	20*	30*	28*	8	32	34	34	2	37	35	35	-2	28*	32	31	3
P14	40	51	44	4	38	38	38	0	36	35	35	-1	40	20*	34	-6	36	34	35	-1

For the overall cognitive index (FCI) between T1-T2 10/12 children increased their score, 1/12 decreased their score and 1/12 stayed the same. Between T2-T3, 7/12 children increased their score and 5/12 children decreased their score. For the overall motor index (TMC) between T1-T2 4/12 children increased their score, 6/12 decreased and 2/12 stayed the same. Between T2-T3, 2/12 children increased their score, 7/12 decreased their score and 3/12 stayed the same. For the cognitive indices, the magnitude of change between T1-T3 varies from a decrease of 12 standard points to a maximum 32-point increase, both for Visual Processing. For the motor indices, the largest decrease between T1-T3 is a loss of 14 points for Strength & Agility with a maximum gain of 11 points for Manual Coordination

Each child's profile of changes over time for all cognitive and motor indices is plotted in Figure 4.4. This change was calculated as the difference in scores as a percentage of the score at Time 1 for T1-T2 comparisons and Time 2 for T2-T3 comparisons. This was to take into account the different distributions of the standardised measures. These graphs highlight that there appears to be little consistent longitudinal affect on the magnitude of difference in scores from one time point to the next. Taken together, an overall impression suggests greater change in the cognitive indices, and much less alteration across time for the motor scores. For example, PO2 demonstrates relatively large gains in the cognitive indices between T1 and T2 with a subsequent decrease between T2 and T3, whereas more variation is seen for the motor indices, with decreases generally seen between T1-T2.

Comparison between P01 and P06: Comparing individual profiles across participants shows there to be little systematic explanation for differences between patients. P01 demonstrates reasonably large gains on all the cognitive indices except Fluid Reasoning between T1 and T2, with further increases in Visual Processing, Crystallised Ability and the Fluid Crystallised index between T2 and T3. In contrast, P06 shows a slight increase in Crystallised Ability between

T1 and T2, no change in scores for Short Term Memory, Fluid Reasoning and the Fluid Crystallised index, and a decrease for Visual Processing and Long Term Storage & Retrieval. Between T2 and T3, P06 decreases on all cognitive indices except Visual Processing and Crystallised Ability where scores increase. Overall, between T1 and T3 P06 decreases on Short Term Memory, Long Term Storage & Retrieval, Fluid Reasoning and the Fluid Crystallised Index, shows no change for Visual Processing and improves on Crystallised Ability, whereas P01 improves on all cognitive indices except Fluid Reasoning. Similarly changes in the motor indices across time are different for these patients. P01 demonstrates very little variation across time, with a small gain for Fine Manual Control, Body Coordination and the Total Motor Composite overall between T1 and T3, no difference for Manual Coordination and a decrease for Strength & Agility. In comparison, P06 decreases in all motor indices between T1 and T3. Taken together, these results suggest that P06 is more severely affected across both cognitive and motor areas of functioning, despite similar prognostic factors. P06 has a shorter interval since diagnosis (33 months) than P01 (77 months) which may account for these differences, although generally more time since treatment is believed to result in a poorer outcome in children with CSI. These two patients highlight the importance of an individual approach to assessment and rehabilitation and emphasises the need for regular follow-up.

Comparison between P02 and P09: For the cognitive indices, these two participants show similar increases between T1 and T2, although they are more marked in P02. These children differ largely in Time Post Treatment (P02=68 months; P09=5 months) and it is therefore slightly unexpected that both children demonstrate an increase in scores, and that it is of a higher magnitude in P02 who has a longer interval post treatment. Between T2 and T3 however, P02 demonstrates a decline for all indices expect Fluid Reasoning whereas P09 shows further improvements in all cognitive indices except Crystallised Ability. Overall therefore between T1 and T3, for Visual Processing, Long Term Storage

& Retrieval, Crystallised Ability and the Fluid Crystallised Index, P09 shows greater gains, as may be expected from their ages at test. This is contrary to the difference illustrated by P01 and P06 in the example above. A similar pattern can be seen for the differences in their motor scores across time. Whilst P02 shows very little change across time, P09 is more variable, with some skills improving between testing sessions. Overall between T1 and T3 P09 improves in Manual Coordination, Strength & Agility and the Total Motor Composite score, whereas P02 decreases on all indices. Both these children are performing within one standard deviation on the test norm mean (i.e. ≥85) across all cognitive indices and within two standard deviations of the test norm mean (i.e. >30) for all motor indices, which suggests their functioning may not have been severely affected by treatment for a cerebellar tumour and that their profiles across time may not reflect that seen for children with more malignant tumours.

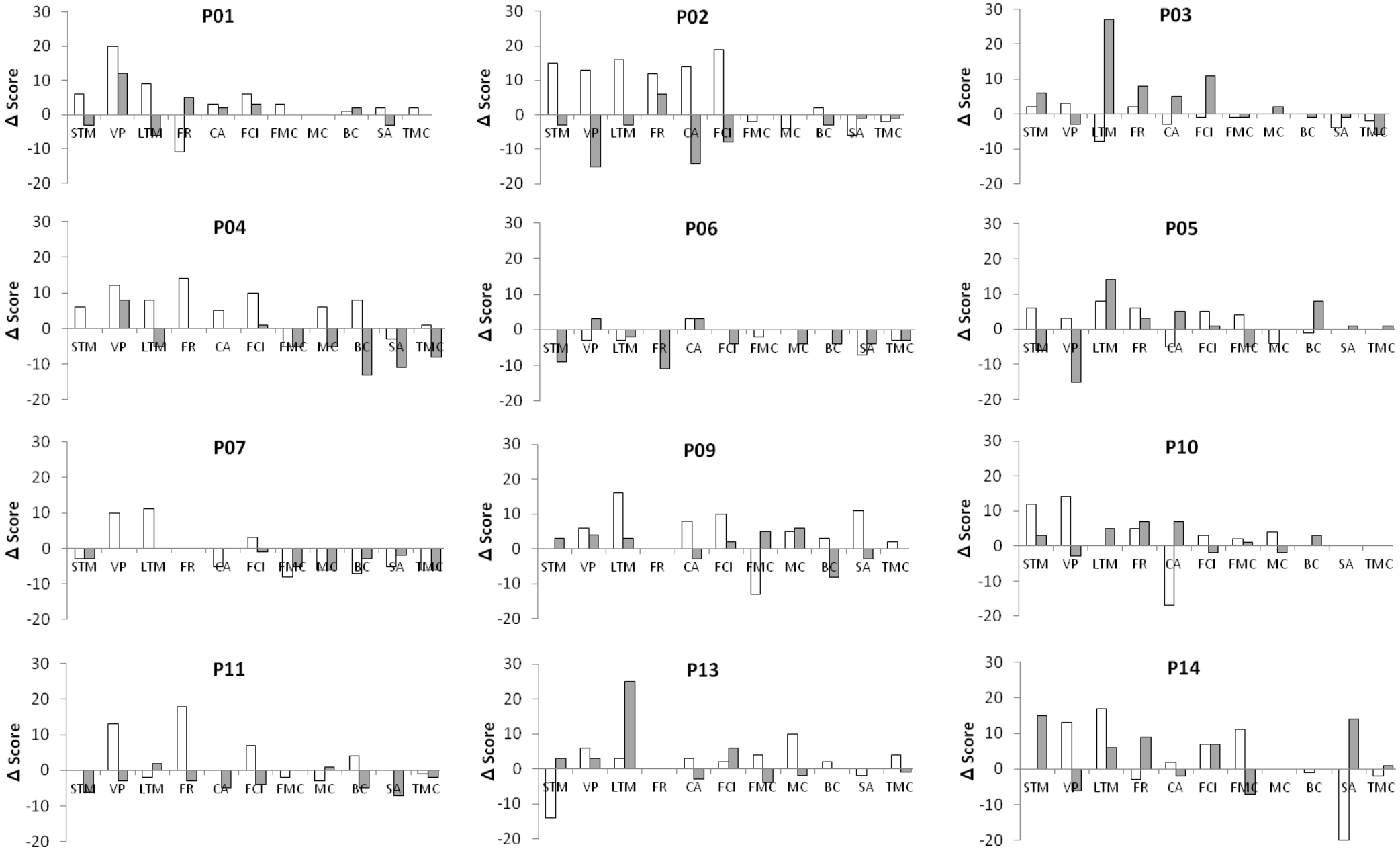


Figure 4.4 Individual profiles of change in scores across the three testing sessions for cognitive and motor score □ **= T2-T1** ■ **= T3-T2**
STM-Short Term memory, VP-Visual Processing, LTM-Long Term Storage & Retrieval, FR-Fluid Reasoning, CA-Crystallised Ability, FCI-Fluid Crystallised Index, FMC-Fine Manual Control, MC-Manual Coordination, BC-Body Coordination, SA-Strength & Agility, TMC-Total Motor Composite

4.3.2 Qualitative differences in longitudinal outcome

The cognitive and motor skills in the patient sample at the first stage of testing (T1) has been demonstrated to be highly interrelated, despite being a highly heterogeneous group (see Chapter 3). Correlations for all time points have been calculated here, as the sample is slightly different due to loss to follow-up. Significant, positive correlations were found for all three time points between the overall cognitive (FCI) and motor (TMC) indices (T1. r=.679, p=.015; T2. r=.866, p<.001; T3. r=.742, p=.006). These coefficients were not found to be significantly different using Fisher's z test (Figure 4.5.1).

In typically-developing children, this relationship between cognitive and motor abilities has been found to be underpinned more specifically by the interrelation of visual processing and fine motor skills, which is thought to remain stable across childhood (see Chapter 2). To establish whether insult to the cerebellum affects the developmental link between these two skills, the correlations between the Visual Processing and Fine Manual Control indices were calculated. Significant positive correlations were found for all time points (T1. r=.668, p=.017; T2. r=.695, p=.012; T3. r=.777, p=.003) with no significant differences found between the coefficients (Figure 4.5.2).

To further investigate whether the changes in patient scores in the cognitive and motor domains were comparable to those of the controls, children were grouped according to whether they improved in both domains (patient N=4, control N=5), improved on the cognitive overall index (FCI) and decreased on the motor cognitive index (TMC) (patient N=6, control N=12), decreased on FCI and improved on TMC (patient N=0, control N=8), or decreased in both domains (patient N=1, control N=12). Comparison between frequencies for the patient and control children revealed no significant difference (χ^2=4.257, p=.235), suggesting that the pattern of change across the cognitive and motor domains was not significantly different for the patient participants than for the typically-developing children. Combined with the findings from Chapter 3, these

results suggest that Model 1 may not be an accurate representation of the data and that the change in scores across time in the patient group may not be qualitatively different from that seen in typically-developing children.

Figure 4.5.1 Correlations between cognitive (FCI) and motor (TMC) functioning in the patient sample across separate time points

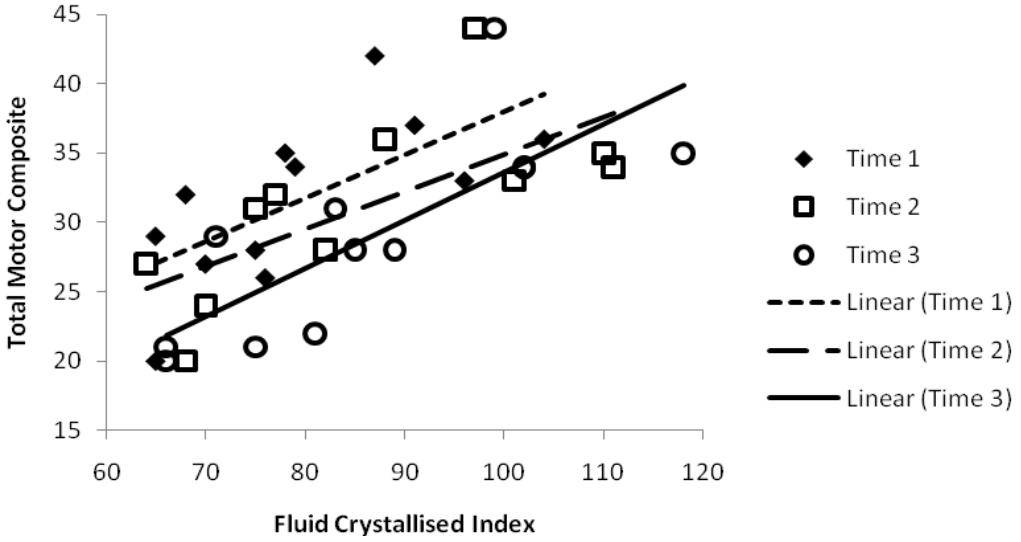
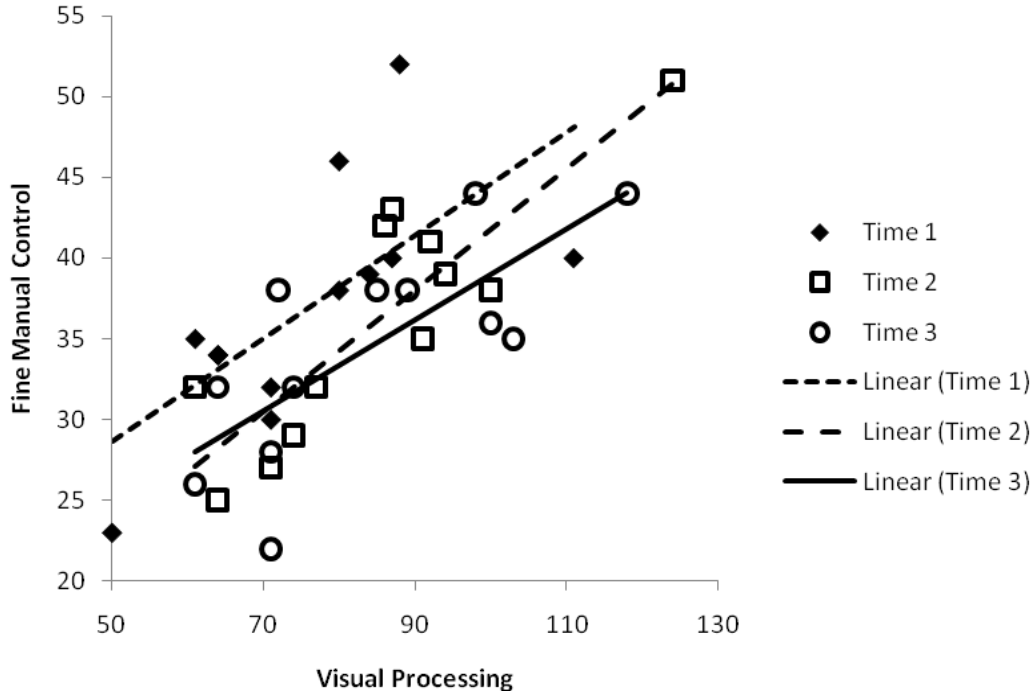


Figure 4.5.2 Correlations between Visual Processing and Fine Manual Control in the patient sample across separate time points



4.3.3 Quantitative differences in longitudinal outcome between patients and controls; standard scores

Evidence for each of the quantitative models outlined above was considered using both standard and raw scores. Initially, for each cognitive and motor index separately the number of children whose standard score improved, declined or remained the same was determined, and the frequency for the patient sample was compared to that of the control group using chi square analyses (Table 4.4). Significant differences in frequency of distribution across the three outcome groups (i.e. improved, declined, or remained the same) were found between the control and patient groups for the Long Term Storage & Retrieval and Fluid Crystallised Index cognitive indices. No significant differences in the frequencies were observed for the motor indices. Subsequent pairwise analysis revealed that for Long Term Storage & Retrieval the patient group had a significantly higher proportion of children with increased scores than in the control group ($z=2.552$, $p=.011$). The same pattern was found for the FCI index with significantly higher proportion of patients improving than in the control group ($z=2.924$, $p=.004$) and a higher proportion of control children showing a decrease in scores over time than in the patient group $z=2.652$, $p=.008$). For these indices therefore, a higher proportion of the patient sample demonstrated an increase in standard score across time than would be expected based on the typically-developing group.

It is interesting that this result was found for the overall cognitive index (FCI), which may be viewed as comparable to the full scale IQ scores reported in many previous studies, but that it is not a universal pattern seen across all cognitive indices measured in this study. The larger proportion of patient participants who demonstrated an increase in FCI over time compared to the control groups suggests that Model 3b may account for many children in this sample. However it should be noted that the individual analyses highlighted that some patient's scores were found to decrease or remain constant, suggesting

that different aspects of Model 3 or Models 2a, b or c may be better able to account for the developmental progression of some children following cerebellar tumour. Again, using standard scores alone, it was not possible to determine which may be the more appropriate of these two models.

Table 4.4 Comparison of frequency of children whose index scores increase, decrease or remain constant over time in the patient (P) and control (C) groups

	Index	Group	Frequency of children			$\chi^2_{(2)}$	p
			Increase	Decrease	Same		
KABC-II	Short Term Memory	P	7	4	1	2.14	.342
		C	15	22	4		
	Visual Processing	P	8	2	2	2.97	.227
		C	19	18	4		
	Long Term Storage & Retrieval	P	10	1	1	7.05	.030
		C	17	20	4		
	Fluid Reasoning	P	7	2	0	2.38	.304
		C	12	13	0		
	Crystallised Ability	P	5	3	4	4.44	.109
		C	18	19	4		
	Fluid Crystallised index	P	11	1	0	8.57	.014
		C	18	21	2		
BOT-2	Fine Manual Control	P	3	8	1	1.44	.487
		C	18	21	2		
	Manual Coordination	P	5	5	2	3.60	.166
		C	22	18	1		
	Body Coordination	P	4	8	0	.934	.627
		C	13	25	3		
	Strength & Agility	P	2	9	1	1.28	.526
		C	14	26	1		
	Total Motor Composite	P	4	7	1	.018	.991
		C	13	25	3		

The magnitude of change for the patient and control groups was compared by examining the difference values between each participant standard scores at T1 and T2. Results revealed a significant difference between the

patient and control groups for Long Term Storage & Retrieval (z=-2.99, *p*=.002) and the FCI index (z=-2.94, *p*=.003) of the cognitive indices, with the patients demonstrating a larger gain in scores over time than the control children (Figure 4.3). No significant differences were found for the difference scores between the two groups for the motor indices (Figure 4.4).

Figure 4.6 highlights that for the cognitive indices, no significant differences were found between the T1 and T2 scores for the control participants using Wilcoxon signed rank tests, in line with expectations of standardised measures. In contrast, a significant increase was seen in the patients for Long Term Storage & Retrieval (z=-2.63, *p*=.006) and the FCI (z=-2.75, *p*=.003), a trend towards a significant increase was seen for Visual Processing (z=-1.89, *p*=.063) and Fluid Reasoning (z=-1.90, *p*=.059) and no difference was seen for Short Term Memory and Crystallised Ability which remained stable over time.

Figure 4.7 demonstrates that whilst some of the mean control standard scores for the motor indices remained stable with time, others decreased with time. In particular a significant decline was found between T1 and T2 in the control standard scores for Body Coordination (z=-2.13, *p*=.033), Strength & Agility (z=-1.88, *p*=.030) and the Total Motor Composite (z=-2.09, *p*=.036). This has important implications when interpreting the results of the patient sample as any decrease may be a product of the test, rather than an increasing deficit in the patient participants. In contrast, the only significant decrease for the patient sample was for the Strength & Agility subtest (z=-2.01, *p*=.044).

Figure 4.6 Standard scores on the cognitive indices at T1 and T2 (T3) for patients and controls Control ——— Patient ·····

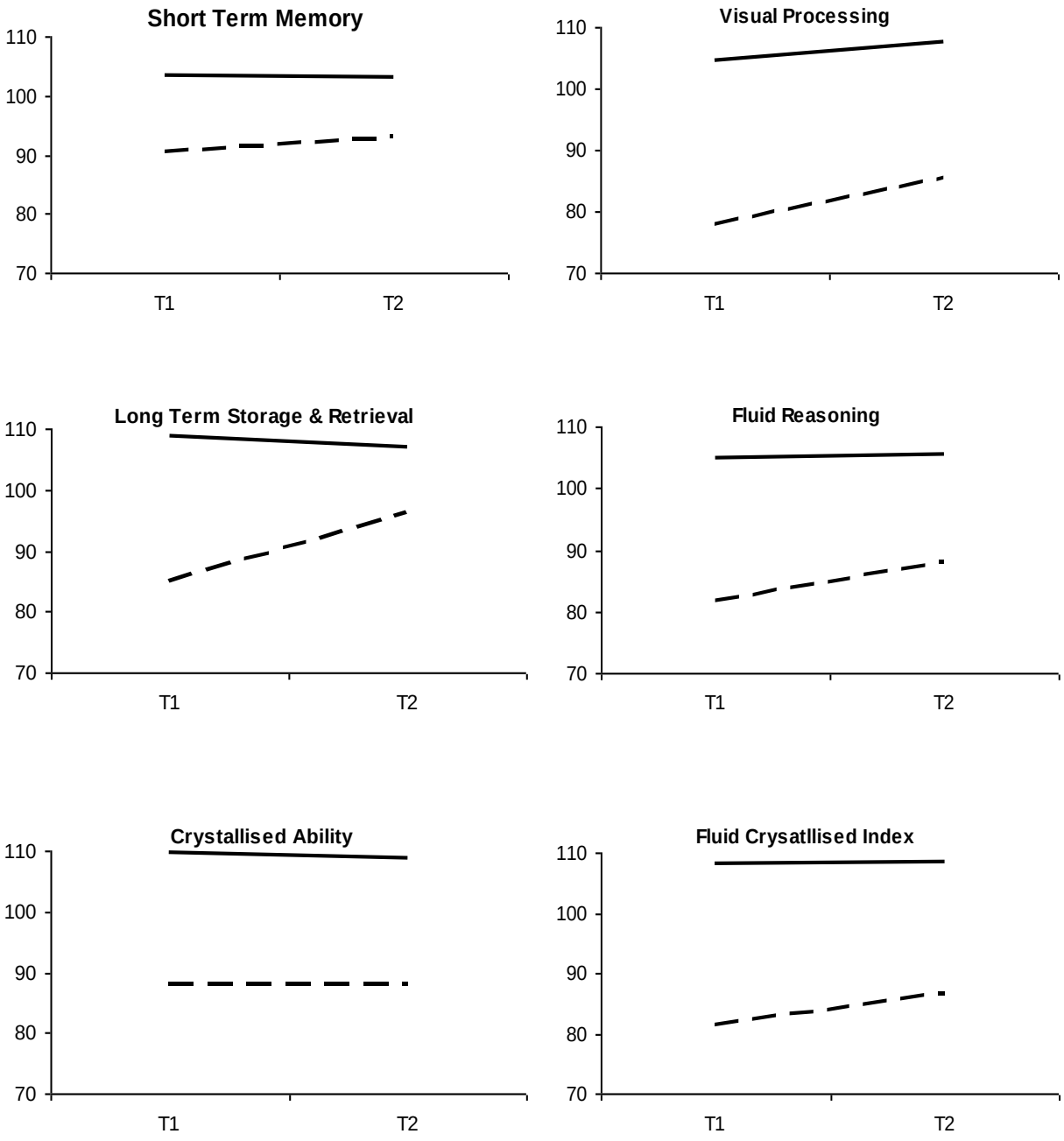
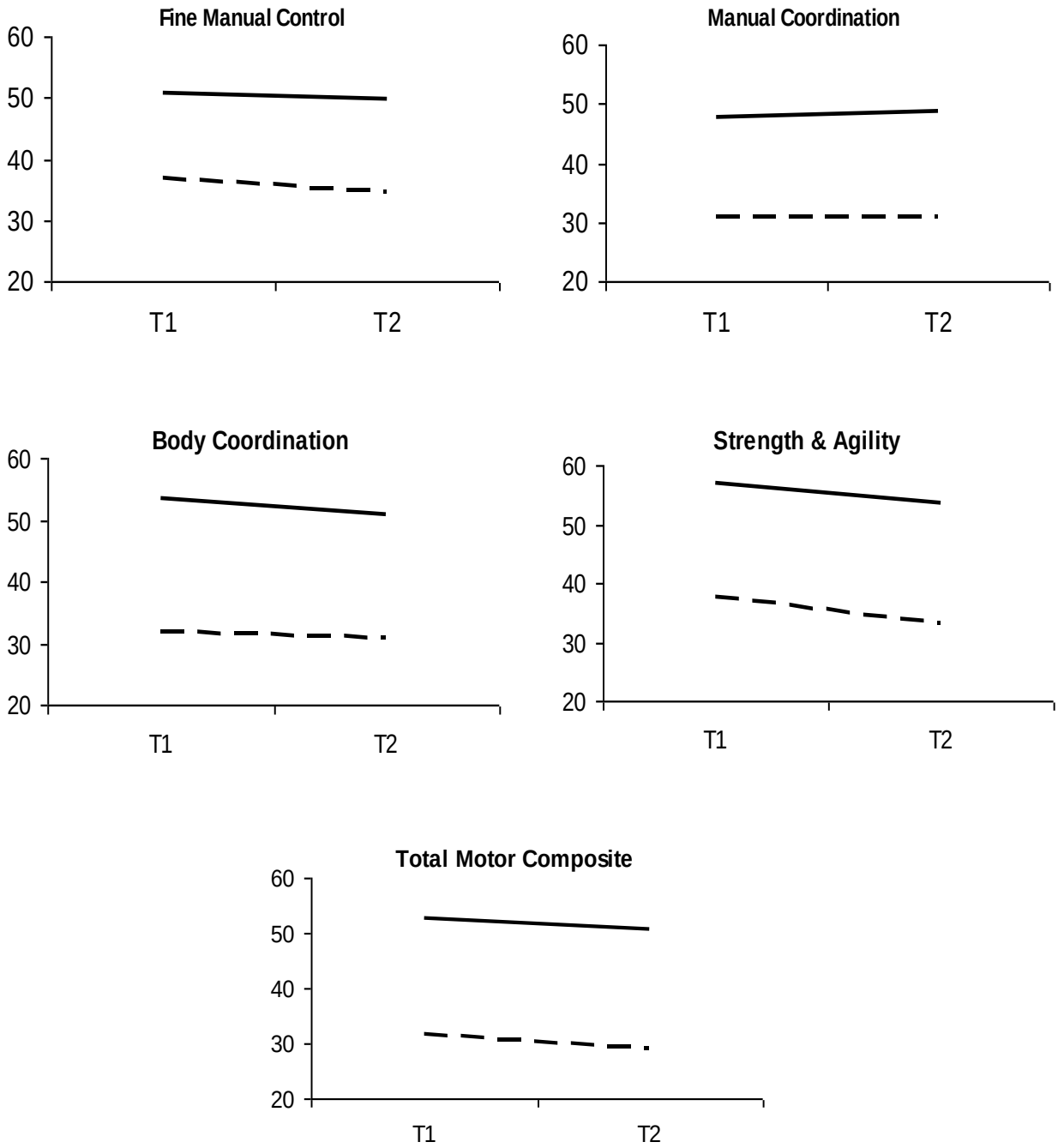


Figure 4.7 Standard scores on the motor indices at T1 and T2 (T3) for patients and controls **Control** —— **Patient** ·····



4.3.4 Quantitative differences in longitudinal outcome between patients and controls; raw scores

The same analyses as reported in the previous section were repeated for the raw scores of the subtests of the standardised measures. As only the core subtests were administered to the typically-developing sample (see Chapter 2, Figure 2.1) only the core subtests were included in this analysis. Children were divided into groups depending on whether their raw scores increased, decreased or remained constant over time, and the frequencies for the patient and control participants across these different outcome groups were compared (Table 4.5).

Similarly to the index standard scores reported above, for many of the subtest raw scores the proportions of children improving, declining or remaining the same were not found to differ significantly between the patient and control samples with the exception of Upper Limb Coordination from the BOT-2. Subsequent pairwise comparisons suggested that for Upper Limb Coordination a significantly higher proportion of the control children increased scores over time than in the patient group ($z=2.923$, $p=.004$) whereas a significantly higher proportion of the patient group remained constant over time than in the control group ($z=2.602$, $p=.01$).

These results suggest that for most of the skills measured in this study, the proportion of patients who decreased, increased or remained the same in raw scores, for both cognitive and motor skills, was not significantly different than in the control group. For these measures, this similarity between the two groups suggests that developmental progression in the patients is comparable to that seen in typically-developing children. These results suggest that Models 3a, b or c may be most applicable, as patients are not significantly differing from a typical developmental progression. For the motor measure in which a difference was observed, it was found that a higher proportion of the control group improved whilst a higher proportion of the patients remained the same. This suggested that a higher proportion of patients are failing to progress at a typical

rate than would be expected based on a typical population. For this subtest therefore, it may be that Models 2a, b or c may be most appropriate. To further distinguish between these models raw and standardised scores must be considered in conjunction and this is addressed in the discussion.

Table 4.5 Comparison of frequency of children whose subtest scores increase, decrease or remain constant over time in the patient (P) and control (C) groups

	Index	Subtest	Group	Frequency of children			$\chi^2_{(2)}$	p
				Increase	Decrease	Same		
KABC-II	Short Term Memory	Number Recall	P	9	2	1	1.20	.549
			C	25	7	9		
		Word Order	P	8	4	0	3.77	.152
			C	28	6	7		
	Visual Processing	Rover	P	6	4	0	4.55	.103
			C	34	5	2		
		Triangles	P	11	1	0	1.41	.494
			C	35	2	4		
	Long Term Storage & Retrieval	Atlantis	P	9	3	0	.657	.720
			C	28	11	2		
		Rebus	P	11	1	0	3.64	.162
			C	26	11	4		
		Atlantis Delayed	P	8	1	1	.209	.901
			C	30	6	5		
		Rebus Delayed	P	9	1	0	3.25	.197
			C	25	10	6		
	Fluid Reasoning	Story Completion	P	9	0	1	.888	.642
			C	21	2	2		
		Pattern Reasoning	P	8	2	0	1.86	.394
			C	36	3	2		
	Crystallised Ability	Verbal Knowledge	P	10	1	1	.303	.859
			C	22	2	1		
		Riddles	P	10	1	1	1.10	.577
			C	28	8	5		
BOT-2	Fine Manual Control	Fine Motor Precision	P	7	4	1	1.11	.603
			C	29	8	4		
		Fine Motor Integration	P	9	3	0	1.80	.407
			C	29	7	5		
	Manual Coordination	Manual Dexterity	P	10	1	1	.553	.758
			C	31	7	3		
		Upper Limb Coordination	P	7	2	3	9.26	.010
			C	38	2	1		
	Body Coordination	Bilateral Coordination	P	7	3	2	.102	.950
			C	26	9	6		
		Balance	P	5	4	3	2.29	.318
			C	25	12	4		
	Strength & Agility	Running Speed & Agility	P	7	3	2	1.00	.606
			C	28	10	3		
		Strength	P	3	7	2	5.35	.069
			C	25	14	2		

The difference raw values between T1 and T2 scores on each subtest were compared for each group chi square analyses. For the cognitive subtests results revealed a significant difference for Rebus (z=-2.44, *p*=.014) and the Rebus Delayed only (z=-2.99, *p*=.002), with the patients demonstrating a larger gain in scores over time than the control children (Figure 4.8). For the motor subtests a significant difference was found for Fine Motor Precision (z=-2.206, *p*=.026), Upper Limb Coordination (z=-2.50, *p*=.011) and Strength (z=-2.49, *p*=.011), with the patients demonstrating a greater decline in scores over time (Figure 4.9).

Comparisons between the patient and control scores at each time point separately revealed that at T1 significant differences were found between the two groups for the Rebus (z=-3.13, *p*=.001) and Rebus Delayed (z=-2.660, *p*=.007) subtests of the KABC-II. At T2, no significant differences were found between the patient and control groups for any of the cognitive subtests. Due to the differences in ages between the control and patient groups, the actual raw score values do not provide much information, however the pattern of change suggests that for the cognitive subtests the patient group appear to be progressing at a comparable rate to the control children. Indeed for those subtests on which patients were initially significantly poorer (Rebus & Rebus Delayed) the results suggest that the patients may actually be gaining points at a faster rate than the control children.

For the motor subtests significant differences were found between control and patient performance on the motor subtests at both T1 (max. z=-5.21, *p*<.001; min. z=-2.07, *p*=.038) and T2 (max. z=-5.24, *p*<.001; min. z=-2.51, *p*=.011) with the patients achieving lower scores. The exception to this pattern was the Strength subtest, for which patients were not found to differ from controls at T1 (z=-1.62, *p*=.107), but were performing significantly below controls at T2 (z=-1.62, *p*<.001).

Wilcoxon signed rank tests highlighted that for the control group, significant increases in raw scores were found for all cognitive (max. z=-5.15, p<.001; min. z=-2.29, p=.003) and motor (max. z=-5.33, p<.001; min. z=-2.10, p=.035) subtests between T1 and T2. For the cognitive subtests, a similar pattern was found for the patient group with significant gains in raw scores for all subtests (max. z=-2.75, p=.003; min. z=-2.12, p=.039) except Rover and Word Order. For the motor subtests however, no significant differences were found in performance across time, with the exception of Manual Dexterity (z=-2.14, p=.033). These results suggested that for the majority of the cognitive subtests the patients are improving across time, whereas scores on most of the motor subtests are remaining constant and not progressing similarly to the control sample.

Figure 4.8 KABC-II subtest raw scores for Time 1 and Time 2 to compare control and patient groups with individual patient scores included
Control mean —— Patient mean – – Individual scores —

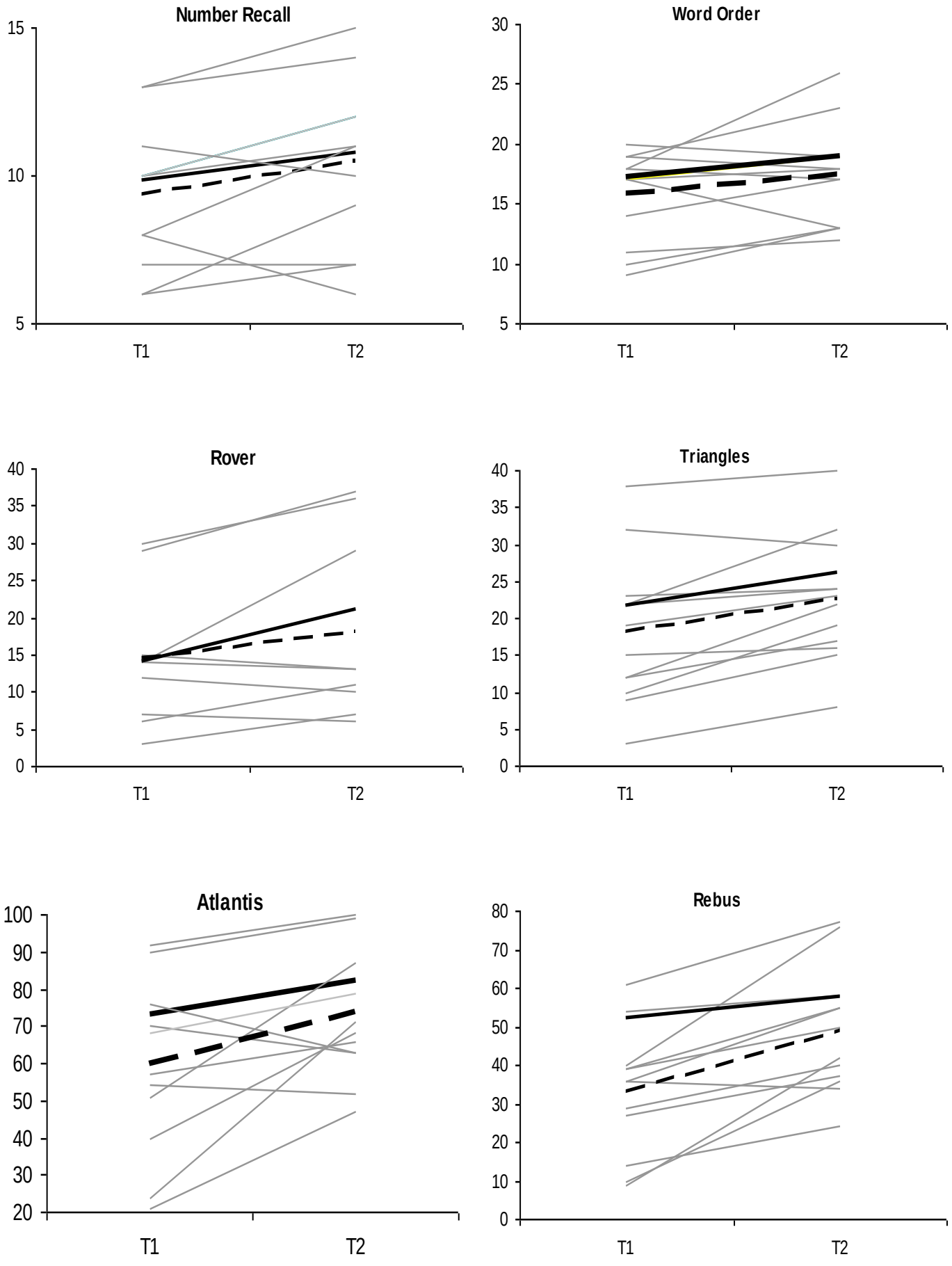


Figure 4.8 Continued

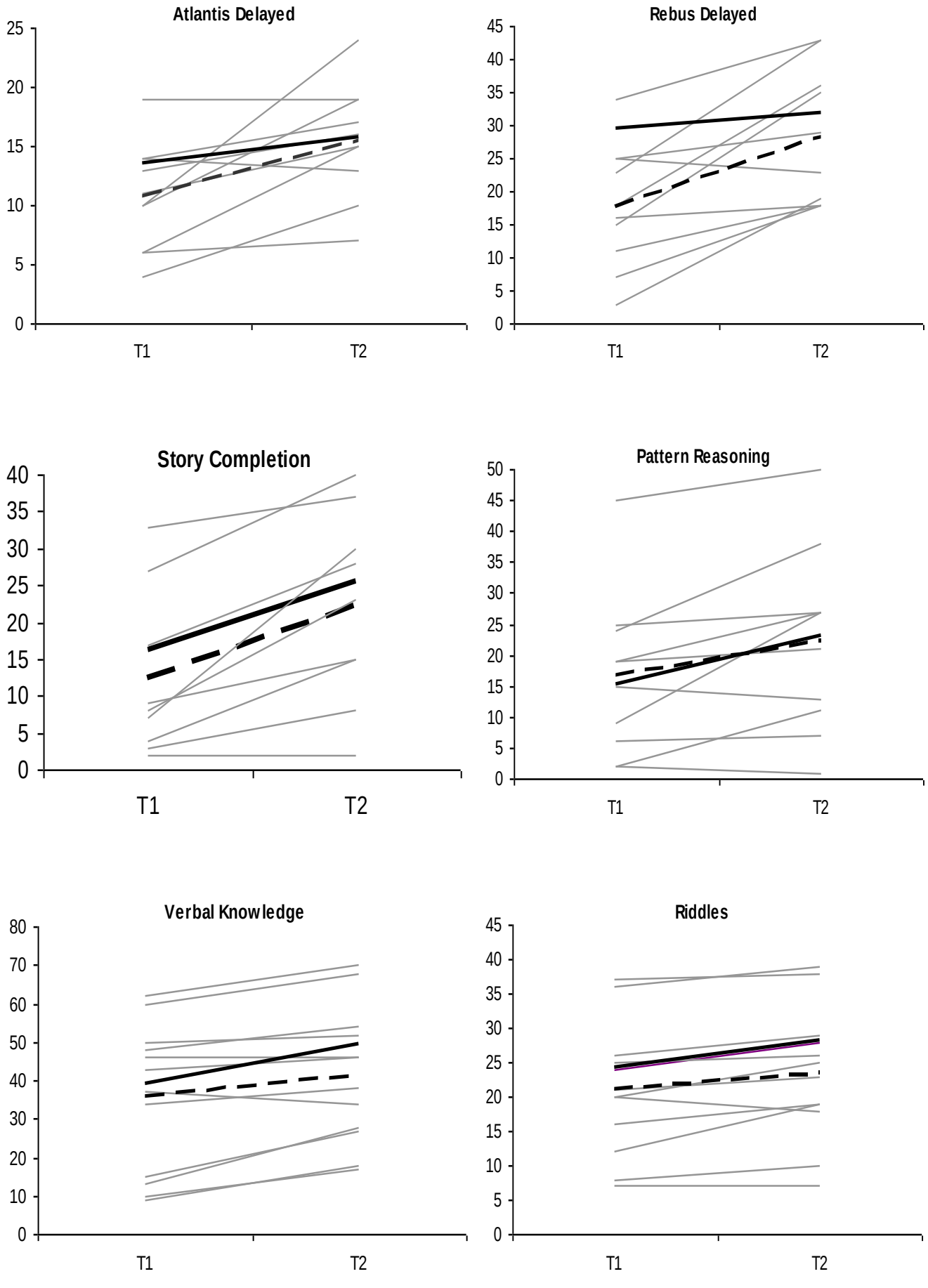
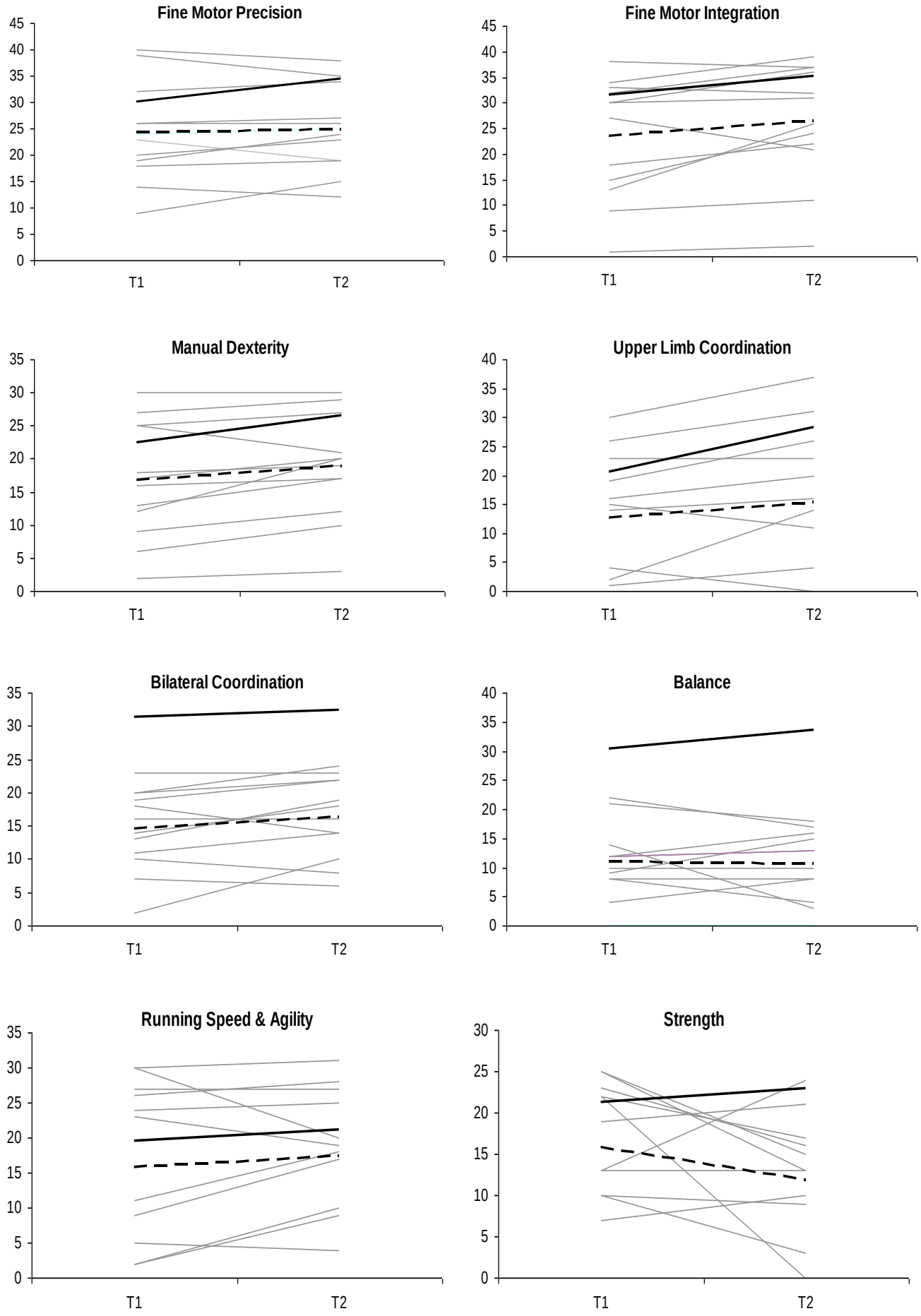


Figure 4.9 BOT-2 subtest raw scores for Time 1 and Time 2 to compare control and patient groups with individual patient scores included
Control mean —— Patient mean – – Individual scores



4.3.5 Index standard score comparisons across time for the patient group

The previous analyses suggest that a general trend seems to be present in the patient scores as standard scores appear to be increasing for the cognitive measures and decreasing for the motor measures. This section examines patient standard and raw scores for three time points to establish whether this general pattern was consistent across all three assessments.

4.3.5.1 Standard scores

Scores on the gross cognitive measure (FCI) were found to change significantly over the three testing sessions (χ^2=11.79, p=.002). Pairwise analyses suggested that FCI improved significantly from T1 to T2 (z=-2.85, p=.002, T=1, r_{T1-T2}=-.58) but there was no significant difference between the scores at T2 and T3 (z=-.51, p=.635, T=32.5, r_{T2-T3}=-.10). A significant difference was also found across time for the Visual Processing index (χ^2=8.93, p=.009). Subsequent pairwise analyses found a significant improvement from T1 to T2 (z=-2.91, p=.002, T=2, r_{T1-T2}=-.60) and no significant change between T2 and T3 (z=-.36, p=.737, T=29, r_{T1-T2}=-.07). Scores for the Long Term Storage & Retrieval index were found to improve across the testing sessions (χ^2=7.64 p=.019) and pairwise analyses revealed a significant increase between T1 and T3 (z=-2.63, p=.006, T=3, r_{T1-T2}=-.53) but with no other differences following Bonferroni correction. No significant changes were found across the different time points for Short Term Memory, Fluid Reasoning and Crystallised Ability. These results are summarised in Table 4.6 and Figure 4.10.

The overall motor score (TMC) was not found to significantly alter across time (χ^2=2.39, p=.303) despite a trend towards decreasing attainment with time (gradient=-1.33). Similarly, no significant alterations with time were found for Fine Manual Control (χ^2=3.12, p=.218), Manual Coordination (χ^2=.222, p=.908) and Body Coordination (χ^2=2.65, p=.284). A significant decrease in scores was noted for Strength & Agility (χ^2=7.66, p=.018). No pairwise comparisons

reached significance following Bonferroni correction, although the trend suggested that the greatest difference was between T1 and T3 (z=-2.01, *p*=.044). These results are summarised in Figure 4.11.

Table 4.6 Analysis of individual cognitive and motor indices across time for all patients. After Bonferroni correction α=.025 for pairwise comparisons (r=effect size)

	Index	Friedman's ANOVA between T1, T2 & T3		Wilcoxon signed rank tests			
		Chi	p	Pair	z	p	r
Cognitive Ability (KABC-II)	Short Term Memory	1.857	.412	-	-	-	-
	Visual Processing	8.933	.009	T1-T2	-2.913	.002	.60
				T2-T3	-.359	.737	
				T1-T3	-1.891	.063	
	Long Term Storage & Retrieval	7.644	.019	T1-T2	-2.185	.028	.45
				T2-T3	-1.336	.205	
				T1-T3	-2.627	.006	.54
	Fluid Reasoning	4.765	.088	-	-	-	-
	Crystallised Ability	.927	.671	-	-	-	-
	Fluid Crystallised Index	11.787	.002	T1-T2	-2.849	.002	.58
				T2-T3	-.511	.635	
				T1-T3	-2.747	.003	.56
Motor Ability (BOT-2)	Fine Manual Control	3.116	.218	-	-	-	-
	Manual Coordination	.222	.908	-	-	-	-
	Body Coordination	2.651	.284	-	-	-	-
	Strength & Agility	7.659	.018	T1-T2	-1.541	.137	
				T2-T3	-1.585	.127	
				T1-T3	-2.005	.044	.32
	Total Motor Composite	2.390	.330	-	-	-	-

Figure 4.10 Mean cognitive standard scores for all patients across T1, T2 and T3 for each index. Significant differences are marked * m is the gradient of slope

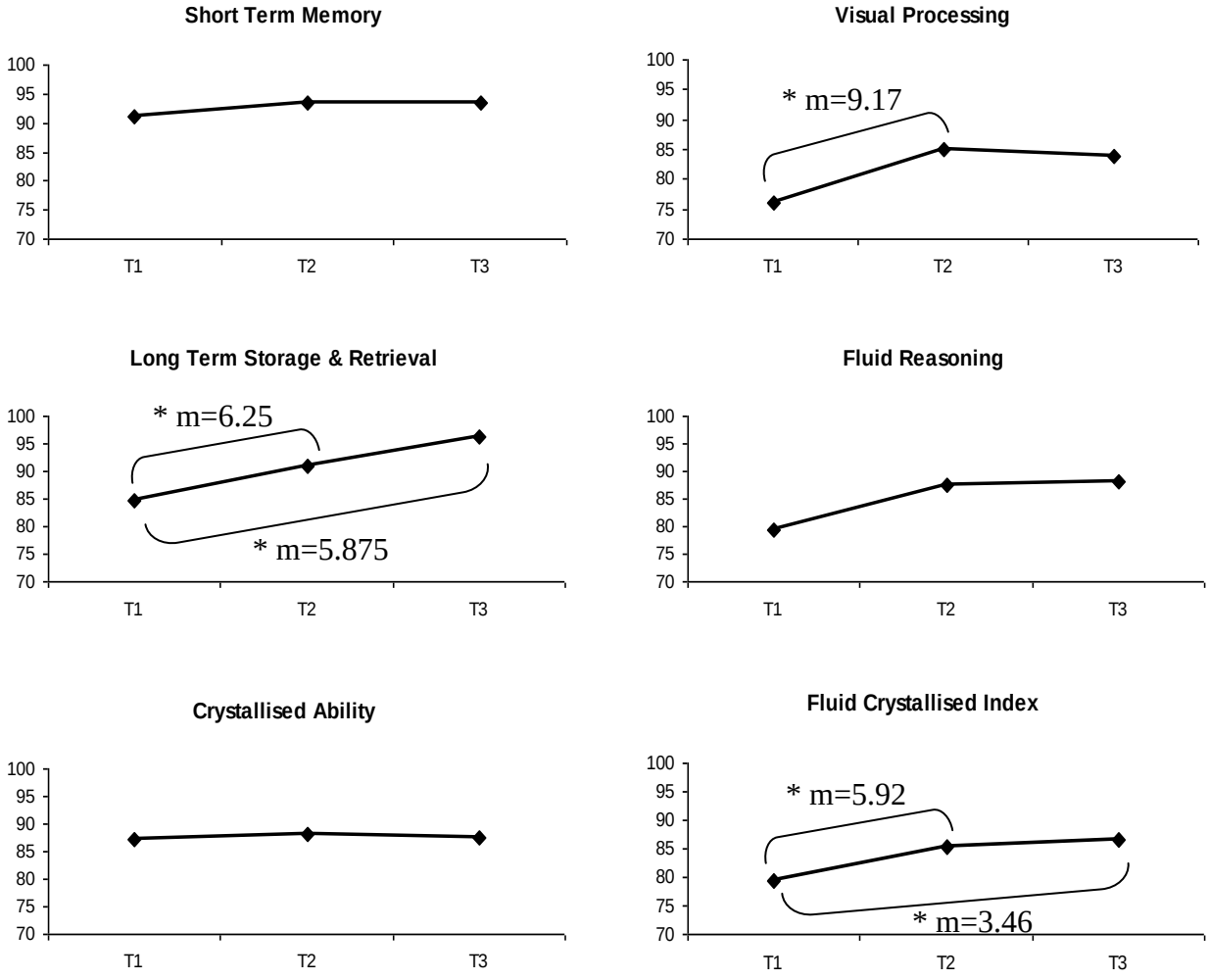
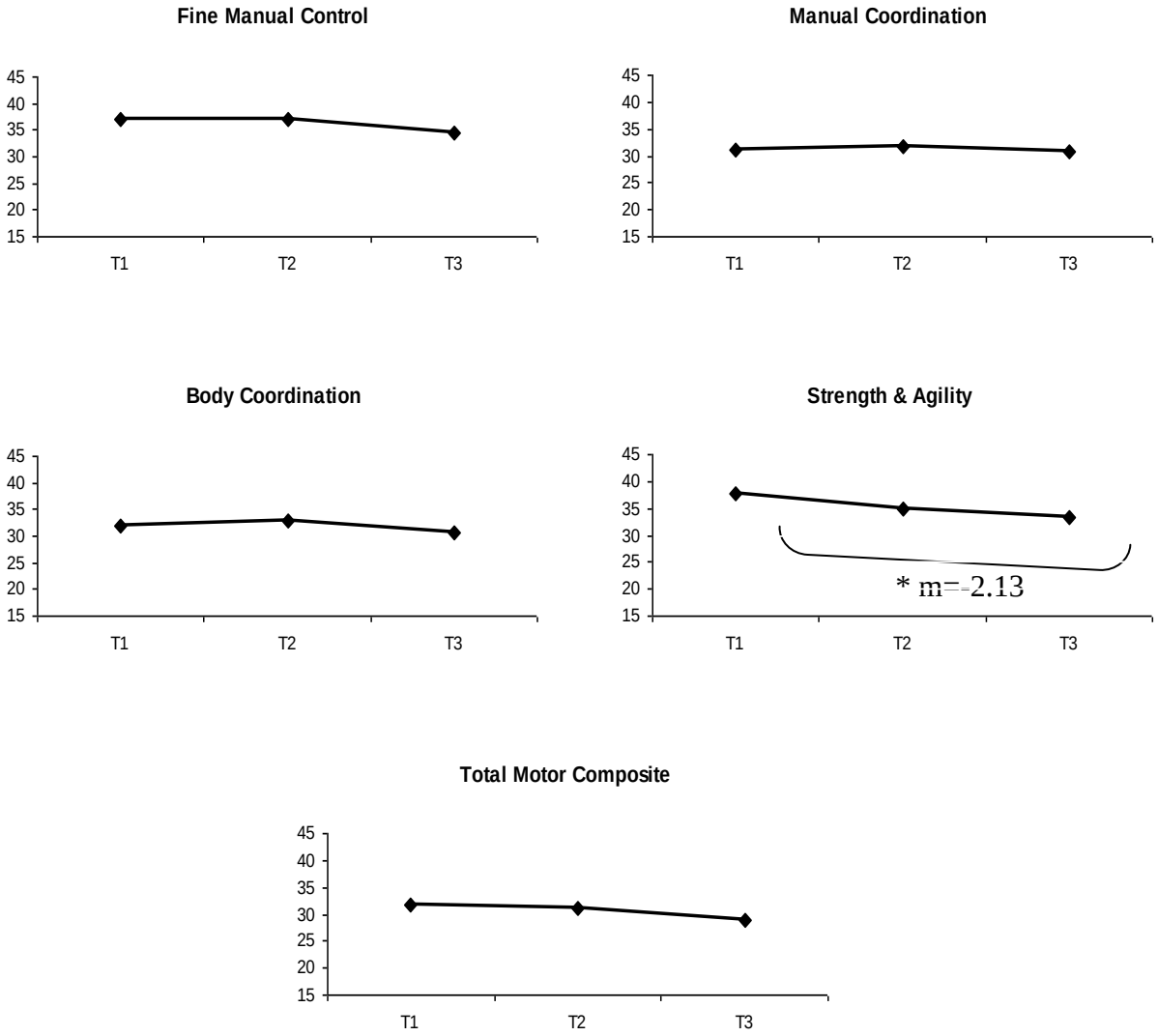


Figure 4.11 Mean motor standard scores for all patients across T1, T2 and T3 for each index. Significant differences are marked * m is the gradient of the slope



4.3.5.2 Raw scores

A significant main effect of time was found in the patient sample for most of the cognitive subtests (see Table 4.7). Pairwise analyses revealed that all main effects were in a positive direction with raw scores increasing with time. Unlike the standardised scores significant increases were shown between both T1-T2 and T2-T3 suggesting that raw scores continue to increase even though standard scores show no significant improvement.

A significant main effect of time was found for only one of the motor subtests, Manual Dexterity ((χ^2=8.773, *p*=.010). Subsequent pairwise analyses revealed a significant increase between T1 and T2 (z=-2.63, *p*=.006, T=3, r_{T1-T2}=-.53) and between T1 and T3 (z=-2.63, *p*=.006, T=3, r_{T1-T2}=-.53). None of the other subtests were found to alter significantly with time, although scores were found to increase across time for all subtests except Balance and Strength, which decreased with time. These results are summarised in Table 4.8.

Table 4.7 Analysis of individual raw scores for the cognitive subtests of the KABC-11 across time for all participants. After Bonferroni corrections α=.025 for pairwise comparisons, r=effect size

Index	Subtest	Friedman's ANOVA between T1, T2 & T3		Wilcoxon signed rank tests			
		Chi	p	Pair	z	p	r
Short Term Memory	Number Recall	2.783	.252	T1-T2	-1.979	.055	0.40
				T2-T3	-.276	.786	
				T1-T3	-2.122	.039	0.43
	Word Order	1.714	.463	-	-	-	-
	Hand Movements	.133	.959	-	-	-	-
Visual Processing	Triangles	12.977	.001	T1-T2	-2.347	.016	0.48
				T2-T3	-1.131	.289	
				T1-T3	-2.753	.003	0.56
	Rover	.400	.886	-	-	-	-
	Block Counting	2.324	.330	-	-	-	-
	Gestalt Closure	15.167	<001	T1-T2	-1.898	.057	0.39
				T2-T3	-2.655	.005	0.54
				T1-T3	-2.126	.028	0.43
Long Term Storage & Retrieval	Atlantis	2.783	.252	-	-	-	-
	Rebus	14.217	<.001	T1-T2	-2.714	.004	0.55
				T2-T3	-2.492	.010	0.51
				T1-T3	-2.984	.001	0.61
	Atlantis Delayed	6.703	.033	T1-T2	-1.071	.160	
				T2-T3	-1.993	.023	0.41
				T1-T3	-2.494	.012	0.51
	Rebus Delayed	9.800	.006	T1-T2	-1.581	.063	
				T2-T3	-2.237	.023	0.46
				T1-T3	-2.654	.006	0.54
Fluid Reasoning	Pattern Reasoning	4.421	.113	-	-	-	-
	Story Completion	11.371	.001	T1-T2	-2.492	.012	0.60
				T2-T3	-2.349	.016	0.48
				T1-T3	-2.524	.008	0.52
Crystallised Ability	Expressive vocabulary	10.714	.003	T1-T2	-1.314	.195	
				T2-T3	-1.425	.188	
				T1-T3	-2.988	.001	0.61
	Verbal Knowledge	8.468	.012	T1-T2	-1.258	.225	
				T2-T3	-2.201	.025	0.45
				T1-T3	-2.713	.004	0.55
	Riddles	11.128	.002	T1-T2	-1.615	.109	
				T2-T3	-1.620	.117	
				T1-T3	-2.590	.007	0.53

Table 4.8 Analysis of individual raw scores for the motor subtests of the BOT-2 across time for all participants. After Bonferroni corrections α=.017 for pairwise comparisons, r=effect size

Index	Subtest	Friedman's ANOVA between T1, T2 & T3		Wilcoxon signed rank tests			
		Chi	p	Pair	z	p	r
Fine Manual Control	Fine Motor Precision	.326	.890	-	-	-	-
	Fine Motor Integration	4.136	.140	-	-	-	-
Manual Coordination	Manual Dexterity	8.773	.010	T1-T2 T2-T3 T1-T3	-2.416 -.313 -2.144	.016 .820 .033	0.50 0.44
	Upper Limb Coordination	1.40	.525	-	-	-	-
Body Coordination	Bilateral Coordination	4.227	.120	-	-	-	-
	Balance	.190	.924	-	-	-	-
Strength & Agility	Running Speed & Agility	.667	.763	-	-	-	-
	Strength	.905	.672	-	-	-	-

4.3.6 Impact of prognostic factors

The statistical results for relationships between the difference prognostic factors and the change in scores between T1, T2 and T3 are detailed in Table 4.9. The correlations between Age at Diagnosis and the gradient between all three time points revealed no significant interrelations for any of the cognitive (maximum: r=.591, p=.043) or motor (maximum: r=.141, p=.663) indices following Bonferroni correction. The correlations performed between Age at Diagnosis and the difference in scores between T1-T2 yielded no significant results for the cognitive (maximum: r=-.546, p=.066) or motor (maximum: r=-.234, p=.465) indices. Similarly, the difference scores between T2-T3 were not significantly correlated with the cognitive (maximum: r=.342, p=.276) or motor (maximum: r=-.338, p=.282) indices. No significant differences were found between Age at Diagnosis and the difference in raw scores calculated between T1-T3 for the cognitive (maximum: r=.554, p=.063) or motor subtests (maximum: r=.454, p=.138).

The correlation between Time Post Treatment and the gradient between the scores for each time point was not found to be significant for any of the cognitive (maximum: r=.498, p=.100) or motor (maximum: r=-.483, p=.112) indices. The correlations performed between Time Post Treatment and the difference in scores between T1-T2 (cognitive maximum: r=-.-.403, p=.194; motor maximum: r=-.400, p=.197) and T2-T3 (cognitive maximum: r=-.282 p=.374; motor maximum: r=.343, p=.243) also yielded no significant results. Correlation between the difference in raw scores calculated between T1-T3 and Time Post Treatment revealed no significant differences for the cognitive subtests (maximum: r=-.598, p=.059). The relationship between this factor and the motor raw scores however was found to be significant for several of the subtests; Fine Motor Integration (r=-.648, p=.023), Manual Dexterity (r=-.770, p=.003), Balance (r=-.613, p=.023) and Strength (r=-.761, p=.004), with a longer time since treatment resulting in a larger negative difference.

Tumour Type/Treatment group was not found to significantly affect the change in scores across time, as measured by the gradient between T1, T2 and T3 time points for cognitive (maximum: $H_{(4)}$=6.82, *p*=.098) or motor (maximum: $H_{(4)}$=5.60, *p*=.220) scores. Tumour Type/Treatment group did not significantly affect the difference in scores between T1-T2 (cognitive maximum: $H_{(4)}$=7.41, *p*=.057; motor maximum: $H_{(4)}$=5.23, *p*=.270), or between T2-T3 scores (cognitive maximum: $H_{(4)}$=5.02, *p*=.306; motor maximum: $H_{(4)}$=6.13, *p*=.161).

Hydrocephalus was not found to significantly affect the change in scores across time as measured by the gradient between T1, T2 and T3 time points for cognitive (maximum: $H_{(4)}$=2.86, *p*=.502) or motor (maximum: $H_{(4)}$=6.10, *p*=.05) scores. No significant differences were found between Hydrocephalus groups for differences in scores between T1-T2 (cognitive maximum: $H_{(4)}$=4.44, *p*=.181; motor maximum: $H_{(4)}$=4.58, *p*=.176) and T2-T3 (cognitive maximum: $H_{(4)}$=5.20, *p*=.097; motor maximum: $H_{(4)}$=3.20, *p*=.408)

No effect of sex was found on the change in scores over time (cognitive maximum: z=-1.79, *p*=.085; motor maximum: z=-1.54, *p*=.149 or for the difference scores between T1-T2 (cognitive maximum: z=-1.65, *p*=.113 ; motor maximum: z=-1.03 , *p*=.360) or T2-T3 (cognitive maximum: z=-1.19 ,*p*=.283 ; motor maximum: z=-.854, *p*=.444).

Tumour location was found to affect the change in scores over time for the Short Term Memory index ($H_{(2)}$=.631, *p*=.018). Pairwise analyses revealed that the children with vermis and right hemisphere involvement improved across the testing sessions, whereas the children with vermis involvement only declined slightly (z=-2.33, *p*=.024) although this difference was not found to be significant following Bonferroni correction and should therefore be interpreted with caution. Tumour location was not found to affect difference in scores across time for any other cognitive or motor indices.

Given the variability across individual patients, it is possible to suggest that the magnitude of variation across time may be linked to the overall ability of the child. For example, if a child is performing close to baseline on a measure this may be due to a failure in acquiring the necessary skills during development to scaffold performance on that measure and consequently no longitudinal change would be expected. Additionally, if a child is performing within the typical range for their age group there would be no reason to expect longitudinal change, given that cognitive capacity is postulated to remain constant relative to age.

Correlations were performed between the overall cognitive (FCI) and motor (TMC) scores at T1 and the gradient of change seen for each participant over time on FCI and TMC (Figure 4.12). Scores from the first testing session were entered, as it is informative to establish whether baseline measures can be used to predict changes in performance over time. Neither correlation was found to be significant (FCI, r=.561, p=.058; TMC, r=-.086, p=.790), although the correlation with FCI approached significance, which is perhaps unsurprising given that this index was found to significantly change over time. This suggests that children who perform more highly at T1 are more likely to demonstrate a greater magnitude of improvement over time. For the motor scores no significant correlation was found between score at T1 and the overall changes. This correlation may be limited by the smaller standard deviation of the BOT-2 in comparison to the KABC-II.

Figure 4.12 Correlation (*r*) between the change in scores over time and scores on the overall cognitive (FCI) and motor (TMC) indices at Time 1

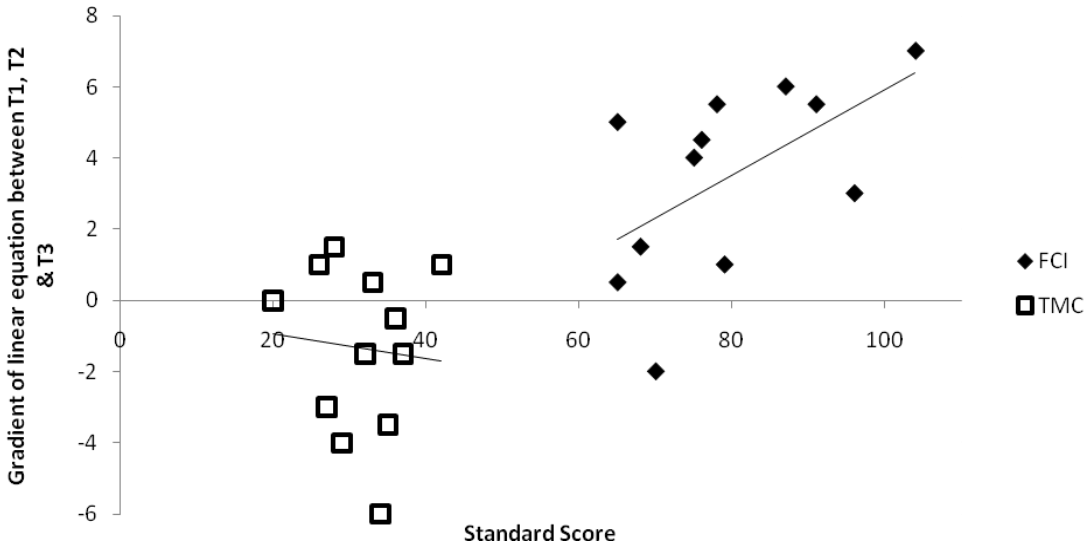


Table 4.9 Correlations (*r*) and difference (H, U) in performance across cognitive and motor indices in relation to the different potential moderator variables. After Bonferroni correction α=.025 for correlation analyses

	Index	Age at Diagnosis (*r*)		Time Post Treatment (*r*)		Tumour Type/ Treatment (H)		Hydrocephalus (H)		Sex (U)		Tumour Location (H)	
		R	p	r	p	H	p	H	p	U	p	H	p
Cognitive Ability (KABC-II)	Short Term Memory	.027	.934	.498	.100	2.63	.729	1.99	.711	6	.103	6.31	.018
	Visual Processing	.032	.921	.233	.467	1.34	.907	2.86	.502	13	.657	.926	.687
	Long Term Storage & Retrieval	.069	.830	-.269	.398	4.55	.380	1.03	.895	5.5	.085	1.78	.454
	Fluid Reasoning	-.491	.180	.497	.174	4.30	.240	2.84	.506	3	.889	1.76	.536
	Crystallised Ability	.591	.043	-.119	.712	6.82	.098	1.83	.715	13.5	.735	.996	.651
	Fluid Crystallised Index	.211	.510	.239	.455	6.16	.155	2.26	.642	15	.901	4.62	.086
Motor Ability (BOT-2)	Fine Manual Control	.140	.665	.254	.425	4.69	.354	2.17	.655	11	.436	.446	.818
	Manual Coordination	.049	.879	-.038	.907	5.16	.285	1.83	.727	15	.903	1.56	.509
	Body Coordination	.141	.663	.125	.699	4.32	.418	6.10	.05	14.5	.869	1.01	.663
	Strength & Agility	-.014	.965	-.483	.112	1.81	.853	2.22	.645	7	.149	.998	.640
	Total Motor Composite	.350	.265	-.252	.429	5.60	.20	2.62	.562	9.5	.147	1.20	.600

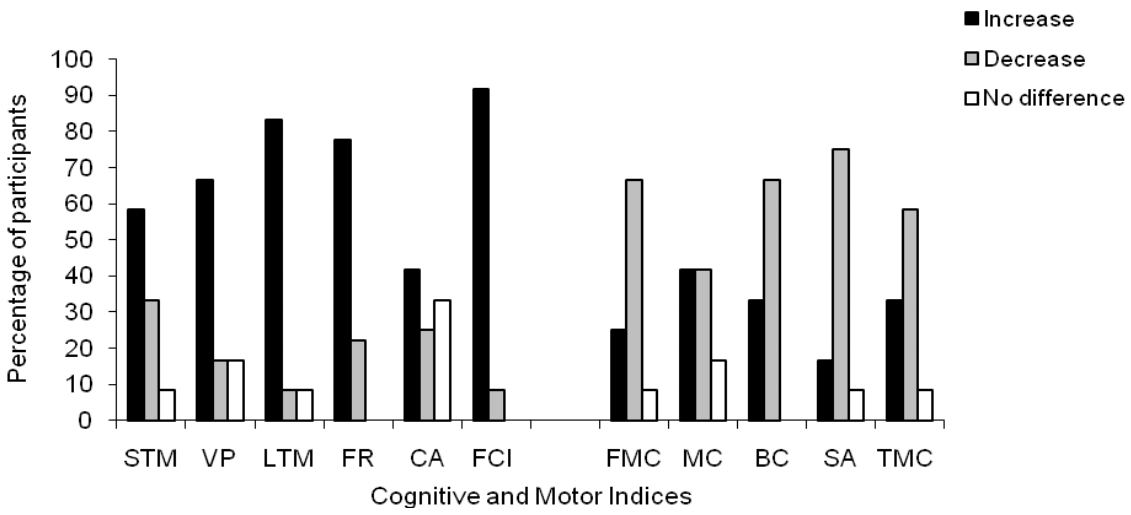
4.4 Discussion

This chapter examined the longitudinal assessment of a range of cognitive and motor measures in a group of 12 children who suffered injury to the cerebellum due to a tumour in the preschool years. Two standardised measures of cognitive and motor skills were administered three times at six-month intervals. The findings from this study are discussed below.

4.4.1 Individual outcome and changes across time

As in Chapter 3, which reports on scores achieved at the first testing session, substantial intra- and inter-variation was found in the scores achieved during the second and third assessments. In addition, the profile of change for the cognitive and motor indices was found to vary across both participants and time. Across time, for the cognitive standardised scores more patients improved (≥+1 point) than declined (≤-1 points), whereas the opposite was seen for the motor scores. The number of patients remaining the same was similar in both domains (Figure 4.10). This finding was not consistent across individuals however and few children showed constant directions of change between Time 1-Time 2 and Time 2-Time 3.

Figure 4.13 Percentage of patients who demonstrated an increase, decrease or no change in scores between T1-T3 for cognitive and motor indices



The difference between individuals can be highlighted by comparing outcomes in patients with similar prognostic factors. Whilst the limited sample in this study makes exact matches difficult, the results found are sufficiently varied to suggest that development of cognitive and motor skills across time may depend on many additional factors, such as time spent away from school and whether the child receives special education measures. Thus the long-term outcome cannot be predicted solely from the prognostic factors considered here.

4.4.1.1 Cognitive indices

The results found in this study, particularly the increase in some children treated with CSI, were contrary to many previous studies which found a decrease (e.g. Grill et al., 1999; Kieffer-Renaux et al., 2000; Mulhern et al., 1999; Mulhern et al., 2004; Radcliffe et al., 1994; Reeves et al., 2006; Ris & Noll, 1994) or no difference in scores over time (e.g. Conklin et al., 2008). For example, P01, P04, P06 and P11 all received PF radiotherapy, with P01 and P06 also receiving CSI and would therefore be expected to display a decrease in

cognitive scores over time. In fact, all of these children, except P06, demonstrated an increase over time for the Fluid Crystallised Index. Whilst it may be argued that this study does not cover a sufficient time period to measure long-term development, the participants are sufficiently varied in time since diagnosis that the results can inform some conclusions. Interestingly, P06 was the only child in these four participants who was below 5 years post diagnosis (33 months) with the others between 6-9 years post diagnosis (P01=77, P03=126 months, P11=110 months). Details from previous studies suggest that it is necessary to study the rate and pattern of decline within the first 5 year period in greater detail because the current assumption is that radiation effects are not manifest immediately, but emerge slowly two to three years after treatment ends. In addition, Palmer et al. (2003) suggested that further investigation into the time point at which the decline in intelligence plateaus also is essential as understanding the expected time course of decline is directly relevant for the timing of effective rehabilitation strategies for these children (Spiegler et al., 2004). Whilst this study was unable to pinpoint any precise timeframes for either an onset of declining abilities or subsequent plateau, the results showed that in PO6, at three years after treatment some cognitive abilities were severely impaired and were declining further over the following year. The increases seen for cognitive scores in the other four children who received CSI suggest that P06 may also demonstrate an increase in scores following a longer time post treatment.

Conversely for the patients who received radiotherapy with a long interval since treatment, their scores were similarly varied as in other patients with some indices severely impaired and others relatively spared. Their standard scores suggested that these children were not continuing to fall further behind their peers and were even increasing their scores over time. This suggested that the long-term effects of radiotherapy may not be as damaging in all patients as indicated by previous studies and that instead of plateauing in performance,

small gains may actually be made. Further assessments into adolescence would be needed to fully support this conclusion. In terms of rehabilitation, the results found here suggest that intervention should be initiated as soon as possible following treatment.

For those patients included in this study with more benign tumours, i.e. astrocytoma, all were found to increase in FCI between T1-T3. In addition, at T3 none of these children (P02, P04, P05, P09 & P14) were significantly impaired across all cognitive indices, and were generally performing close to the test norm mean. This finding disagrees with some previous work which found persistent deficits in these children across time when comparing standardised scores to the test norm samples (e.g. Beebe et al., 2005; Hoppe-Hirsch et al., 1993). The participants in this study varied in time post treatment (5-119 months) suggesting that if there is an initial decrease in scores following treatment due to short-term factors (Ackermann & Hertich, 2000), from very early following treatment a 'catch-up' is seen in these children and typical levels of functioning can be reached.

4.4.1.2 Motor indices

The alteration in motor skills across time appeared to partly support previous findings (e.g. Dennis et al., 1999). For example, P09, who was only 5 months post diagnosis showed variable performance on the motor indices, improving overall between T1 and T3 on Manual Coordination, Strength & Agility and the Total Motor Composite, and decreasing on Fine Manual Control and Body Coordination. Similarly P13 who was 27 months post diagnosis at T1 and suffered an ependymoma, demonstrated an increase for Manual Coordination, Body Coordination and the Total Motor Composite. This supported the hypothesis of Dennis et al., that recovery and development may have an additive effect in younger children with recent treatment. Not all participants agreed with this theory as P07 who was 24 months post diagnosis at T1 was

found to be decreasing relative to peers. None of these participants received CSI or PF radiation supporting the view that impairments in this population were not solely due to radiotherapy. In addition fewer late-onset problems would be expected in these participants, and although previous results suggested they may never reach the same level as typically-developing children (Dennis et al., 1999), P09 appeared to be relatively unimpaired across most motor indices. For the participants with a longer interval since diagnosis, i.e. P03, P04, P11 a decline in scores was still observed, suggesting that even 10 years post treatment a developmental plateau had not been reached.

4.4.2 Evidence for developmental models

The consideration of raw and standard scores in both the patient and control sample allows some conclusions to be drawn concerning the hypothesised models detailed at the beginning of this chapter. The results for the cognitive and motor measures will be explored separately as different patterns of results were found for each.

4.4.2.1 Correlation between cognitive and motor scores across time

The results from Chapter 2 indicated that in typically-developing children the interrelation of the overall cognitive and motor scores remains relatively constant across development. For development in the patient sample to be considered qualitatively similar to typically-developing children, this pattern may also be expected to be found for this group. This longitudinal study suggested that the relationship between cognitive and motor scores does remain relatively stable across time in these patients for both the gross level correlation and the correlation between Visual Processing and Fine Manual Control. This finding further highlights that these domains are tightly bound throughout development and do not dissociate despite deficits in each domain. These results suggested

that the development in the patient population is not deviating from a typical trajectory and therefore do not support Model 1 outlined above.

4.4.2.2 Cognitive skills

In general the patient cognitive standardised scores demonstrated a trend towards improvement between the testing sessions, however significant increases were found only for the long term memory measure and for the overall cognitive score. For the other indices, no significant differences were reported. For the typically-developing children no significant differences were found between the two sessions in line with the expectation that standard scores are believed to remain stable across childhood. These results were further supported by the finding that a higher proportion of patients increased their scores for Long Term Storage & Retrieval and FCI compared to the control sample. Taken together, this data suggested that for most of the cognitive indices, Model 3a may be the most applicable as this was the only model to predict stable standard scores across development. For long term memory Model 3b may be the most valid as this model predicted increasing standardised scores across development.

Examination of the alteration in raw scores over time was also considered in relation to the developmental hypotheses. As expected the typically-developing children demonstrated highly significant improvements across time for all of the cognitive subtests. The patient scores were also found to improve for many of the subtests, excluding Rover, a measure of visual processing, and Word Order, which measures short term memory, although other subtests for both of these abilities were found to improve with time. Comparisons between the patient and control raw score difference values revealed no significant differences for any of the subtests. This suggested that the patients were gaining scores at a similar rate to the control children. In conjunction with the standard score results, these findings supported the prediction made by Model

3a; patients appeared to be showing developmental progression commensurate with the typically-developing children despite many demonstrating severe impairments. For those subtests which were found to differ (Rebus and Rebus Delayed, both measures of long term memory) the patients were found to show a greater increase across time than the control children. When considered in conjunction with the standard scores for the Long Term Storage & Retrieval index, these results again support Model 3b for this cognitive ability as the patients appear to be demonstrating a level of 'catch-up' to the typically-developing participants. This finding must be interpreted with caution however, as the other subtests for long term memory, Atlantis and Atlantis Delayed, were not found to demonstrate an increased rate of development in the patient sample. This suggested that the Rebus and Rebus Delayed measures may be more sensitive to improvement in the patient sample and serves to emphasise that the choice of test used may affect the outcome and therefore a variety of measures should be used if feasible. This may be due to the characteristics of Rebus compared to Atlantis; Rebus bears greater similarities to learning to read, and may therefore be measuring skills that children are acquiring in an academic setting to a greater extent than the Atlantis subtest.

Given the limited testing period for this study, it was not possible to determine whether any of the cognitive abilities demonstrated a plateauing across development in the patient sample. Those patients who had the longest interval between treatment and testing, P03 and P04, both demonstrated increases for most standardised and raw scores, and the analyses for the prognostic factors highlighted no significant relationship between the change in standardised and raw scores over time. Taken as a whole these results suggested that patients were not reaching a developmental plateau for these cognitive skills.

4.4.2.3 Motor skills

In contrast to the findings for the cognitive indices, the control participants demonstrated a decline in standard scores for Body Coordination, Strength & Agility and the overall motor composite (TMC). This suggested that for these abilities a stable standardised score may not be expected in a typically-developing population. One possible explanation for this finding is that the motor standardised measure used in this study was normed on a sample of American children. Whilst differences in the acquisition of motor skills, particularly gross motor scores as suggested here, would seem to be unlikely between American and UK children it may be a contributing factor to these findings. Sample effects may also be driving this result; however the decrease in scores across time was seen in 25/41 of the control children suggesting it was not driven by a few anomalous participants. The patient sample also demonstrated a decrease in standardised scores across the assessments, however only the Strength & Agility index reached significance. No difference was found between the proportion of patients and control children who improved, declined or remained the same for any of the motor indices suggesting that the development of the patient sample was similar to that of the controls. Given the similarity between the patient and control samples, the results for the Fine Manual Control, Manual Coordination and Strength & Agility indices offered support for Model 3a, as although the standard scores were not remaining constant for all the indices, the data from the control sample suggested this is not the case in typical development. The results from the index (Body Coordination), in which the typically-developing sample showed a significant decline across time and the patients did not, suggested that for this ability the patients were demonstrating a slight 'catch-up' to the control children (Model 2a) although the difference values for this index were not found to significantly differ between the two groups.

The raw scores for the motor subtests revealed that the proportion of children who increased, decreased or stayed the same across time did not differ in the control and patient groups except for Upper Limb Coordination, in which a higher proportion of the patients decreased than would be expected based on the control sample. Similarly for many of the motor subtests little variation was recorded in the difference values for the two groups. The exception was Upper Limb Coordination in which a higher proportion of patients were found to remain constant than in the control group whilst a higher proportion of the control group increased in scores.

In addition to the proportion of each group that gained, declined or remained constant, the magnitude of change in each group was considered. Across time the raw scores of typically-developing children were found to increase for all of the motor skills measures. This suggested that the decrease found in the standard scores for the control sample may have been due to the standardisation procedure, rather than these children failing to improve in motor abilities. In contrast, the patients demonstrated no significant differences in motor raw scores across time, with the exception of an increase for Manual Dexterity. This suggested that unlike the control sample, even though there was no difference between the proportion of children improving or decreasing the magnitude of loss of scores in the patient group were higher, and the gain in scores correspondingly lower, than seen in the control group. This highlighted that many patients were failing to acquire appropriate motor skills and were continuing to perform at a significantly reduced level in comparison to peers. For this pattern of results Model 2a appears to be the most applicable.

Other factors must also be considered in drawing firm conclusions. Again given the limited time span of the study it is difficult to determine whether any developmental plateaus are demonstrated by these patients for motor abilities. The analyses of the impact of prognostic factors highlighted that time post treatment was significantly related to the alteration of some motor raw scores

across time. In particular, for fine motor skills, balancing and strength, a longer interval since treatment resulted in a larger decrease in raw scores. Although no significant differences were found between the time post treatment and change in standard scores, the analyses for the raw scores indicated patients may continue to decrease in ability for many years following treatment. This suggested that Model 2b may in fact be most appropriate, with a long time delay elapsing before a developmental plateau is seen. This conclusion would seem to be in contrast with previous longitudinal findings, especially those of Dennis et al., who reported an increase in motor skills over time with a similar trajectory to that described by the different aspects of Model 3.

4.4.3 Longitudinal changes in cognitive and motor index scores

4.4.3.1 Cognitive Indices

Analyses of the patients' individual cognitive indices across time revealed a significant gain across time for Visual Processing, Long Term Storage & Retrieval and the Fluid Crystallised Index. Subsequent analyses revealed that the significant gain for both of these measures was between T1-T2 and T1-T3. Examination for the individual results suggested that these increases were seen in the majority of patients (10/12 for Visual Processing, 11/12 for Long Term Storage & Retrieval, 11/12 for FCI). All the other indices demonstrated an increase in scores over time, although none reached significance.

An important consideration for a longitudinal study employing the same measures throughout is the impact of practice effects due to familiarity with the tasks, experience solving the tasks and solving novel problems by developing strategies (Kaufman, 1994). The manual for the KABC-II reports practise effects found after a follow-up period of one month in typically-developing children across all age groups (Kaufman & Kaufman, 2004, p. 90-91). Small gains were found for Short Term Memory (between -.8 and 2.2 points) and Crystallised Ability (3-4 points). Slightly larger increases were found for Visual Processing

and Fluid Reasoning (7-10 points) and the largest gain was found for Long Term Storage & Retrieval (7-18 points). Whilst this study was conducted over a longer timeframe, it should be considered that practise effects may be artificially inflating any increases noted, particularly in the cognitive measures where children may become familiar with the stimuli. Anecdotally, many children did not appear to remember many details, either general or task- specific, from earlier testing sessions.

The gains reported in the KABC-II manual indicate that a significant increase in scores for Long Term Storage & Retrieval over time may in part be due to practice effects. However, it may be argued that practice effects are not solely responsible for an increase in scores, a significant increase was not seen for all subtests of this index (as discussed above) and a corresponding significant increase was not seen between T2 and T3 which would be expected if practise effects were the cause. A significant increase was also found for Visual Processing between T1 and T2 and Figure 4.4 suggests that it was seen for all participants with the exception of P06 who demonstrated a decrease of 3 points. As with Long Term Storage & Retrieval, the increase for Visual Processing was not repeated between T2 and T3. The individual subtests which constitute the Visual Processing index, Triangles and Rover, are tasks which may not be similar to those children generally encounter. It is therefore possible, that the improvement seen on this task was due to a familiarity with the stimuli and improving strategy as suggested by Kaufman (1994). Despite this, it is possible to argue that visual processing is a skill that all children are constantly using, unlike a more abstract ability such as novel problem solving or deductive reasoning as measured by Fluid Reasoning. It may therefore be expected that visual processing would improve at a faster rate than other abilities, although this explanation does not account for why a corresponding increase was not seen for this ability between T2-T3. Overall, given the inter- and intra-individual variation in alteration in scores over time and considering the evidence from the

raw and standardised comparisons to the control sample, it does not appear that practice effects are solely responsible for the gains seen in patient scores over time.

4.4.3.2 Motor Indices

For the motor measures, only Strength & Agility was found to significantly decrease across time, with the largest difference found between T1-T3, although this failed to reach significance following Bonferroni correction. Scores on all other motor indices were found to decline over time although none reached significance. One possible explanation for the significant decrease in strength and agility is that balance in these children was found to be severely impaired which may limit everyday movements such as running and playing normal games causing these children to become progressively weaker than their peers. This limitation may be expected to result in poor development of coordination and strength measured by this index. In addition, previous research has suggested that parents of children who have suffered a brain tumour may develop a long-lasting fear of losing their child, despite the child's recovery (e.g. Aukema, Last, Schouten-van Meetereen, & Grootenhuis, 2010). The consequence of this fear may lead parents to perceive the child as having increased vulnerability and manifest as overprotective behaviour (e.g. Coletti et al., 2008). This may prevent the child playing as typically-developing children, hindering the development of strength and agility and developmental milestones (Stam, Grootenhuis, & Last, 2005). In contrast, other motor skills such as Fine Manual Control and Manual Coordination may receive more practice performing school work and in everyday tasks. Whilst the work with typically-developing children (Chapter 2) suggested that the Strength & Agility index was not strongly correlated with cognitive functioning, especially in later childhood, this trend should nevertheless be further investigated. In infants however it may be hypothesised that gross motor skills are highly important in learning about the

world (e.g. Campos et al., 2000) and any decline in these skills in early childhood should be given rehabilitative attention.

One important note for this analysis is to highlight the limitation and implication of drawing firm conclusions from a limited sample. Inspection of Figure 4.4 reveals that P14 demonstrated a large decrease in Strength and Agility between T1 and T2 that appeared to be incongruous to scores on other motor indices. This suggests that P14 may in fact be driving the main effect found in this index. Nevertheless, a steady decrease or maintenance of a significantly impaired level in motor scores was found for many participants, suggesting that this score may not be causing undue conclusions, indeed the analysis excluding this participant was still approaching significance ($z=-1.84$, $p=.066$). This finding also raises a further consideration, that children who display a large discrepancy between two time points which appears to be incongruous with their overall pattern of functioning (such as P14 on the Strength and Agility index or P10 on the Crystallised Ability Index, see Figure 5.1), may be producing such a variation due to poor performance on a particular day. This highlights the importance of multiple testing sessions if possible, to ensure an accurate assessment is obtained and appropriate rehabilitation can be formulated, e.g. P14 is performing within the typical range at T1 and T3 for Strength & Agility and is unlikely to need rehabilitation.

4.4.4 Impact of prognostic factors on magnitude of longitudinal change in scores

The prognostic factors examined here, Age at Diagnosis, Time Post Treatment, Tumour Type/Treatment, Hydrocephalus, Sex and Tumour Location were not found to significantly impact on the change in cognitive and motor standard scores over time. This is in contrast to the findings in Chapter 3 in which Age at Diagnosis was found to have an impact on performance, with a younger age at diagnosis resulting in a poorer outcome. Previous studies have also reported that a poorer outcome results from a younger age at insult;

however, the findings of this study appear to suggest that whilst the age at diagnosis may impact upon the level of impairment, it does not affect the rate of development for either cognitive or motor scores. Chapter 3 suggested a trend between an increasing time interval since treatment and poorer outcome. For the standardised scores, this trend was not supported by the results of this study as no relationship between time post diagnosis and alteration in scores was found. For some of the raw motor scores however, a different pattern was found, with a longer time since treatment resulting in a greater loss of scores over time. This suggests that motor skills continue to decline for many years following treatment.

Similarly to Age at Diagnosis, in Chapter 3 the tumour histology and treatment received was found to significantly affect both cognitive and motor functioning, with those treated for medulloblastoma with CSI and PF radiotherapy most impaired and children with astrocytoma and surgery alone least affected. Tumour type and treatment were not found to significantly impact upon the alteration in scores over time suggesting that this factor affects the level of impairment but not the developmental progression. It should be noted however, that with a small heterogeneous sample it is difficult to draw firm conclusions concerning the impact of difference prognostic factors which are likely to be interrelated.

In Chapter 3 tumour location was found to have an impact on one cognitive index; children with vermis involvement only were found to demonstrate greater deficits on Visual Processing than those children with additional hemispheric damage. In addition, tumour location was significantly related to the overall motor score (TMC) as children with RH damage were more impaired than children with LH damage. For this study tumour location was found to impact on the change in Short Term Memory scores only; children with vermis and RH involvement showed an improvement in scores and those with vermis involvement only declining. Some previous studies have suggested that

the vermis and paravermis may be the most critical sites of injury for subsequent outcome (e.g. Dias et al., 2005). Many children in this study sustained damage to the vermis and the cerebellar hemispheres, so it is unlikely that this finding would be robust when considered over a larger group with more clearly defined areas of damage. This difference was not found to reach significance following Bonferroni correction and should be interpreted with caution. In addition, it should be considered that the patients with vermis involvement only included many who suffered medulloblastoma and radiotherapy. This result may therefore be reflecting many other prognostic factors as it may be expected that the vermis-only group would show a greater decline in scores considering the additional characteristics of these children.

In addition to the prognostic factors discussed above, this study examined the impact of overall ability in each domain upon longitudinal change. The results for the cognitive index (FCI) were approaching significance and suggested that children who performed more highly upon initial assessment demonstrated a greater magnitude of change in scores over time. This implies that children who were less severely impaired showed a greater potential for recovery of function whilst children who have been severely affected will fall progressively further behind peers. Other prognostic factors are likely to be confounded with this result, as the children who performed most highly at T1 were those treated for an astrocytoma with surgery alone and a younger age at diagnosis was found to adversely affect outcome. The finding here suggests that these prognostic factors not only give some indication of overall impairment but may be important in predicting longitudinal change. It should be noted that with one exception (P06) all children nevertheless improved on the overall cognitive measure irrespective of their initial score. This finding suggested that longitudinal assessment in this population may be particularly important for all children, even those with a low performance at baseline, as alterations in ability may have implications for the focus of rehabilitation. This is especially the case

for children who are not improving in one area similarly to other abilities; for example P02 demonstrated substantial increases in Short Term Memory, Long Term Storage & Retrieval, Fluid Reasoning and the Fluid Crystallised Index, whereas performance on Visual Processing was found to decrease. In P02 remediation should target Visual Processing abilities, which may in turn also benefit the declining motor scores in this child.

For the motor index (TMC), no significant association with overall ability was found. This may be due to both the lower spread of scores seen for the TMC and the lack of significant change in the standardised motor scores over the different time points. This finding suggests that multiple testing sessions may not be as important for motor skills as for cognitive abilities as less substantial change would be expected between testing sessions, and does not place children of a lower ability more at risk of declining in performance. The trend from this data suggests the opposite may well be the case.

4.4.5 Conclusion

The results reported here indicated that over a year of testing most patients, irrespective of tumour type, location, treatment, age at diagnosis and time since treatment, demonstrated substantial improvements across many of the cognitive indices measured. The trend in the data suggested that the children who were performing most highly at baseline had the largest potential for improvement, whilst those who were significantly impaired showed minimal gains or decreases over time. In contrast, the results suggested that many children were decreasing on the motor indices measured over time, with the most significant decrease seen for strength and agility scores. Again, the prognostic factors considered here did not appear to account for the magnitude of change in these patients.

The comparison of alterations in raw and standard scores over time in the patient group with those seen for the control children enable tentative

conclusions to be drawn concerning the developmental hypotheses proposed at the beginning of this chapter. The results suggested that development in this sample is qualitatively the same as in typically-developing children but quantitatively delayed. When considered as a group, the patient scores demonstrated that for most of the cognitive abilities considered here, Model 3a was the most appropriate and that development in these children was occurring at a rate equivalent to that evident in the control group. As emphasised, this is in stark contrast to previous reports and highlights that group representations in previous studies may mask some improvement shown by individuals with malignant and benign tumours alike. In comparison, patient performance on the motor assessment across time suggested that not only were these children failing to gain motor abilities at an appropriate rate, some were also losing skills over time. These results of declining ability over time suggest that for motor functioning Model 2b may be the most applicable.

This study has therefore addressed some of the limitations found in previous studies. The results further previous research by indicating that patients with cerebellar tumours can be found to improve across time, and that the pattern of development in this sample is largely similar to that seen in typically-developing children. For the cognitive measures, those patients who were performing more highly tended to make the most improvements whereas the rate of development for poorer performing patients was slower. For the motor measures this was not found to be the case. These results highlighted the importance of regular assessment in this population to determine areas of weakness, which may appear throughout development even in children 10 years post treatment. Ideally these may inform a tailored rehabilitation which may be able to build upon the increases in cognitive scores seen in these patients, such as reported in individual case studies for interventions in children with cerebellar tumour (e.g. Penkman & Scott-Lane, 2007; Callu et al., 2008), but in reality, they may be used in school settings to ensure the child receives appropriate

support. For motor abilities, these results suggested that on-going physiotherapy might be required for some patients for a substantial time post treatment.

5 Specific versus general impairment in cognitive and scholastic functioning following cerebellar tumour injury sustained in the preschool years

5.1 Background Literature

Over the past few decades accumulating evidence has implicated the cerebellum in a variety of cognitive processes including executive functioning, visuospatial skills, memory, and language. Damage sustained to the cerebellum due to tumour in childhood has been demonstrated to have a negative impact on both general cognitive functioning (e.g. Beebe et al., 2005; Davis et al., 2010; Grill et al., 1999; Konczak & Timmann, 2007; Mulhern et al., 2004; Ris et al., 2001) and scholastic attainment (e.g. Copeland et al., 1999), which in turn impacts upon the quality of life for child survivors (e.g. Bull & Kennedy, 2008; Mostow et al., 1991). A case study following an 8 year old boy treated for medulloblastoma reported that intense academic remediation led to improvement in grapheme knowledge and basic reading decoding skills, but not in mathematics according to the Wechsler Individual Achievement Test (WIAT-II; Wechsler, 2005) (Penkman & Scott-Lane, 2007). Another remediation case study of a boy treated for medulloblastoma at 18 months highlighted deficits in attention, working memory, manual and visual abilities, who nevertheless was able to progress through school due to an individualised remediation plan (Callu et al., 2008). Previous studies have highlighted that additional factors such as treatment received, particularly radiotherapy, age at diagnosis and time missed from school can contribute to a poorer outcome (e.g. Mabbott et al., 2005). Despite these contributing prognostic factors, results implicating the cerebellum in language and mathematics in both typically-developing normal readers and children with developmental disorders, suggest that specific deficits in scholastic abilities may be expected following cerebellar damage due to tumour. Given the evidence that individualised rehabilitation programmes may be effective in improving developmental outcome, it is important to examine academic skills in

this group whilst controlling for cognitive ability to determine at which level remediation should be targeted. The identification of any discrepancies between cognitive abilities and academic achievement to highlight specific areas of weakness may have important implications for effective rehabilitation within this population. As few previous studies with cerebellar patients have controlled for cognitive impairments when measuring academic skills, it is difficult to establish whether deficits in scholastic abilities, including reading, writing and mathematics arise due to poor underlying cognitive capacity, or whether scholastic functioning is affected above and beyond a level that would be expected based on general cognitive functioning. The contribution of the cerebellum to scholastic skills may be process-specific, that is, it has a role in linguistic and/or mathematical processing above and beyond a more general supervisory role. Conversely, it is possible that the cerebellum has been implicated in language and other academic skills due to the more general executive function control processes it is known to facilitate. This distinction is summarised in a review by De Smet and colleagues which outlined hypotheses forwarded to account for cerebellar contribution to linguistic processing, including the timing hypothesis; that the cerebellum is necessary for the timing and modulation of language skills and the direct cerebellar hypothesis; or that it is involved in several specific aspects of linguistic processing such as organisation, construction and execution (De Smet, Baillieux, De Deyn, Mariën, & Paquier, 2007).

This chapter aims to investigate the development of academic abilities in children who have suffered an injury to the cerebellum following treatment for a tumour in the preschool years, to establish whether any difficulties with scholastic skills reflect specific or more general cognitive impairments.

5.1.1 Evidence for a specific cerebellar role in language

The majority of research investigating cerebellar contribution to academic skills has focused on language and reading skills, rather than mathematics. Evidence for a specific role of the cerebellum in language processing may be taken from imaging and lesion studies with both adults and children.

5.1.1.1 Imaging studies

There is currently much debate concerning the role of the cerebellum in linguistic and reading processes. A recent review by Stoodley and Stein (in press) drew from imaging (e.g. Carreiras, Mechelli, Estevez, & Price, 2007; Joubert et al., 2004), anatomical (e.g. Eckert et al., 2003; Leonard et al., 2001) and lesion studies (e.g. Moretti, Bava, Torre, Antonello, & Gazzato, 2002; Scott et al., 2001) to conclude that the cerebellum should be considered an important component of the reading network, although its precise contribution to this network has yet to be fully understood. Results from anatomical imaging studies suggest that the cerebellum has a specific role in a language network, supported by evidence that as the cerebellum has evolved, reciprocal connections to frontal areas have undergone similar expansion (e.g. Middleton & Strick, 1994; Schmahmann & Pandya, 1995). These connections have been shown to be between phylogenetically new parts of the lateral cerebellum and contralateral prefrontal areas; Broca's area and the supplementary motor area (Engelborghs, Mariën, Martin & De Deyn, 1998). This anatomical evidence is highly suggestive of a cerebellar contribution to language processing.

Further evidence for cerebellar participation in reading and language can also be taken from functional imaging studies, many of which have been completed with adult participants. In an early imaging study to investigate cerebellar processing during language tasks in adults, Petersen and Fiez (1993) used positron emission tomography (PET) to demonstrate cerebellar activation during a verb for noun generation task. Importantly, this and similar studies

(Petersen et al., 1988; Petersen, Fox, Posner, Mintun, Raichle, 1989) demonstrated that cerebellar activation was not present solely because of the motor response of the task, but also due to the cognitive word processing. These studies also revealed that both visual and auditory presentation activated common areas of the right cerebellar hemisphere in the vermal lobule IV and lateral lobule VI, with additional activation seen in crus IA on the left for visual stimuli. Further studies have reported similar results of right lateral cerebellum activation for word generation tasks with adults (e.g. Martin, Haxby, Lalonde, Wiggs & Ungerleider, 1995; Raichle, Fiez, Videen, MacLeod, & Pardo, 1994).

Fulbright and colleagues (1999) used functional magnetic resonance imaging (fMRI) to report that in adults the cerebellum is activated during reading and appears to be differentially involved in phonologic and semantic tasks. Phonological processing was found to involve the middle and posterior aspects of the superior fissure, the adjacent simple lobule and semilunar module bilaterally. Semantic processing was found to activate these areas also, with additional involvement seen in the inferior vermis and the deep nuclear region on the right. Another fMRI study found that the right cerebellar hemisphere was activated for silent word and non-word reading in adults (Senaha, Martin, Amaro, Campi & Caramelli, 2005). In their study, Moretti et al. (2003) concluded that cerebellar activity during linguistic processing centres predominantly on lobule VI in the right hemisphere, the adjacent part of the crus I, and the vermis at lobules IV - VIIA. In a further fMRI study Mechelli and colleagues reported that reading nonwords relative to words increased activation in a number of brain regions, including the cerebellum (Mechelli, Gorno-Tempini & Price, 2003). Several review papers (e.g. Mariën, Engelborghs, Fabbro & De Deyn, 2001; Paquier & Mariën, 2005; Silveri & Misciagna, 2000; Stoodley & Stein, in press; Vlachos, Papathanasiou, & Andreou, 2007) have suggested that there is a valid case for cerebellar involvement in language processing above and beyond purely articulatory contributions, a conclusion which is supported by results from

cerebellar lesion studies as well as imaging and behavioural studies that have investigated cerebellar functioning during reading tasks with dyslexic readers (see section 5.1.3 below).

5.1.1.2 Lesion studies

The role of the cerebellum in language and reading has also been investigated in patients with cerebellar damage. A wealth of lesion studies with both adult and child patients have highlighted functional divisions within the cerebellum. For example the vermis appears important for affective processing, the anterior cerebellar lobe for motor control and the posterior cerebellum for cognitive functioning (e.g. Levisohn et al., 2000; Schmahmann, 2007; Schmahmann & Sherman, 1998). More particularly, it has been suggested that midline tumours produce deficits in spatial memory and perceptual-motor skills, whereas cerebellar hemisphere tumours affect academic achievement and verbal memory (Copeland et al., 1999). Support has been demonstrated for right cerebellar hemisphere in language whilst the left cerebellar hemisphere appears to be connected with visuospatial functioning (e.g. Scott et al., 2001).

5.1.1.2.1 Linguistic impairments in adults

Contrary to findings from neuroimaging studies, one of the first case reports of an adult patient with a right cerebellar infarct recorded no reading deficit, although impairment on a verb generation was found (Fiez et al., 1992), which suggests a specific cerebellar role in language processing. Reading in this patient may be intact if cerebellar regions are differentially involved in reading processes (Ben-Yehudah & Fiez, 2008), as activation is seen in bilateral medial and paramedial areas for reading both words and nonwords activation, with increased activation in the right lateral cerebellum for nonwords than words (Fiez, Balota, Raichle & Petersen, 1999). Difficulties on verb generation tasks in

adults with degenerative and ischemic cerebellar lesions have not been consistently replicated (Richter et al., 2004; Richter et al., 2007).

5.1.1.2.2 Linguistic impairments in children

Unlike in adult patients (Fiez et al., 1999), no impairment was noted on a verb generation task in children and adolescents with acute focal cerebellar lesions (Frank et al., 2007). Similarly no evidence of aphasia was found in children and adolescents who had been treated for cerebellar astrocytoma although a small increase in reaction times on a verb-generation task was noted in children with left-sided lesions (Richter et al., 2005). These differences from adult studies suggest that functioning following cerebellar insult in children may benefit from greater plasticity, with different mechanisms governing subsequent processing in adults and children.

Other studies have reported deficits in expressive language problems in children with cerebellar injury, such as word-finding and non-fluent speech (e.g. Aarsen et al., 2004; Akshoomoff, Courchesne, Press, & Iragui, 1992; Levisohn et al., 2000). In their study with children, Riva and Giorgi (2000) reported that patients with lesions of the right cerebellar hemisphere had mild abnormalities on expressive language tasks and formulation of sentences whereas children with left cerebellar hemisphere tumours were impaired on non-verbal skills. These patients with left cerebellar damage were also impaired on naming and comprehension tasks, but had intact complex language processing skills such as syntactic comprehension. A further study examining the outcome of children with cerebellar malformations (e.g. agensis, hypoplasia, dysphasia) reported a range of language disabilities, including semantic and grammatical deficits and difficulties with verbal production assessed using standardised measures, in almost all participants, ranging from mild impairment to completely absent language (Tavano et al., 2007). The authors suggested these results support a cerebellar role in language processing and acquisition of both comprehension,

either through core (lexical and morphosyntactic information) or supporting (executive function processes e.g. verbal working memory) mechanisms.

Further evidence for a cerebellar contribution to language processing is taken from the occurrence of cerebellar mutism, or posterior fossa syndrome, in patients who have undergone treatment for posterior fossa tumours. Whilst mutism usually occurs in children (e.g. Kingma, Mooij, Metzemaekers, Leeuw, 1994; Ozgur, Berberian, & Aryan, 2006; Pollack, 1997; Pollack, Polinko, Albright, Towbin, & Fitz, 1995; Riva & Giorgi, 2000; van Dongen, Catsman-Berrevoets, van Mourik, 1994) instances in adult patients have also been documented (see Coplin, Kim, Kliot, & Bird, 1997 for review). Mutism usually consists of a brief interval of normal speech followed by days or weeks of mutism and returning speech that may be normal or dysarthric and is often accompanied by emotional and behavioural changes, such as irritability or autism-like symptoms. The precise location of damage or confounding causes, i.e. infection, which result in mutism remain unclear; however there is some suggestion that midline damage, particularly the inferior vermis, and extra-cerebellar components such as brain-stem involvement and hydrocephalus, may be important (Gordon, 1996; van Dongen et al, 1994). Riva and Giorgi (2000) reported that six out of eleven children in their study developed mutism following treatment for a tumour in the vermis, four with speech anarthria and two with language disturbance. The first group recovered their ability to use expressive language initially and eventually re-acquired normal speech. Conversely, the second group were capable of producing language but had poor syntactic comprehension and auditory sequential memory. Even three years post-treatment, this second group retained these language difficulties, suggesting little plasticity in the recovery of these language aspects following damage. These two subgroups of patients encompass the two approaches to mutism (Konczak & Timmann, 2007); either that it is an extreme form of ataxic dysarthria, i.e. difficulties with the timing, force and direction of speech motor movements (e.g. van Calenbergh, Van de

Laar, Plets, Goffin, & Casaer, 1995) or conversely that it is a language disorder at a cognitive, rather than production, level (Riva, 1998). It is likely that both occur and that factors such as the location of damage and confounding factors, in addition to damage in other brain areas, e.g. brainstem tegmentum (Pollack et al., 1995), may account for these differences in outcome following posterior fossa syndrome and raise questions concerning the classification of these patients into a single group.

5.1.2 Evidence for a general cerebellar role in language

5.1.2.1 Lesion studies

Conflicting with the studies reported above, some research investigating both adult and child patients suggests a more general, executive function cerebellar role in language processing.

5.1.2.1.1 Linguistic impairments in adults

Deficits on phonological and semantic tasks have been found in adult patients with cerebellar lesions (Leggio, Solida, Silveri, Gainotti, & Molinari, 1995), with medial lesions more closely associated with motor deficits and lateral, particularly right, cerebellar damage to verbal fluency deficits. These findings were supported by a subsequent study which suggested that verbal fluency impairment in cerebellar patients may be due to problems with specific phonemic retrieval strategies and not the result of a motor speech impairment (Leggio et al., 2000). This latter study found no lateralised effects of cerebellar influence on verbal fluency but that deficits were more pronounced on phonological tasks. Given the postulated role of the cerebellum in planning and learning procedures, the authors suggest phonological tasks may be more affected because they rely upon novel searching strategies that are not automised. Conversely, no language impairments, and only very mild naming deficits, were reported in a study of adult patients who had suffered a cerebellar

stroke (Beldarrain, Garcia-Moncó, Quintana, Llorens, & Rodeño, 1997). It is possible that the naming difficulties recorded were representative of a verbal fluency deficit. Mariën and colleagues used results from single-photon emission computed tomography (SPECT) to propose that the aphasia seen in some adult patients following right cerebellar damage may be due to the effects of diaschisis, that is, a loss of excitatory impulses through cerebello-ponto-thalamo-cortical pathways (Sönmezoglu, Sperling, Henriksen, Tfelt-Hansen, & Larsen, 1993) resulting in reduced function in remote brain regions involved in language processing (Mariën et al.,1996; Mariën, Endelborghs, Pickut, & De Deyn, 2000).

Agrammatism has also been found following cerebellar injury in adults (e.g. Fabbro, Moretti, & Bava, 2000; Gasparini et al., 1999; Justus, 2004; Kalashnikova, Zueva, Pugacheva, & Korsakova, 2005; Mariën et al., 1996, 2000; Schmahmann & Sherman, 1998; Silveri, Leggio, & Molinari, 1994; Zettin et al., 1997), with a number of these studies also reporting aphasic difficulties in these patients. It is increasingly recognised that agrammatic speech may result from difficulties in phonological representation, lexical retrieval or working memory, as opposed to loss of grammatical knowledge (e.g. Dick, Bates, Wulfeck, Utman, Dronkers, & Gernsbacher, 2001) and that the deficits may be seen as a result of impairments in executive functions, rather than an alteration language processes and representations (Fabbro et al., 2000). It should be considered that many studies investigating linguistic deficits in adults with cerebellar injury emphasize that only minor deficits in grammar are present (e.g. Justus, 2004).

5.1.2.1.2 Reading difficulties in adults

In a study with adult cerebellar patients, those with vermis and paravermis lesions demonstrated more reading mistakes than control participants when reading single words and nonwords as well as continuous passages although they were not impaired on cognitive (Raven Standard

Progressive Matrices; Raven, 1976) or language tasks (Bilingual Aphasia Test; Paradis & Canzanella, 1990) (Moretti et al., 2002). These patients were shown to have oculomotor difficulties which are believed to be associated with cerebellar control (Crowdy, Hollands, Ferguson, & Marple-Horvat, 2000) and which are thought to affect reading in developmental dyslexia as children with dyslexia show an abnormal pattern of the saccadic eye movements during reading (Fowler, 1991). Moretti and colleagues (2002, 2003) concluded that these patients exhibited acquired dyslexia, either through alteration in oculomotor function, or because of cerebellar links to attention and alerting, as well as language processes. Beaton (2004) however argues that these patients do not show performance commensurate with that of adults with acquired dyslexia, as the errors appear to lie in articulation of output rather than being reading difficulties at a cognitive level, and improvements are not seen in accuracy and regularisation errors when context is provided, as is usual in dyslexia (Ellis, McDougall & Monk, 1998). Another study examining adult patients with cerebellar damage due to stroke found that participants with right cerebellar damage demonstrated a greater deficit than those with damage in other locations on reading and language tasks compared to controls (Karaci, Öztürk, Özbakir, & Cansaran, 2008). A single case study of a patient with damage to the right superior cerebellar artery reported deficits in linguistic processing that was classified as surface dyslexia (Mariën et al., 2009). The patient also showed signs of dysgraphia with difficulty writing irregular (i.e. words in which one or more letters do not represent their most common sounds) and ambiguous words (i.e. words with more than one meaning). SPECT was used to ascertain that there was no damage to areas outside the cerebellum, suggesting that the cerebellum is an important component of the reading network. In contrast to the findings of Morretti and colleagues (2002, 2003) adults with focal cerebellar damage following stroke were not found to perform differently from matched controls on basic reading skills and naming of single

words and nonwords. However, deficits were seen on tasks of phonological processing (Ben-Yehudah & Fiez, 2008) and, together with Moretti et al. (2003), suggest that the cerebellum is not necessary for skilled reading in adults but may have a refining role in the process. The authors suggested the cerebellum may perform in an executive functioning capacity, monitoring articulation as part of a more general role in error monitoring. Deficits seen in cerebellar patients may therefore be the result of a deficit in a more general capacity that may impact on reading processes. These studies with adult patients do not address the possibility that cerebellar contribution to reading may be most vital at the stage of acquisition. Indeed, as Stoodley and Stein (in press) note in their review, this proposed role of the cerebellum as a monitor of articulatory errors may be particularly pertinent during the acquisition of phonological skills in literacy development. This may also account for the differences between studies with adult patients, as high frequency words would not require this input whereas novel nonwords would have a greater need for error monitoring.

5.1.2.1.3 Reading difficulties in children

Whilst deficits in language processing have been seen following cerebellar damage in child populations (e.g. Riva & Giorgi, 2000), and some studies report on academic outcome, relatively little research has been conducted that specifically focuses on reading abilities in children with cerebellar damage. Scott et al. (2001) reported that two out of three children they studied with right cerebellar damage sustained during the preschool years were classified as dyslexic (aged 7 and 9 years), suggesting that this early injury hindered development of verbal and literacy skills. Studies that examine reading following cerebellar injury in early childhood may help to further uncover cerebellar contribution to the acquisition of language and reading skills. A major consideration of these studies however, particularly concerning children of a very young age at diagnosis, is whether a premorbid language processing deficit was

present or whether any difficulties are a direct result of the tumour and treatment received.

The evidence from imaging, anatomical and lesion studies is therefore inconclusive concerning the contribution of the cerebellum to language and reading skills in either a general or specific capacity. The results reported in previous chapters suggested that impairments in different domains are associated in this patient group, i.e. cognitive and motor skills were found to correlate in this sample. This link between the level of deficits across domains is suggestive of an overarching, general cerebellar role in each aspect of functioning, rather than a specific contribution to each, however it is not possible to draw a firm conclusion based on previous research with this patient group.

5.1.3 The cerebellum and developmental dyslexia

Developmental dyslexia is defined as a specific and continuing failure to acquire reading skills, despite typical teaching, intelligence and socio-cultural opportunities (World Health Organisation, 1993). The role of the cerebellum in linguistic processing has been implicated in developmental dyslexia and is a highly debated topic. A vast quantity of research has been conducted to elucidate the underlying nature of the deficit in dyslexic readers and has given rise to a number of hypotheses. One theory that has attracted significant interest is the automaticity/cerebellar theory (Nicolson et al., 2001) which proposes that dyslexia is the result of a mild cerebellar impairment that gives rise to both balance and phonological problems, in addition to a slowed central processing speed. It suggests that a cerebellar deficit may lead to a lack of skill automatisation which is necessary for both motor and language/reading tasks. Support and dissent for this theory can be gathered from a range of anatomical, imaging and behavioural studies. Studying patients who have suffered damage to the cerebellum early in development may also provide a direct way of assessing the cerebellar deficit hypothesis, as it may be expected that these

patients would all demonstrate reading difficulties should the hypothesis be valid.

Anatomical studies (e.g. Finch, Nicolson, & Fawcett, 2002; Galaburda et al., 1985; Livingstone, Rosen, Drislane, & Galaburda, 1991) have reported significant differences between the number of large and small cells in the cerebellum and inferior olive in brains of dyslexic and control adults. These studies, however, all examined the same limited cohort and as noted by Beaton (2002) it is unlikely they are representative of typical dyslexic brains and the results should be interpreted with caution.

Some imaging studies have highlighted that dyslexics have cerebellar symmetry in comparison to the asymmetry displayed in control brains (e.g. Kibby, Fancher, Markanen, & Hynd, 2008; Rae et al., 2002) whilst others have found greater leftward asymmetry of the posterior and anterior lobes of the cerebellum in those with reading difficulties (Eckert et al., 2003; Leonard et al., 2001). Eckert et al. stress that the dyslexic children did not have difficulty with the motor skills necessary for learning to read, i.e. oral-motor control of mouth movements, but nonetheless they had problems learning to read. The right cerebellar declive and the right lentiform nucleus were the brain areas found to most discriminate dyslexic individuals from normal readers (Pernet, Andersson, Paulesu, & Demonet, 2009) although the authors highlighted that these findings do not preclude other brain regions being implicated in dyslexia. It should be noted that differences have also been found in other brain regions including the cerebral hemispheres, the corpus callosum, the left temporal lobe, the planum temporale, the insula and the inferior frontal gyrus (Eckert et al., 2003; Galaburda et al., 1985; Habib, 2000). Dyslexic adults have also been demonstrated to have a larger volume of white matter in both cerebellar hemispheres, even once overall volume had been taken into account, which is taken to be a sign of excessive connectivity and abnormal myelination (Laycock et al., 2008). The authors suggested that this could create 'physiological noise'

which would manifest as difficulties with neural timing, integrating information accurately, and information processing. If this is indeed the case, it suggests that these individuals do not have a specific reading difficulty, but may also experience difficulties with other skills for which the cerebellum is necessary.

Differences in cerebellar activation were detected in dyslexic children on a noun-verb association paradigm in an fMRI study (Baillieux, Vandervliet, Manto, Parizel, De Deyn, & Mariën, 2009). Dyslexic children demonstrated bilaterally distributed and more diffuse activation patterns in the cerebellum involving Crus I, Crus II, hemispheric lobule V, VI and vermal lobules IV, VI and VII. The authors proposed that these findings demonstrated an abnormality in intra-cerebellar distribution of activity in dyslexic individuals and that developmental dyslexia may therefore be due to a core difficulty in processing information in the cerebellar cortex.

A number of behavioural studies have highlighted that dyslexic children exhibit difficulties on balancing tasks (Fawcett, Nicolson, & Maclagan, 2001; Kasselimis, Margarity, & Vlachos, 2008; Moe-Nilsson, Helbostad, Talcott, & Toennessen, 2003; Stoodley, Fawcett, Nicolson, & Stein, 2005; Yap & van der Leij, 1994) and other cerebellar tests including dynamic measures such as tapping (Fawcett et al., 2001) and differences in gait, with dyslexic children walking with shorter steps at a higher rate (Moe-Nilsson et al., 2003). Dyslexic individuals have also been shown to have deficits on time estimation tasks, a skill thought to be regulated by the cerebellum (Nicolson, Fawcett, & Dean, 1995) in addition to measures of implicit learning (children: Vicari, Marotta, Menghini, Molinari, & Petrosini, 2003; adults: Howard, Howard, Japikse, & Eden, 2006; Stoodley, Harrison, & Stein, 2006). In contrast to these studies, others have reported no deficit in implicit learning in dyslexic adults (e.g. Kelly, Griffiths, & Frith, 2002; Waber et al., 2003). Howard et al. have suggested that these conflicting reports may be due to differences in task demands concerning the complexity of the sequences to be learned. As the cerebellum has a role in

learning new skills, tasks that draw on this role may elicit greater differences between dyslexic and typically-developing individuals.

Despite studies supporting a cerebellar role in reading, the cerebellar deficit hypothesis of dyslexia has received mixed reviews and is highly controversial, not least because of claims that an exercise-based treatment targeted at cerebellar function can help to address the symptoms of dyslexia (Reynolds & Nicolson, 2007; Reynolds, Nicolson, & Hambly, 2003). Some authors have argued that any reservations about the role of the cerebellum should be fully examined before this is marketed as a treatment (e.g. Rack, Snowling, Hulme, & Gibbs, 2007) and have questioned both the design and rigour of these studies (Bishop, 2007). Other concerns include the actual proportion of dyslexics presenting with cerebellar impairment in previous studies and have suggested that results may be confounded by the inclusion of dyslexic participants with comorbid attention deficit hyperactivity disorder (ADHD). Some studies have failed to replicate such a high incidence of signs of cerebellar dysfunction in dyslexic children as found by Nicolson and colleagues (e.g. Ramus, Pidgeon, & Frith, 2003; Van Daal & van der Leij, 1999) and suggested that of those who did have motor difficulties, a high proportion also had ADHD or developmental coordination disorder (DCD) (Ramus et al., 2003). A meta-analysis concluded that previous significant findings of motor deficiencies in studies with dyslexic children were likely to be due to the inclusion of participants who had ADHD or below average IQ (Rochelle & Talcott, 2006). A recent study assessed cerebellar functions in children with reading disabilities who had failed to respond to a reading intervention, (e.g. instruction in phonics, reading practise, identification of narrative components etc.) in the first year of school (Barth et al., 2010). The results, in conjunction with previous studies (e.g. Kibby et al., 2008; Savage, Frederickson, Goodwin, Patni, Smith, & Tuersley, 2005), provide little evidence that reading proficiency, or response to the reading intervention, was related to cerebellar functions as assessed by

bead-threading and balance tasks. In contrast, the findings did suggest that phonological awareness, rapid naming and lexical knowledge are important for reading proficiency. Finally, Zeffiro and Eden (2001) have highlighted that if individuals with development dyslexia have a cerebellar abnormality, it may be expected that they would demonstrate more severe symptoms of cerebellar clinical syndrome than have currently been recorded in dyslexic children.

5.1.4 The cerebellum and mathematical ability

In lesion studies following damage to the cerebellum, mathematic skills are rarely investigated and it is unclear whether this is because these abilities are not adversely affected, or because they are simply not included in outcome measures. In addition, it is not known whether any deficits in mathematics seen in cerebellar patients are due to a general intellectual decline, or whether a more specific impact is seen on mathematic skills. For effective rehabilitation, this area requires similar clarification to the reading impairments that have been reported in this population. Mathematics functioning is usually considered to be subserved by parietal and prefrontal areas (e.g. Rickard, Romero, Basso, Wharton, Flitman, & Grafman, 2000) and the intraparietal sulcus (e.g. Dehaene, Piazza, Pinel, & Cohen, 2003); however, some studies have highlighted that for complex, rapid arithmetic processing additional areas are recruited, including the cerebellum as part of the cortico-thalamic-cerebellar circuits (Feng, Fan, Yu, Lu, & Tang, 2008; Kucian, Loenneker, Dietrich, Martin, & von Aster, 2005; Menon, Rivera, White, Glover, & Reiss, 2000). Conklin and colleagues reported on both academic and cognitive outcomes in a large sample of children (N=87) treated for an ependymoma with radiation therapy (Conklin et al., 2008). The results of this study indicated that whilst the group mean was below the test norm mean (100) for reading (87), maths (86) and spelling (86) before conformal radiation therapy was administered, a decline in scores over the course of treatment was seen for reading and spelling but not for maths. This suggested that the tumour

itself and/or resection may have had a detrimental effect on the academic abilities measured, and although radiotherapy did not cause a further decline in maths, recovery of functioning in maths to the test norm level was not seen either. Conversely, another study involving children with medulloblastoma and ependymoma treated with radiation therapy found that these patients became progressively behind their peers in academic measures such as reading, spelling and mathematics in the time post treatment, even when the decline in intellectual skills was considered (Mabbott et al., 2005). Both these studies focused on patients who had received radiotherapy, and it is therefore difficult to posit a direct role of the cerebellum in mathematics. From these studies however, mathematical performance is likely to be influenced by deficits in processing speed, working memory, attention and long term storage of mathematical facts (e.g. Menon, 2010; Temple, 2002), many of which are thought to have cerebellar involvement and have been shown to be impaired in these children.

Another line of investigation examines the numerical abilities of children classified as dyslexic. Whilst it remains controversial whether or not dyslexic children exhibit mathematical difficulties as few empirical studies have been conducted in this area, those that have suggested that the weakness lies in arithmetic fact recall (e.g. Simmons & Singleton, 2006; Turner Ellis, Miles & Wheeler, 1996). Others have posited that mathematical problems occur separately from reading disabilities (e.g. Landerl, Bevan, & Butterworth, 2004). It has been estimated that approximately 40% of children with dyslexia have difficulty with maths (Lewis, Hitch & Walker, 1994) although this overlap may be the result of the language aspect needed for maths rather than difficulties with the concepts of space and quantity in dyslexic children (e.g. Simmons & Singleton, 2009). In children classified as dyscalculic or with mathematical disabilities, independent of reading difficulties, no specific hypothesis concerning cerebellar involvement has been forwarded. One suggestion to account for the

difficulties seen in children with dyscalculia is that they have difficulties with both semantic (e.g. Geary, Hamson, & Hoard 2000; Geary & Hoard, 2001) and working memory (Geary, 1993; Siegel & Ryan, 1989; Swanson, Jerman, & Zheng, 2009); however, these findings have not been universally supported (e.g. Landerl et al., 2004; Temple & Sherwood, 2002).

It has been suggested that another controversial hypothesis forwarded to account for dyslexia may also be pertinent to the case of dyscalculia. The temporal-processing theory of dyslexia suggests that the phonological and visual impairments reported in dyslexic children are the result of a deficit in processing temporal information in either the visual or auditory modality (e.g. Habib, 2000), although support for this theory has not been consistently found (e.g. McAnally, Hansen, Cornelissen, & Stein, 1997; Nittrouer, 1999). Habib (2000) has posited that dyscalculia may also result from a deficit in time-dependent cognitive processing as sequential processing may be necessary as the mental representation of quantities. Furthermore, Habib suggested that the cerebellum may be implicated in the light of this hypothesis in the role of a 'pacemaker' to temporally coordinate activity in different cortical regions (e.g. Ivry, 1997). As with some of the evidence for a cerebellar role in language, this hypothesis places the role of the cerebellum in a more general, rather than process specific capacity.

Unlike dyslexia, few studies have reported a link between dyscalculia and motor control, although it may simply be that the interrelation has not been extensively studied specifically in this population. One such study investigated the motor abilities of children with arithmetic difficulties in comparison to children with reading and spelling problems and children with general academic impairment (Rourke & Strang, 1978). The authors reported that the children with mathematical problems only were impaired on motor and tactile-perceptual skills relative to the other groups, even though the groups did not differ significantly on WISC full IQ scores. In addition, many studies investigating the

association of motor and academic skills in typically-developing children have reported a link between these areas and in particular have focused upon the predictive power of early motor skills on subsequent achievement scores in mathematics (Tramontana, Hooper, & Selzer, 1988).

5.1.5 Current Study

In this study we report a case series of 12 children treated for cerebellar tumour in the preschool years and examine their academic functioning, taking into consideration their general level of cognitive function. This is achieved by using complementary standardised cognitive and academic measures administered in the same testing session. In addition to highlighting individual profile differences in outcome, any systematic deficits recorded across all participants may help to shed light on cerebellar contribution to academic skills. By using participants who suffered a cerebellar insult in the pre-school years, it ensures that any damage was incurred before formal education was started which may further clarify the role of the cerebellum in the acquisition of academic skills. As in previous chapters the impact of prognostic factors will also be considered in relation to academic attainment and discrepancy with cognitive functioning.

5.1.6 Hypotheses

Two main hypotheses, outlined below, may be drawn from the previous literature concerning the academic functioning in children with cerebellar injury.

- If the role of the cerebellum in cognitive processing is non-specific, i.e. it has a function that is universally employed for many aspects of cognitive functioning, such as temporal processing and error detection, then no specific effects of cerebellar damage on academic functioning may be expected. Chapters 3 and 4 highlighted that many of the participants in this investigation have a delay in the development of at least one area of cognitive control and

one aspect of motor control. Given the postulated link between cognitive, motor and academic scores, it may therefore be predicted that those children with cognitive and motor deficits will also show academic impairment for their age at a level commensurate with their other deficits. Similarly, for those children in this study who have not been found to have severe cognitive or motor impairment, i.e. P02, P05 & P14, their academic functioning may also be expected to be in line with their cognitive abilities. For this model, scores for cognitive skills should correlate positively with scores for academic indices and the strength of the correlations should be similar to those seen in typically-developing children.

- If the cerebellum has a specific role in reading and language skills as suggested by the cerebellar hypothesis of dyslexia and in completing mathematical problems, then a deficit in academic scores may be seen above and beyond that which would be expected given the level of general cognitive functioning in these children. In this instance, even those children who do not demonstrate a general cognitive impairment (i.e. P02, P05 & P14) may be expected to show an impairment in more specific academic skills and those that are impaired on general cognitive measures may show additional impairments in scholastic skills. In addition, the strength of correlation between cognitive and academic scores in the cerebellar patients should differ from those seen for typically-developing children.

The use of complementary cognitive and academic standardised measures with the patients in this study may enable differentiation of these two hypotheses. It is possible however that these predictions may be confounded by differences in prognostic factors across participants, which may have an impact on academic functioning. For example it is important to consider age at diagnosis, tumour type and treatment, tumour location and time post treatment. Specifically, the following hypotheses may be outlined from previous literature:

- Both imaging and lesions studies suggest that for reading skills at least, a differential hypothesis may be forwarded based on the location of the damage within the cerebellum. Previous research appears to indicate that damage to the right cerebellum may result in more severe deficits in language and reading skills. In this small heterogeneous sample, it is difficult to divide participants into clear groups based on tumour location, however the participants with right hemisphere (RH) and vermis involvement (i.e. P02, P03 & P10) may be expected to perform more poorly on reading and language measures than participants with damage to the left hemisphere (LH) and vermis.
- Although the impact of age at diagnosis may be attenuated by including participants diagnosed ≤ 5 years, if the cerebellum is necessary for the acquisition of language and reading skills, then it is possible that a difference may be seen between the youngest child at diagnosis (18 months) and the oldest child at diagnosis (93 months).

5.2 Method

5.2.1 Participant information

Of the 15 patients who participated in this overall investigation (Chapter 3), 12 children participated in the current investigation. These were the same 12 who completed the longitudinal follow-up assessments (Chapter 4). For the three children who did not complete the assessments for this study (P08, P12 & P15), the loss-to-follow-up reasons were the same as those given for the longitudinal follow-up assessments reported in Chapter 4. Due to practical difficulties only 11 children completed all measures for this study as EH was unable to complete the WPPSI-II due to logistical difficulties with testing. Details concerning inclusion criteria, demographics, tumour and treatment details for each patient are reported in Chapter 3.

5.2.2 Procedure

Each child completed a standardised measure of academic ability (WIAT-II^{UK}; Wechsler, 2005) and a standardised measure of cognitive skills (WISC-IV^{UK}; Wechsler, 2004/WPPSI-III^{UK}; Wechsler, 2003) which were administered in a single testing session. Tests were completed over one session lasting approximately two hours with regular breaks. The WIAT-II was conducted first for all children, followed by the WISC-IV/WPPSI-III to ensure that no differences in scores as a result of test order were introduced across participants.

5.2.3 Assessments

The Wechsler Individual Achievement Test - Second UK Edition (WIAT-II) was used to assess language, numerical and reading abilities. This is an age-adjusted standardised measure suitable for 4 to 16 year olds. Nine core subtests are presented as a series of tasks and scores on these individual subtests are grouped to produce scores for broader processing areas, namely Reading, Mathematics, Written Language and Oral Language. Scores on these

broad abilities are then combined to produce the Total Composite score which is the general measure of academic ability given by this test (μ= 100, σ = 15).

The Wechsler Intelligence Scale for Children - Fourth UK Edition (WISC-IV) was used as a measure of intellectual ability for participants aged 6 years and over as this age-adjusted standardised measure is suitable for 6 to 16 year olds. This measure consists of 10 core subtests which are grouped to produce scores on broader processing areas, namely Verbal Comprehension, Perceptual Reasoning, Working Memory and Psychomotor Speed. Scores on these broad abilities are combined to produce the Full Scale IQ (FSIQ) which is the general measure of cognitive ability (μ = 100, σ = 15).

The Wechsler Pre-school & Primary Scale of Intelligence - Third UK Edition (WPPSI-III) was used as a measure of intellectual ability for the participant aged 5 (P07) as this age-adjusted standardised test is suitable for 2 to 7 year olds. This measure consists of 8 core subtests which are grouped to produce scores on broader processing areas, namely Verbal IQ, Performance IQ, and Processing Speed. Scores on these broad abilities are combined to produce the Full Scale IQ (FSIQ). An additional composite score of General Language processing can also be computed but does not contribute to the FSIQ.

Both the WISC-IV and the WPPSI-III are used in conjunction with the WIAT-II to assess to what extent a child is performing on scholastic measures at a level that is consistent with their overall cognitive ability level, as based on the standardising sample of the measures. These comparisons between observed and expected levels of academic attainment should enable differentiation of the two hypotheses outlined in this chapter and allow conclusions to be drawn concerning the nature of the cerebellar contribution to scholastic skills. The use of these two complementary measures enables a comparison between cognitive and academic skills that would not have been possible using the cognitive scores from the KABC-II measure previously administered. The comparisons between a child's cognitive ability can be based either on their FSIQ, their Verbal

Comprehension Index (VCI) or their Perceptual Reasoning Index (PRI). For this study, comparisons made for all three measures will be reported.

5.2.4 Statistical analyses

The results from this study were investigated using both a case series and group approach. For this study standardised scores were used for all analyses and the data was analysed using the following methods.

5.2.4.1 Main analyses

The initial analyses focused upon elucidating the role of the cerebellum in academic functioning by considering academic performance in comparison to more general cognitive capacity.

1) The extent of cognitive impairment following a cerebellar injury sustained in the preschool years was investigated by assessing individual functioning in verbal comprehension, perceptual reasoning, working memory and processing speed, as measured by the WISC-IV/WPPSI-III. Children with severe deficits were identified using the clinical criteria for significant impairment, i.e. 2SD below the mean of the test normative sample. Scores were also examined to determine whether participants demonstrated any consistent discrepancies between scores on each of the composite indices of the WISC-IV. In addition, the base rates (BR) were calculated for each individual. The BR is the percentage of the norm sample that obtained a difference between their scores on a pair of indices by a specific amount or more and is calculated for each pair of index score comparisons separately. A low BR indicates that the difference value is uncommon, and it has been suggested that a difference between scores occurring in less than 10-15% of the standardisation sample should be judged as unusual (Sattler, 2001). The BR for the discrepancies between index scores for each individual can

be calculated according to either a standardising sample based on age (Overall) or based on each participant's FSIQ score (Ability). The base rates for both these comparison samples were calculated as these patients were not all performing at a level appropriate for their age. Variation across cognitive indices was examined by analysing the differences between index scores across participants using Fisher's exact tests (due to low frequencies). A Friedman's ANOVA was also conducted on the actual difference values across all participants to establish whether the magnitude of difference varied significantly across the cognitive indices.

2) The academic functioning in reading, mathematics, written language and oral expression as measured by the WIAT-II was also investigated across participants, again by assessing individual cases.
3) The relationship between performance on the WISC-IV/WPPSI-III and the WIAT-II was examined using a series of Pearson's correlations with Bonferroni correction (α=.01; 0.05/5). Using the test norm statistics it was possible to compare the correlation coefficients for the patient sample with those recorded for the norm sample using Fisher's z.
4) The difference between obtained scores on the WIAT-II and those predicted for each participant based upon their WISC-IV scores was investigated by examining individual cases. These predicted scores are provided by the standardised test and are based on the standardising sample. In addition, any variation in the magnitude of difference values between obtained and expected scores for each index was assessed by entering the difference values for each index into a Friedman's ANOVA. Pairwise analyses for significant main effects were conducted using Wilcoxon paired rank tests. Bonferroni correction was applied to the pairwise analyses giving a significance level of α=.0167 (.05/3). These analyses were repeated separately for predicted scores based on the Full

Scale IQ (FSIQ), Verbal Comprehension Index (VCI) and Perceptual Reasoning Index (PRI).

5.2.4.2 Further analyses

Other analyses were conducted to explore the data in closer detail using results.

5) The relationship between the KABC-II scores taken at the second testing session (see Chapter 4) and scores on the WIAT-II was investigated using Pearson's correlations with Bonferroni correction (α=.0083; 0.05/6). The KABC-II Time 2 scores were used as these were recorded closest to the data collection for this study (≤3 months for all participants). As the KABC-II measures different aspects of cognitive control than the WISC-IV/WPPSI-III, these additional analyses enable further aspects of cognitive functioning to be related to academic skills. In addition, the KABC-II (Chapter 2) overall cognitive index (FCI) was correlated with the Full-Scale IQ from the WISC to investigate the reliability of assessing cognitive performance using two different measures.
6) The relationship between academic functioning as measured by the WIAT-II and motor abilities as measured by the BOT-2 was assessed using Pearson's correlation coefficient with Bonferroni correction (α=.0071; .05/7). For this investigation scores on the BOT-2 were taken from the second testing session (see Chapter 4) as this data was collected at the closest time point to the WIAT-II scores (≤ 3 months for all participants).
7) Prognostic factors were considered in relation to academic and cognitive scores, as assessed by the WISC-IV/WPPSI-III, in addition to the difference values between the obtained and predicted scores for the WIAT-II. The impact of Age at Diagnosis and Time Post Treatment were assessed using Pearson correlations with Bonferroni correction (α=.025; .05/2). For the WISC-IV and WIAT-II standard scores the effect of

Tumour Type/Treatment was assessed using a series of Chi square tests to explore differences between groups, with Bonferroni correction (α=.0125; .05/4). Tumour Location and Mutism were similarly assessed using a series of Chi square analyses. Any difference between the male and female participants was assessed using a t-test. The impact of prognostic factors on the difference values between obtained and predicted scores on the WIAT-II were investigated using non-parametric rank order statistics to accommodate positive and negative values. The impact of Tumour Type/Treatment, Tumour Location and Mutism were assessed using Kruskal-Wallis. Pairwise analyses were conducted for any overall main effects using Mann Whitney U tests, with Bonferroni correction as above. The impact of Sex upon change in scores over time was assessed using Mann Whitney U tests. The impact of Hydrocephalus on cognitive and academic scores was not assessed in this chapter as it is considered for all measures separately in Chapter 7. The impact of Mutism was assessed in this chapter as it may be expected that those patients with Mutism demonstrate the most severe difficulties with language.

5.3 Results

5.3.1 Performance on the WISC-IV/WPPSI-III

Table 5.1 reports the standard scores for the four cognitive indices and FSIQ score of the WISC-IV for each participant in addition to the group means and standard deviations for each index. Similarly to the cognitive scores from the KABC-II (Chapter 3), there is variability in test performance both within and between patients and across indices; 8/11 (64%) were significantly impaired on at least one of the WISC-IV/WPPSI-III indices and 7 of these same children showed a significant impairment on the Total Composite score. For the different indices significant impairments were seen for; 7/11 (64%) on Verbal

Comprehension, 4/10 (40%) on Perceptual Reasoning, 6/10 (60%) on Working Memory and 6/11 (55%) for Processing Speed. The FSIQ mean was significantly below the test mean (2SD) and although the index means were all above this cut-off, they were all lower than the test norm of 100 (min μ= 71, max μ= 78.9). The standard deviations of the patient sample for the indices were similar to the test norm of 15 (min σ= 13.22, max σ= 16.88) with the exception of Working Memory (σ= 22.22) indicating greater variability in performance for this measure. Closer inspection of scores for this index highlighted that the patients who were unimpaired on this measure generally performed more highly than on other indices, suggesting that this function is either relatively preserved or severely impaired.

Table 5.1 Standard scores for cognitive development measured by the WISC-IV/WPPSI-III (test norm μ = 100; σ = 15) * -2SD from the test norm mean

Child	Verbal Comprehension	Perceptual Reasoning	Working Memory	Processing Speed	Full Scale
P01	61*	94	74	65*	68*
P02	77	84	107	94	86
P03	53*	55*	59*	56*	46*
P04	67*	96	65*	70*	70*
P05	102	92	102	85	95
P06	69*	67*	59*	56*	56*
P07[1]	90	**Performance**[6] 93	-	75	82
P09[7]	-	-	-	-	-
P10	61*	61*	62*	65*	54*
P11	63*	63*	56*	78	57*
P13	59*	79	52*	88	62*
P14	98	98	107	68*	91
μ	*71*	*78.9*	*74.3*	*72.5*	*68.5*
σ	*16.59*	*16.22*	*22.22*	*13.22*	*16.88*

[6] P07 completed the WPPSI-III which does not include a Perceptual Reasoning or Working Memory index, but does include a Performance Index.

[7] P09 did not complete this section of the study

Individual discrepancies between the indices of the WISC-IV are shown in Table 5.2 along with the base rates for all significant differences (BR). No systematic pattern of discrepancy was evident, both across and within participants. Three participants did not demonstrate any discrepancies between their index scores, however these children, P03, P06 and P10, were severely impaired across all cognitive indices. Of the other children who were significantly impaired on at least one index, P01, P04 and P13 performed significantly higher on the Perceptual Reasoning than many of the other indices, whilst P11 performed higher on Processing Speed than any other index. P04, P11 and P13 scored lowest on the Working Memory index, followed by the Verbal Comprehension index. Of the children who did not demonstrate such pervasive impairments, the pattern of discrepancy was somewhat different, with the Working Memory index being least impaired. P05 and P14 both showed a significant decrease on the Processing Speed index relative to other indices whereas P02 performed significantly higher on Working Memory than all other indices. There was therefore little consistency within and across patients, suggesting that there may be no systematic effect of cerebellar tumour on individual variation, although it is difficult to draw firm conclusions from a small heterogeneous sample.

Table 5.2 WISC Discrepancy analysis showing differences (D) between index scores (VCI= Verbal Comprehension; PRI=Perceptual Reasoning; WMI=Working Memory, PSI=Processing Speed) and the base rate (BR) for significant differences (* $p \leq .05$), according to both the Overall standardising sample and the Ability matched sample for each participant

Child		VCI - PRI		VCI - WMI		VCI - PSI		PRI - WMI		PRI - PSI		WMI - PSI	
		D	BR	D	BR	D	BR	D	BR	D	BR	D	BR
P01	Overall	-	1.1	-	18.5	-4	-	20*	10	29*	2.4	9	-
	Ability	33*	0.5	13*	22		-		6.5		1.1		-
P02	Overall	-7	-	-	2	-	15.9	-	6.2	-10	-	13*	21.5
	Ability		-	30*	3.4	17*	20.9	23*	7.7	-10	-		20.3
P03	Overall	-2	-	-6	-	-3	-	-4	-	-1	-	3	-
	Ability		-		-		-		-		-		-
P04	Overall	-	1.9	2	-	-3	-	31*	2.4	26*	4.2	-5	-
	Ability	29*	2.2	2	-		-		2.7		2.2		-
P05	Overall	10	-	0	-	17*	14.7	-10	-	7	-	7	-
	Ability		-		-		14.9		-		-		-
P06	Overall	2	-	10	-	13	-	8	-	11	-	3	-
	Ability		-		-		-		-		-		-
P07	Overall	-		-		-		-		-		-	
	Ability												
P09	Overall	-		-		-		-		-		-	
	Ability												
P10	Overall	0	-	-1	-	-4	-	-1	-	-4	-	-3	-
	Ability		-		-	-4	-	-1	-	-4	-	-3	-
P11	Overall	0	-	7	-	-	19.1	7	-	-	16.4	-	9.2
	Ability		-		-	15*	24.7		-	15*	17.7	22*	8.1
P13	Overall	-	6.7	7	-	-	4.1	27*	4.0	-9	-	-	1
	Ability	20*	8.1	7	-	29*	5.9		4.3		-	36*	1.1
P14	Overall	0	-	-9	-	30*	3	-9	-	30*	2	39*	1
	Ability		-		-		2.4		-		2.3		1

Table 5.3 summarises the index pairwise comparisons across all indices and participants, detailing the number of times an index was found to be significantly higher or lower than another index. Thirty comparisons were made for each index (10 participants with comparisons to three other indices). Fisher's exact tests between the proportion of incidences an index was higher and the number of times it was significantly lower than another index revealed a significant difference in the proportions for Verbal Comprehension and Perceptual Reasoning (p=.008), supporting the conclusion that Perceptual Reasoning appears to be the least impaired whilst Verbal Comprehension is the most affected. Contrary to this finding, a Friedman's ANOVA compared the actual difference values across the pairwise comparisons for all indices and revealed no significant variation between difference scores (χ^2 = 1.837, p=.871), suggesting that the magnitude of difference was not significant when all participant scores were taken into account.

Table 5.3 Proportion of comparisons for which the individual WISC-IV indices were significantly higher or lower than other indices

Index	Significantly higher than other indices	Significantly lower than other indices
Verbal Comprehension	2/30	8/30
Perceptual Reasoning	9/30	2/30
Processing Speed	6/30	7/30
Working Memory	5/30	5/30

5.3.2 Performance on the WIAT-II

The standard scores for the four indices and Total Composite score of the WIAT-II are reported in Table 5.4 for each participant in addition to the group means and standard deviations. Variability was evident between patients, however compared to scores on the WISC-IV there appeared to be lower intra-individual variation; 6/12 (50%) children were significantly impaired on at least one index, with the same participants all impaired on the Total Composite. For the four indices significant impairments were seen in the same six participants, with the exception of Oral Language in which only 4/12 (33%) were significantly impaired. This was reflected in the group means for each index; mean scores were significantly below the test norm mean of 100 for Reading (μ=70.4), Mathematics (μ=67.75) and Written Language (μ=68.5) but not for Oral Language (μ=79.67). Similarly, the standard deviation for Oral Language was comparable to that of the test norm of 15 (σ=14.96) whereas it was higher for the other indices indicating a wider spread of results (min σ= 22.10, max σ= 25.14). The highest variability was seen for Written Language, which may reflect differences in motor impairment in this sample (cf. Chapters 3, 4). This high variability for the other indices may also be due to the clear division within the sample between those with significant cognitive impairments (i.e. P01, P03, P04, P06, P10 & P11) and those with relatively spared functioning (i.e. P02, P05, P07, P09 & P14). Inspection of the WIAT-II index scores suggested this is the case with the possible exception of P13, and potentially P07 (although P07 completed insufficient indices to draw firm conclusions), who was borderline impaired across all academic indices. It should be noted that both of these children had a relatively short time post treatment and were still both less than 7 years of age. It is possible that with these two participants a longer time post treatment may result in a more severe delay of academic skills as they fail to develop at the same rate as their peers.

Table 5.4 Standard scores for academic attainment measured by the WIAT-II (test norm μ = 100; σ = 15) * -2SD from the test norm mean [8]

Child	Reading	Mathematics	Written Language	Oral Language	Total Composite
P01	44*	66*	46*	66*	51*
P02	101	84	86	82	87
P03	53*	43*	61*	69*	54*
P04	67*	46*	41*	86	59*
P05	96	94	103	93	96
P06	63*	40*	50*	68*	53*
P07	-	78	-	82	-
P09	-	92	-	91	-
P10	47*	48*	40*	60*	45*
P11	57*	57*	48*	72	56*
P13	74	71	79	73	71
P14	102	94	104	114	103
μ	*70.4*	*67.75*	*68.5*	*79.67*	*67.5*
σ	*22.10*	*20.69*	*25.14*	*14.96*	*20.66*

[8] Standard scores are not reported for P07 and P09 for Reading and Written Language as they did not complete these tests due to young age

5.3.3 WIAT-II performance compared to WISC-IV performance

Correlations were performed to investigate the relationship between WISC-IV and WIAT-II scores (Table 5.5). The results from the norm sample (minimum N = 637) suggested that performance on cognitive and scholastic measures are closely related, with significant correlations reported between all indices of both standardised measures (max. r=.77, p<.001; min. r=.22, p<.001). These correlations revealed that Processing Speed, with the lowest r values, was the cognitive ability least related to academic functioning. In the patient sample (N=10) significant positive correlations were found between Verbal Comprehension and all academic indices. Perceptual reasoning was significantly positively correlated with Mathematics and Oral Language, although these were not significant following Bonferroni correction. Working Memory was found to be significantly positively correlated with all academic indices, although the correlation with Oral Language was no longer significant after Bonferroni correction. Processing speed was only found to correlate with Mathematics, although again this failed to reach significance at the adjusted level. The FSIQ was found to be strongly positively associated with all academic indices. Across the WIAT-II indices therefore, only Mathematics was found to correlate with all cognitive indices. The strength of the correlation coefficients was stronger for the patient sample despite fewer reaching significance (possibly due to difference in N across the patient and normative samples), with a similar decrease in strength seen between Processing Speed and the academic indices. Comparison of the correlations coefficients for the norm sample and the patient group using Fisher's z revealed no significant differences between each pair of correlations, suggesting that despite a small patient sample, which may preclude some of the correlations reaching significance, the pattern of correlations is typical of a much larger sample of typically-developing children.

Table 5.5 Correlations (*r*) between scores on the WIAT-II and WISC-IV indices for the cerebellar patients (N=10) and for the standardising sample (minimum N=637). Fisher's z scores to compare correlation coefficients between groups, after Bonferroni correction α=.01

Cognitive ability (WISC-IV) Index		Academic ability (WIAT-II) Reading	Mathematics	Written Language	Oral Language	Total Composite
Verbal Comprehension	Patient r	.828	.795	.789	.844	.877
	p	.003	.006	.007	.002	.001
	Control r	.67	.62	.52	.64	.74
	p	<.0001	<.0001	<.0001	<.0001	<.0001
	z	.98	.95	.102	1.67	1.08
	p	.327	.342	.204	.095	.280
Perceptual Reasoning	Patient r	.550	.650	.448	.689	.609
	p	.100	.042	.194	.028	.062
	Control r	.52	.58	.41	.47	.6
	p	<.0001	<.0001	<.0001	<.0001	<.0001
	z	.11	.3	.12	.88	.04
	p	.912	.764	.905	.379	.969
Working Memory	Patient r	.818	.839	.764	.745	.849
	p	.004	.002	.010	.013	.002
	Control r	.52	.52	.37	.35	.53
	p	<.0001	<.0001	<.0001	<.0001	<.0001
	z	1.51	1.69	1.63	1.57	1.74
	p	.131	.091	.103	.116	.082
Processing Speed	Patient r	.612	.659	.528	.273	.563
	p	.060	.038	.117	.446	.090
	Control r	.26	.29	.25	.22	.31
	p	<.0001	<.0001	<.0001	<.0001	<.0001
	z	1.17	1.3	.87	.15	.83
	p	.242	.194	.384	.881	.407
Full Scale IQ	Patient r	.860	.859	.778	.816	.896
	p	.001	<.001	.008	.004	<.001
	Control r	.69	.72	.52	.61	.77
	p	<.0001	<.0001	<.0001	<.0001	<.0001
	z	1.17	1	1.22	1.15	1.13
	p	.242	.317	.223	.250	.259

By using two comparable standardised measures with these participants, it was possible to ascertain the scores participants were predicted to achieve on the WIAT-II on the basis of their WISC-IV scores, based on scores from the normative sample. The discrepancy between these predicted scores and the scores participants actually obtained was calculated and the base rate established, similar to the WISC-IV index discrepancy analysis above. Predicted scores can be calculated using participants' scores on the Verbal Comprehension (VCI), the Perceptual Reasoning (PRI) or the Full Scale IQ (FSIQ) indices of the WISC-IV. For this study, predicted scores based on all three indices were calculated as the participants showed variable performances across these measures. In general VCI was found to be most impaired and PRI the least impaired. Given the opposite trends in these indices, and the fact that they both contribute to the FSIQ, the predicted scores based on the three indices might yield contrasting results. Significant differences between observed and predicted scores are reported in Table 5.6 and illustrated in Figure 5.1 for each participant individually.

The six children who were significantly impaired across the WIAT-II indices (P01, P03, P04, P06, P10 & P11) also demonstrated significant discrepancies between observed and predicted scores, based on their FSIQ scores, with their academic performance being lower than expected based on their cognitive abilities. Of these children, two were significantly lower than expected on all of the academic indices (P01 & P10), three were lower on four of the indices, excluding Oral Language (P04, P06 & P11) and P03 was lower on three of the indices, excluding Oral Language and the Total Composite score. In comparison, of those children who were not significantly impaired on the WIAT-II (P02, P05, P07, P13 & P14) three demonstrated no significant differences between their predicted and obtained scores on all indices (P05, P07 & P13), whilst P14 performed significantly higher than expected on four of the indices (excluding Mathematics) and P02 scored significantly higher than predicted on

Reading, but was lower than expected on Written Language and Oral Comprehension. Table 5.6 demonstrates that a similar pattern of discrepancy was recorded for the analysis based on the children's VCI cognitive scores, although the differences are generally larger and the base rates are lower than for comparisons based on the FSIQ scores.

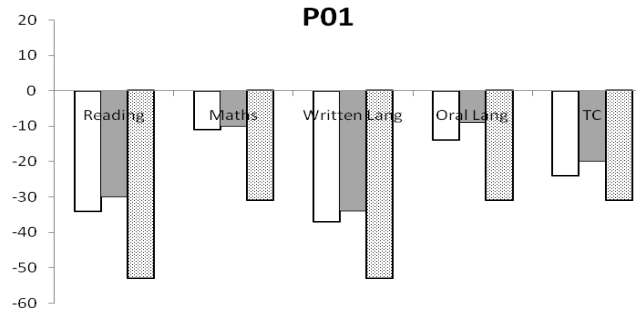
For the discrepancy analysis based on PRI scores, of the six participants who were significantly impaired on WIAT-II indices, five performed significantly lower than predicted on all the indices (P01, P03, P04, P06, & P10) whilst P11 was significantly lower on four of the indices. The base rates for these discrepancies were generally smaller than those for the FSIQ and VCI comparisons with the majority below 15%, indicating that these differences were less common in the norm group. Of the children who were not significantly impaired on the WIAT-II indices, P05 demonstrated no significant differences between predicted and obtained scores, P14 performed significantly higher than expected on Oral Language and P02 was significantly higher on Reading and significantly lower on Oral Language. For those participants who were not significantly impaired but did show diminished performance on the WIAT-II (P07 & P13), the discrepancy analysis based on PRI scores separated these participants from those children who were not significantly impaired in cognitive skills. Both P07 and P13 performed significantly lower than predicted on all academic indices, similarly to those children who were significantly impaired in cognitive skills. Despite this, the differences between observed and predicted scores for P07 and P13 were not as large as those seen for the children with severe cognitive impairments and the base rates were correspondingly higher for P07 and P13.

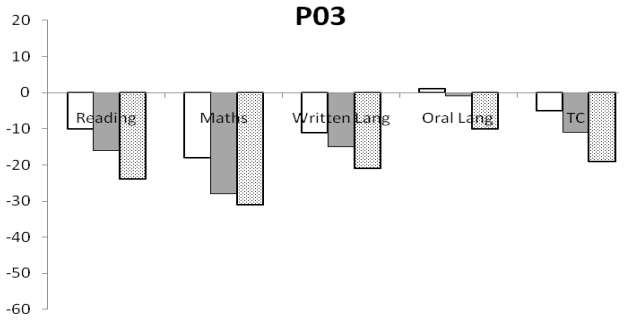
When expected scores were predicted using the FSIQ score, across all participants and indices, of those observed scores that were significantly different from the predicted scores, 27/52 (52%) were significantly lower than the predicted scores and 5/52 (10%) were significantly higher. When the VCI

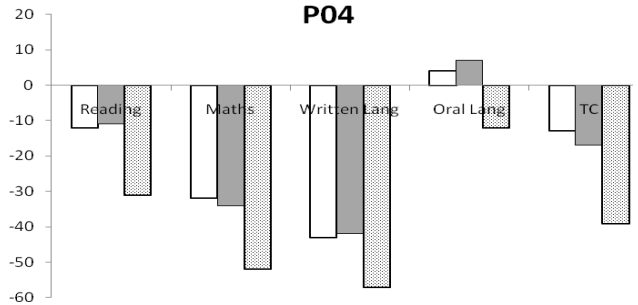
scores were used to make predictions for the WIAT-II indices 27/52 (52%) of the observed scores were significantly lower than the predicted scores and 2/52 (4%) were significantly higher. For the comparison based on PRI scores 38/52 (73%) of participant scores were significantly lower than predicted and 2/52 (4%) were significantly higher. Across all the indices, Reading, Written Language and Oral Language had participants who scored significantly higher than predicted whereas for the Mathematics index obtained scores were only the same or lower than those predicted.

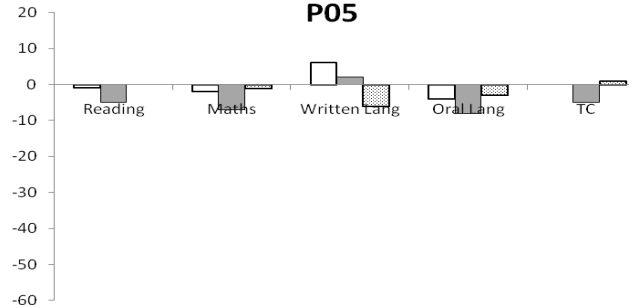
Table 5.6 Discrepancy analysis of predicted WIAT-II scores based on FSIQ, VCI & PRI indices from the WISC-IV/WPPSI-III showing differences (D) between observed and predicted scores and the base rate (BR) for significant differences (* $p \leq .05$), a negative difference indicates that the obtained score was lower than the predicted score

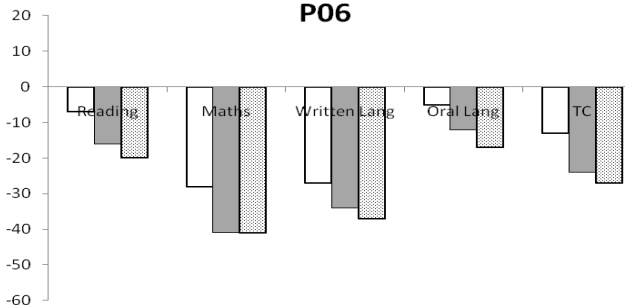
Child	Ability Score	Reading		Mathematics		Written Language		Oral Language		Total Composite	
		D	BR	D	BR	D	BR	D	BR	D	BR
	FSIQ	-34*	<1	-11*	15-20	-37*	1	-14*	10-15	-24*	<1
P01	VCI	-30*	<1	-10*	20-25	-34*	1-2	-9	-	-20*	3
	PRI	-53*	<1	-31*	1-2	-52*	<1	-31*	1-2	-31*	<1
	FSIQ	11*	15-20	-6	-	-7*	-	-9*	20-25	-2	-
P02	VCI	16*	5-10	-2	-	-2	<25	-3	-	4	-
	PRI	9*	25	-7	-	-8	-	-11*	20-25	-3	-
	FSIQ	-10*	20	-18*	5-10	-11*	25	1	-	-5	-
P03	VCI	-16*	10	-28*	1-2	-15*	15-20	-1	-	-11*	15
	PRI	-24*	4	-31*	1-2	-21*	10	-10*	20-25	-19*	5-10
	FSIQ	-12*	15	-32*	<1	-43*	<1	4	-	-13*	10
P04	VCI	-11*	15-20	-34*	<1	-42*	<1	7	-	-17*	5
	PRI	-31*	1-2	-52*	<1	-57*	<1	-12*	20	-39*	<1
	FSIQ	-1	-	-2	-	6	-	-4	-	0	-
P05	VCI	-5	-	-7	-	2	-	-8	-	-5	-
	PRI	0	-	-1	-	-6	-	-3	-	1	-
	FSIQ	-7*	>25	-28*	<1	-27*	4	-5		-13*	10
P06	VCI	-16*	15	-41*	<1	-34*	1-2	-12*	15-20	-24*	1
	PRI	-20*	5-10	-41*	<1	-37*	1-2	-17*	10-15	-27*	1-2
	FSIQ			-7	-			-4	-		
P07	VCI	-	-	-14*	10-15	-	-	-9	-	-	-
	PIQ			-17*	5-10			-15*	10-15		
	FSIQ										
P09	VCI	-	-	-	-	-	-	-	-	-	-
	PRI										
	FSIQ	-21*	3	-19*	5	-36*	1-2	-12*	15-20	-20*	2
P10	VCI	-27*	1	-28*	1-2	-40*	<1	-15*	10-15	-26*	<1
	PRI	-33*	<1	-30*	1-2	-44*	<1	-22*	5-10	-32*	<1
	FSIQ	-13*	10-15	-12*	15	-30*	2-3	-2	-	-11*	10-15
P11	VCI	-18*	5-10	-20*	5-10	-33*	1-2	-4	-	-17*	5
	PRI	-24*	4	-22*	5	-37*	1-2	-11*	20-25	-22*	4
	FSIQ	0	-	-2	-	-1	-	-4	-	0	-
P13	VCI	1	-	-4	-	0	-	-1	-	1	-
	PRI	-15*	10-15	-17*	10	-12*	20-25	-17*	10-15	-16*	10
	FSIQ	8*	25	0	-	9*	-	19*	5-10	10*	15
P14	VCI	3	-	-5	-	5	-	15*	10-15	4	-
	PRI	3	-	-5	-	5	-	15*	15	4	-

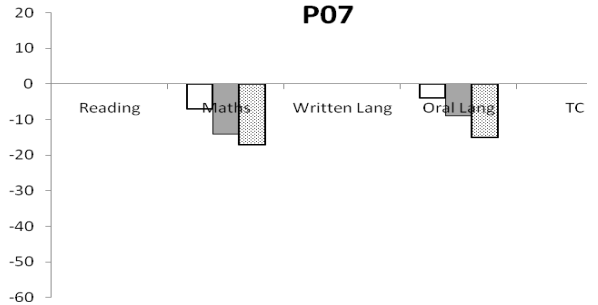


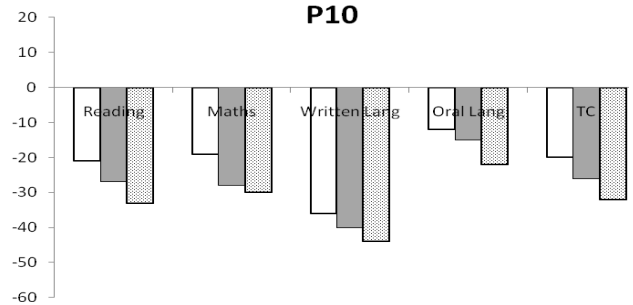


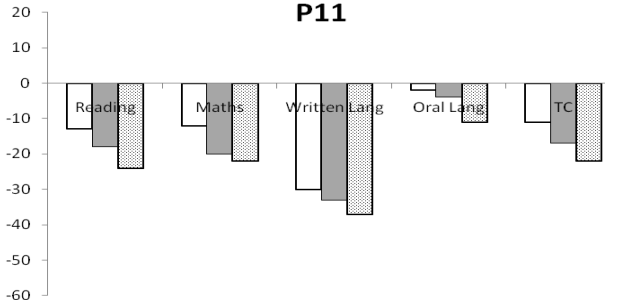


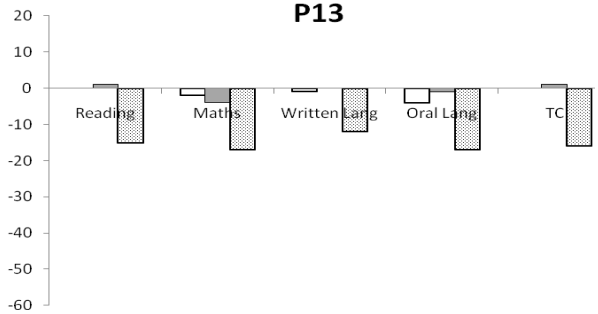












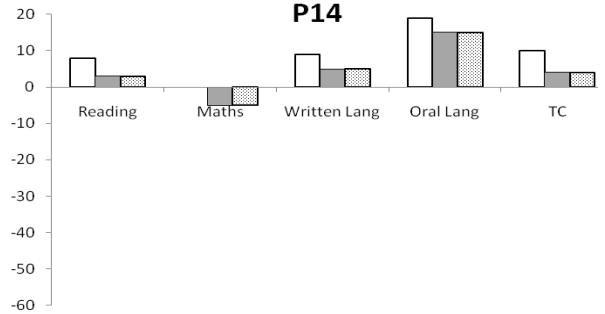
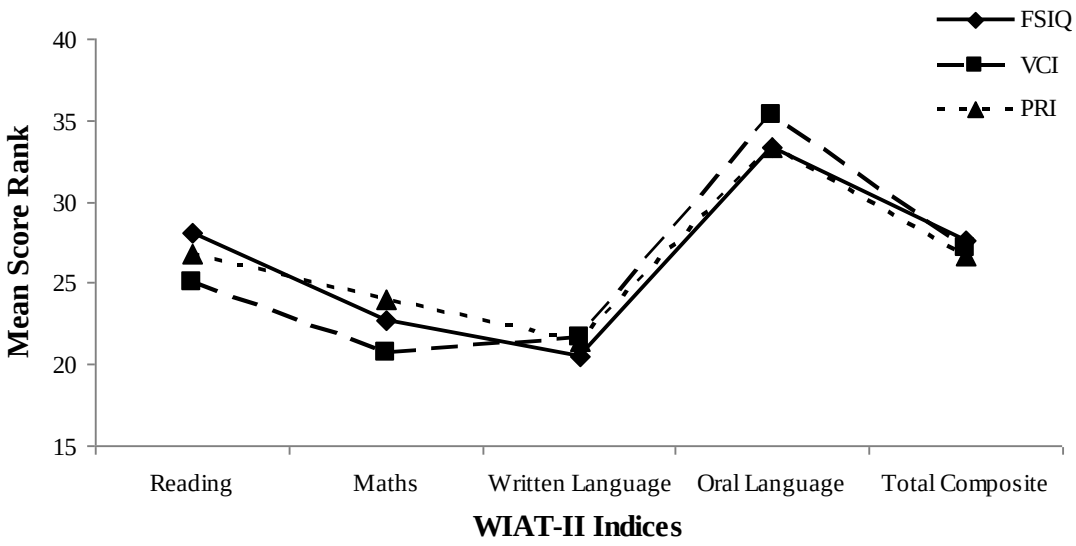


Figure 5.1 Individual profiles of difference values between predicted and achieved scores for WIAT-II indices Reading, Mathematics, Written Language, Oral Language and the Total Composite based on FSIQ□ VIQ■ PRI▩ performance. A negative value indicates performance was poorer than expected

Any variation across academic indices (WIAT-II) in the differences between obtained and predicted scores was investigated using Friedman's ANOVAs. For the predicted scores based on the FSIQ score, no main effect of index (i.e. Reading, Mathematics, Written Language, Oral Language and Total Composite) was found (χ^2=8.642, *p*=.071) although it was approaching significance. A significant difference was found across the academic indices for the scores predicted based on the VCI index (χ^2=12.203, *p*=.011). Subsequent pairwise analyses suggested that the differences between predicted and observed scores were larger for Mathematics than Reading (z=1.989, *p*=.022) and Oral Language (z=2.402, *p*=.008), although only Oral Language remained significant following Bonferroni correction. In addition, Written Language was found to have a larger difference between observed and predicted scores than Reading (z=1.837, *p*=.032) and Oral Language (z=2.145, *p*=.016) although again only Oral Language was significant after Bonferroni correction.

For predicted scores based on the PRI scores no main effect was found (χ^2=8.746, *p*=.062) although again it was approaching significance. Figure 5.2 illustrates the mean rank scores for the difference values between predicted and actual scores for each academic index. Rank scores were used to overcome the difficulty with positive and negative differences. This figure highlights that for all comparisons Mathematics and Written Language demonstrate the largest negative difference between predicted and achieved score, i.e. performance was lower than expected. In contrast the scores obtained for Oral Language show consistently lower differences from the predicted scores than the other WIAT-II indices.

Figure 5.2 Mean rank values across indices for the difference between predicted and actual scores based on Full Scale IQ (FSIQ), Verbal Comprehension (VCI) and Perceptual Reasoning (PRI) performance



5.3.4 Relationship between academic scores and KABC-II and BOT-2 scores

In comparison to the scores from the KABC-II at Time 2 which were collected within 3 months of this data (Chapter 4), of the 7 children significantly impaired on the FSIQ measured here, only 4 were significantly impaired on the FCI. In addition, one child, P07 was found to be significantly impaired in one area of the KABC-II but was above the cut-off for all scores on the WISC-IV. This suggests that these two measures may be tapping different aspects of cognitive control.[9]

In addition to correlating WIAT-II scores with WISC-IV scores, the academic indices were also correlated with the cognitive scores from the KABC-II, taken at time 2 (Table 5.7). The results revealed that whilst Short Term Memory was not significantly associated with any of the academic indices, significant positive correlations were found between all other indices (excluding

[9] The correlation between FSIQ (WISC-IV) and FCI (KABC-II) was found to be positive and significant (r=.961, p<.001) suggesting reliability of cognitive performance in these patients when assessed with different measures.

Written Language and Fluid Reasoning), although not all remained significant following Bonferroni correction.

Table 5.7 Pearson correlation coefficients (*r*) between academic indices of the WIAT-II and the indices of the KABC-II, after Bonferroni correction α=.0083

			WIAT-II Indices				
			Reading	**Mathematics**	**Written Language**	**Oral Language**	**Total Composite**
KABC-II Indices	**Short Term Memory**	r	.521	.463	.478	.292	.522
		p	.122	.130	.163	.357	.122
	Visual Processing	r	.693	.677	.651	.804	.773
		p	.026	.016	.042	.002	.009
	Long Term Storage & Retrieval	r	.773	.760	.630	.717	.753
		p	.009	.004	.051	.009	.012
	Fluid Reasoning	r	.775	.801	.644	.793	.979
		p	.014	.009	.061	.011	.010
	Crystallised Ability	r	.890	.760	.701	.787	.848
		p	.001	.004	.024	.002	.002
	Fluid Crystallised Index	r	.885	.837	.748	.837	.890
		p	.001	.001	.013	.001	.001

Correlations were performed between the academic indices of the WIAT-II and different areas of motor control as measured by the indices of the BOT-2. Standard scores from the balance and pegboard components of the BOT-2 were also correlated with academic scores. Balancing scores were highlighted, in particular to address the cerebellar deficit hypothesis for dyslexia as previous studies have largely cited difficulties on balance measures to implicate the cerebellum in dyslexia (e.g. Brookes & Stirling, 2005; Kasselimis et al., 2008; Stoodley et al., 2005). Others have used the pegboard as a measure of cerebellar functioning in a dyslexic sample (e.g. Fawcett et al., 2001). The correlations are summarised in Table 5.8. As can be seen, significant positive correlations were found between Fine Manual Control and all academic scores, between Manual Coordination and Reading and Oral Language, between Body Coordination and Reading and Oral Language and between the Total Motor Composite and all academic indices (except Written Language). After Bonferroni correction only the correlations between Fine Manual Control and Reading and Oral Language remained significant. Strength & Agility was not found to be associated with any of the academic indices. Similarly, no significant correlations were found between the academic scores and performance on the pegboard task. Scores on the balance task were found to be significantly positively related to performance on Oral Language only, although this was not retained following Bonferroni correction.

Table 5.8 Pearson correlation coefficients (*r*) between academic indices of the WIAT-II and the indices of the BOT-2 and standardised scores for the Balance and Pegboard components of the BOT-2, after Bonferroni correction α=.0071

			WIAT-II Indices				
			Reading	**Mathematics**	**Written Language**	**Oral Language**	**Total Composite**
BOT-2 Indices	**Balance**	r	.477	.438	.187	.627	.412
		p	.164	.155	.605	.029	.237
	Pegboard	r	.367	.107	.234	.473	.361
		p	.297	.740	.515	.121	.306
	Fine Manual Control	r	.787	.607	.745	.802	.845
		p	.007	.036	.013	.002	.002
	Manual Coordination	r	.510	.419	.251	.660	.465
		p	.013	.175	.484	.019	.175
	Body Coordination	r	.639	.505	.396	.625	.549
		p	.047	.094	.262	.030	.100
	Strength & Agility	r	.261	.448	.250	.211	.236
		p	.467	.144	.486	.511	.511
	Total Motor Composite	r	.694	.628	.541	.668	.682
		p	.026	.029	.106	.018	.030

5.3.5 Prognostic factors

The impact of prognostic factors was considered for the WISC-IV/WPPSI-III and the WIAT-II indices in addition to their effect on the discrepancy between the predicted and achieved scores on the WIAT-II, based on the different indices of IQ. The statistical results for these analyses are detailed in Tables 5.9.

5.3.5.1 Impact of prognostic factors on WISC-IV and WIAT-II performance

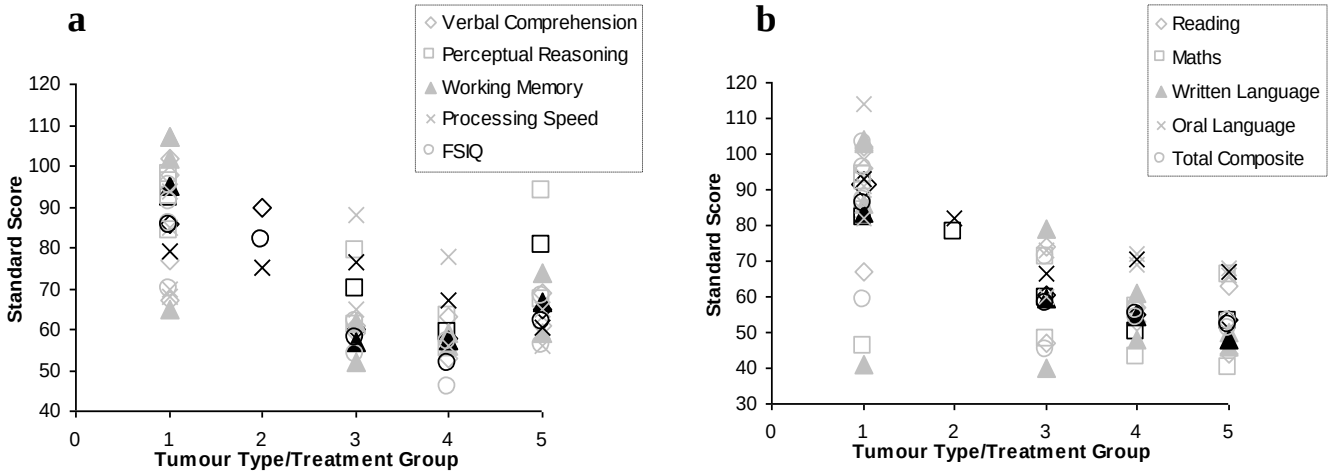
Positive correlations were found between Age at Diagnosis and all of the indices of the WISC-IV and WIAT-II. For the WISC-IV indices moderate positive correlations were found for all indices (min. r=.518; max. r=.816) except Processing Speed (r=.081, p=.824). The correlation with Verbal Comprehension, Perceptual Reasoning and the FSIQ were found to be significant, however only the coefficient for Perceptual Reasoning remained significant following Bonferroni correction. For the WIAT-II indices, the correlation coefficients ranged from mild to moderate, however none were found to be significant (min. r=.396; max. r=.547). Weak negative correlations were found between Time Post Treatment and all indices of the WISC-IV (min .r=-.182; max. r=-.376) and the WIAT-II (min. r=-.167; max. r=-.537) with none found to be significant. No effect of sex was found on performance in either the cognitive or academic indices.

As in previous chapters tumour histology and treatment received were considered in conjunction as tumour type informs the treatment received. A significant main effect of Tumour/Treatment Type was found across all indices of the WISC-IV (max. $\chi^2(4)=40.92$; min. $\chi^2(3)=21.49$) with the exception of Processing Speed ($\chi^2(4)=7.814$, p=.099). Subsequent pairwise analyses highlighted that for Verbal Comprehension, Processing Speed, Working Memory and FSIQ the children with astrocytoma and surgery only performed most highly. For Verbal Comprehension and FSIQ the child with astrocytoma who received

chemotherapy in addition to surgery also performed more highly than the children with ependymoma and medulloblastoma, but did not significantly differ from the children with astrocytoma and surgery alone (Figure 5.4a).

A significant main effect of Tumour/Treatment Type was found across all indices of the WIAT-II (max. $\chi^2(3)=42.93$; min. $\chi^2(4)=22.05$). Subsequent pairwise analyses suggested that for all indices the children with astrocytoma and surgery alone performed more highly that the children with ependymoma and medulloblastoma. For Mathematics the child with astrocytoma who received chemotherapy scored more highly than the two groups of children who suffered a medulloblastoma (Figure 5.4b). For academic scores children with astrocytoma and surgery alone exhibited a large spread of scores, with the lowest scoring children achieving similar levels to children with medulloblastoma, chemotherapy and CSI (Group 5) highlighting that other factors may contribute to developmental outcome, especially for academic skills.

Figure 5.3 Effect of Tumour Type/Treatment on standard scores achieved on the (a) cognitive (WISC-IV) and (b) academic (WIAT-II) indices, bold points represent group means. (1=astrocytoma, surgery; 2=astrocytoma, surgery, chemotherapy; 3=ependymoma, surgery, chemotherapy; 4=medulloblastoma, surgery, chemotherapy, PF radiation; 5=medulloblastoma, surgery, chemotherapy, PF radiation/CSI)

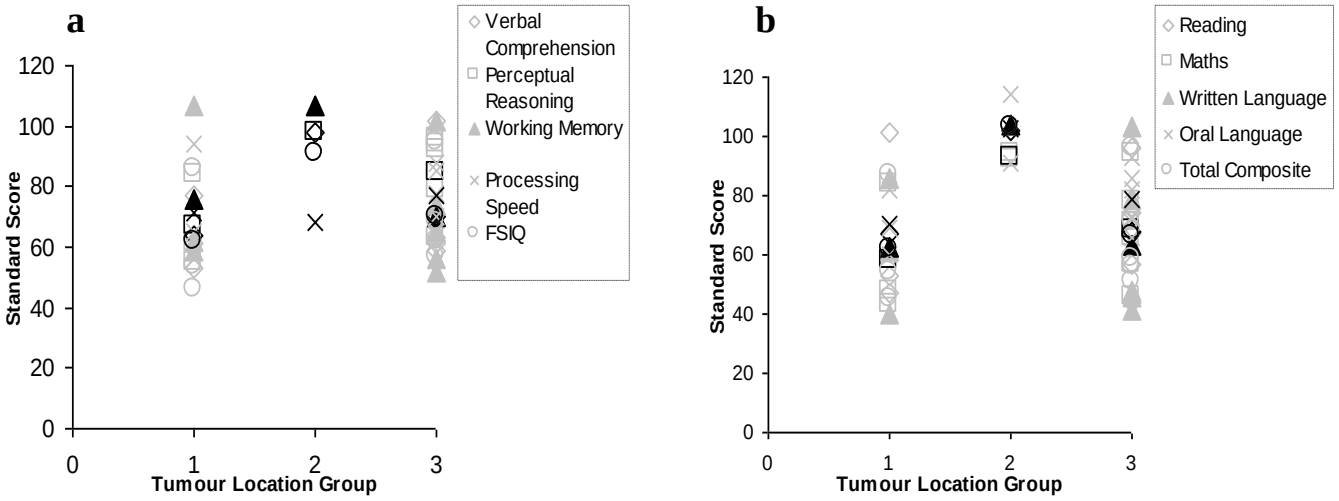


A significant main effect of Tumour Location was found for scores on the Verbal Comprehension, Perceptual Reasoning, Working Memory and FSIQ indices of WISC-IV when the participants were divided according to whether the right hemisphere (RH) and vermis, left hemisphere (LH) and vermis or vermis alone were affected (max. $\chi^2(2)=15.17$; min. $\chi^2(2)=9.19$). No difference was found between groups for Processing Speed ($\chi^2(2)=1.33$, $p=.722$). Pairwise analyses revealed that for Verbal Comprehension, Working Memory and FSIQ, the child with LH and vermis involvement scored more highly than the other two groups and for Perceptual Reasoning the group with RH and vermis involvement performed more poorly than the other groups (Figure 5.5a).

A similar pattern was observed for the academic scores, with an overall effect of tumour location found for all indices of the WIAT-II (max. $\chi^2(2)=21.18$;

min. $\chi^2(2)=14.97$). As above, pairwise analyses suggested that the child with LH/vermis involvement performed more highly than the other groups for all the academic indices (Figure 5.5b). It should be considered that as there is only one child in the LH/vermis group, there is no spread of scores and inclusion of other children with damage in this area would increase the range of scores in this group, perhaps to a similar level as that seen in the other groups. The maximum scores achieved in each group are similar across groups and the lower level is also comparable across the RH/vermis and vermis only group.

Figure 5.4 Effect of Tumour Location on standard scores achieved on the (a) cognitive (WISC-IV) and (b) academic (WIAT-II) indices (1=RH + vermis; 2=LH + vermis; 3=vermis only)



A significant main effect of Mutism was found only for the Processing Speed index of the WISC-IV ($\chi^2(1)=4.69$, $p=.03$) suggesting that those children who had mutism performed more poorly than those without (Figure 5.6a). No other main effects of Mutism were found for the other cognitive indices. A significant main effect of Mutism was found for all the academic indices (max. $\chi^2(2)=29.07$; min. $\chi^2(2)=11.74$) with the largest effect seen for Maths and the lowest effect for the Total Composite. Again, it was the children who suffered mutism that performed more poorly on all measures (Figure 5.6b).

Figure 5.5 Effect of Mutism (1=mutism (N=2); 2=no mutism (N=10)) on standard scores achieved on the (a) cognitive (WISC-IV) and (b) academic (WIAT-II) indices

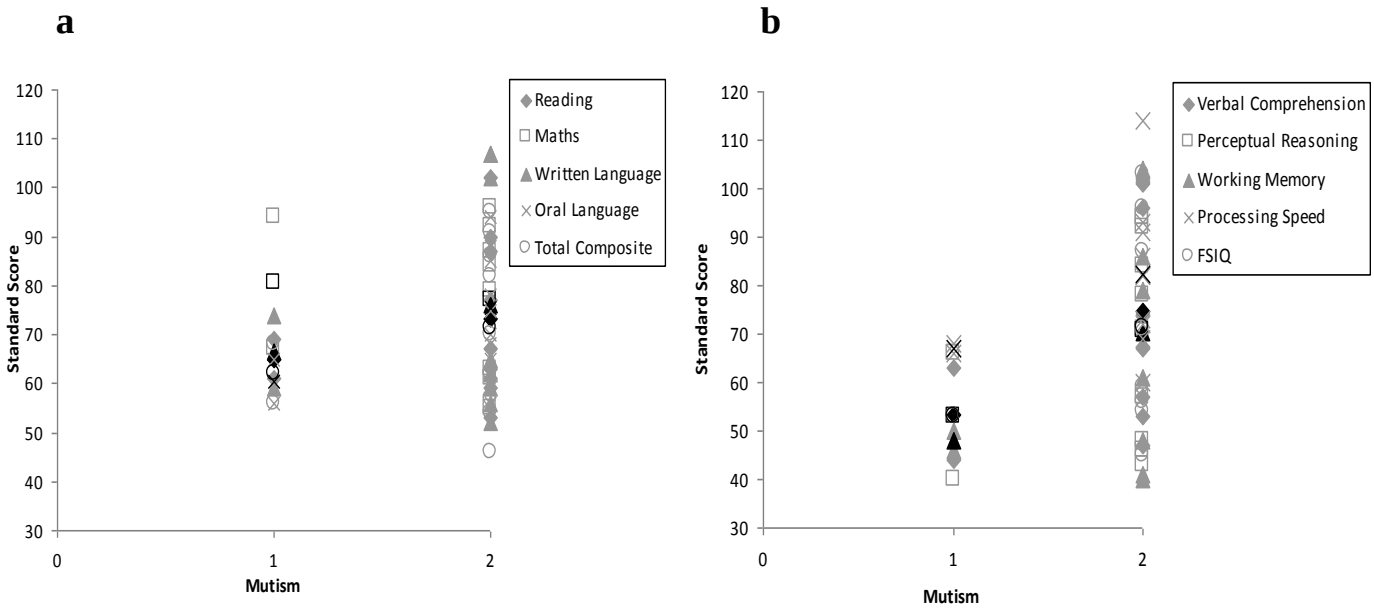


Table 5.9 Correlations (*r*) and difference (χ2) in performance across the cognitive (WISC-IV) and academic (WIAT-II) indices in relation to potential moderator variables, after Bonferroni correction α=.025 for correlation analyses

	Index	Prognostic factors											
		Age at diagnosis		Time post treatment		Tumour type/ treatment		Tumour location		Sex		Mutism	
		r	p	r	p	χ^2	p	χ^2	p	t	p	χ^2	p
WISC-IV/WPPSI-III	Verbal Comprehension	.661	.038	-.359	.308	25.85	<.001	12.16	.007	-1.05	.324	1.54	.215
	Perceptual Reasoning	.816	.004	-.198	.583	21.49	<.001	12.12	.007	-2.20	.052	.234	.629
	Working Memory	.518	.125	-.182	.614	40.9	<.001	15.17	.002	-1.76	.116	2.05	.153
	Processing Speed	.081	.824	-.376	.284	7.81	.099	1.33	.722	7.802	.432	4.69	.030
	FSIQ	.681	.028	-.329	.353	32.04	<.001	9.19	.027	-1.27	.242	2.09	.148
WIAT-II	Reading	.499	.142	-.367	.297	42.93	<.001	14.97	<.001	-.895	.397	12.46	<.001
	Maths	.425	.169	-.537	.072	34.27	<.001	21.01	<.001	-.621	.552	29.07	<.001
	Written Language	.396	.257	-.434	.210	33.76	<.001	21.18	<.001	-.182	.860	19.22	<.001
	Oral Language	.547	.066	-.167	.605	22.05	<.001	16.08	<.001	-1.90	.094	19.40	<.001
	Total Composite	.507	.135	-.339	.338	35.26	<.001	19.27	<.001	-.930	.380	11.74	<.001

5.4 Discussion

This chapter examined the impact of a cerebellar injury due to tumour in the preschool years on cognitive and academic functioning. In addition, data were examined to establish whether any academic deficits could reasonably be assumed to result from a general cognitive deficit, or whether children were scholastically impaired above and beyond their cognitive capacities. The results from this study are discussed below.

5.4.1 Individual outcomes on academic measures and differences in predicted and obtained academic scores

The scores from the academic standardised test highlight that, for the children included in this study, functioning appears to be either significantly lower than peers for all indices or relatively preserved across the range of abilities measured. Whilst some variation was seen between participants there was much less intra-individual variation than has been found with these patients on previous measures administered (see Chapters 3 & 4). In addition, the achievement of scores by some participants close to the test norm mean indicated that academic skills are not necessarily impaired following insult to the cerebellum. The relative uniformity of deficits in those participants who are performing significantly below the test norm mean suggests that these children are exhibiting a general delay, rather than a specific profile of deficit. In addition, as all children were diagnosed in the preschool years, the presence of children with cerebellar damage and intact reading and maths skills suggests that the cerebellum may not play a fundamental role in the acquisition of these skills and that mild cerebellar damage may be well compensated. Some variation was found across indices with maths skills being the most severely affected, as this was the only index in which the observed scores were all the same or lower than those predicted on the basis of IQ. Conversely, Oral

Language was the least affected, with the highest mean score, and in general participants performed closer to their predicted score than for other indices.

Using the accumulated evidence from this chapter it is possible to draw some preliminary conclusions concerning the two main hypotheses set out in the introduction to this chapter. The strong correlations seen between the cognitive (WISC-IV) and academic (WIAT-II) scores in the patient sample suggested that the deficits in academic scores may be the result of a general cognitive deficit. It is certainly the case that those children who were significantly impaired on the FSIQ were also significantly below the test norm mean for the Total Composite of the academic measure. The exception for this was P13, who was impaired on the FSIQ but not the Total Composite; however as discussed above, it is possible that this child will fall further behind peers with increasing time, as this patient finished treatment more recently than many of the other patients. In addition, the similarities between the patient and norm sample correlation coefficients between WISC-IV and WIAT-II scores suggested that the deficits in the patients' academic scores are the result of a general cognitive deficit. The pattern of these correlations may have been expected to differ if cognitive and academic scores were dissociating in the patient sample due a specific role of the cerebellum in academic scores. This case was given further weight by the correlations found between the KABC-II indices and the academic indices. For Crystallised Ability and Long Term Storage & Retrieval, the association with academic tests may be expected, as the skills needed to perform these cognitive tasks appear to be very similar to those required for academic tests. For the same reason, the link between Mathematics and Fluid Reasoning may be expected. The correlations between the other indices however are less explicable and suggest that the general cognitive deficit, as measured by the KABC-II, appears to be impacting on academic scores across the board. This may speak against a specific role of the cerebellum in reading and maths

abilities, although the function it performs in skills which underpin academic success are likely to impact on scholastic tasks.

5.4.2 Link between academic and motor scores

A strong association was reported between motor and academic performance in this group. In particular, the Fine Manual Control index from the BOT-2 was found to correlate strongly with all academic indices. Whilst these correlations are in line with previous research examining the link between motor and scholastic abilities (Son & Meisels, 2006), they may also be reflecting the association between cognitive and motor scores recorded in previous chapters. Given that fine motor skills have been found to be a major component of the relationship between cognitive and motor functioning, it may simply be that the correlations reported in this study were a proxy for the association between cognitive and motor skills. Indeed, this interpretation would fit with a previous study that examined this possibility in typically-developing children (Golstein & Britt, 1994).

Alternatively it is possible that for the most severely impaired children, their cognitive and motor deficits are having an additive effect on scholastic skills, as these difficulties have impacted upon the quality of their interaction with their environment, and hence their ability to learn and improve in academic abilities. Although oral language skills were the least affected of all the academic measures, this skill nonetheless requires fine motor control for precise articulation. This result, together with the finding that other academic skills such as reading or mathematics were more impaired, suggests that deficit in the manual component of fine motor control may have the largest impact on scholastic functioning. An alternative explanation for the higher scores in Oral Language may simply be that children practise this skill more regularly in an everyday setting, even if they have missed substantial time at school.

Interestingly, this study did not highlight a strong association between balancing and academic skills, particularly reading, in these participants. As the measure of balance taken from the BOT-2 was not as sensitive as electronically recorded balancing tasks used in previous studies (e.g. Moe-Nilssen et al., 2003; Stoodley et al., 2005), the limited variation in scores across participants may account for the discrepancy with previous studies. Despite this, most of the children in this study were severely impaired on the balancing tasks, more so than has been reported in children with dyslexia. If the association between balance difficulties, as an indicator of cerebellar dysfunction in dyslexia, and reading skills could account for the core deficit in dyslexia, it would be expected that in these children a similar association may be found. Whilst it is certainly the case that some children demonstrated severely impaired performance on reading, others demonstrated balancing deficits but reading within the normal range. This suggests that cerebellar dysfunction, as measured by balancing tasks, may not be solely able to account for developmental reading difficulties.

5.4.3 Performance on the cognitive indices

Unlike the academic tasks, the cognitive scores obtained in this study reflect the intra- and inter-individual variation seen in performance on the KABC-II (Chapter 3). The split between the severely impaired children and those with higher functioning on the Working Memory is particularly interesting. Working Memory was found to correlate highly with all academic measures, however the Short Term Memory from the KABC-II was not significantly associated with WIAT-II scores. As both these measures included a digit span test, it is likely that the other tasks contributing to Working Memory were driving this effect. In particular, the Letter-Number Sequencing task of the WISC-IV, which contributes to the Working Memory index, requires both numerical and alphabetical knowledge in addition to a short term memory capacity. In contrast, the Word Order task of the Short Term Memory index from the KABC-II does not involve

any knowledge of letters and numbers. It is perhaps therefore unsurprising that Working Memory from the WISC-IV was found to correlate highly with academic measures, but the real impact of this ability on scholastic skills should be considered carefully. When testing cognitive capacity, independently of academic skills, these data suggest that the KABC-II may provide a more useful measure.

5.4.4 Impact of prognostic factors on cognitive and academic outcomes

The impact of the prognostic factors in this study echo the results recorded in previous chapters. In line with previous research (e.g. George et al., 2003) the results pointed towards a trend for a younger age at diagnosis to result in a poorer outcome in both the academic and cognitive measures. The impact of increasing severity of tumour histology in conjunction with more aggressive treatment was again reflected in declining scores in both domains. The children with RH/vermis damage were found to perform more poorly on the academic measures than the children with damage in LH /vermis and the vermis only, in line with previous studies investigating tumour location. However with only one child with LH/vermis group (P14) these results must be treated with caution, particularly because P14 was also one of the least at risk children for other prognostic factors and the highest performing child overall. With participants with LH damage but a more severe prognosis in terms of tumour type, treatment, age at diagnosis etc, the spread of scores in this group may match that reported for the RH/vermis and vermis only group.

Whilst the effect of the prognostic factors found here may be considered to be a proxy for their impact on cognitive functioning, other theories may account for their impact on the academic scores. For example, it has been proposed that radiotherapy directed at the posterior fossa may disrupt the left hemisphere of function in the ventral visual pathway. This process has been demonstrated to occur in typical readers, but is absent in children with dyslexia

(Conklin et al., 2008). In addition, it has been proposed that radiation therapy affects processing speed due to its impact on white matter (e.g. Reddick et al., 1998; Palmer et al., 2002). However, for both the typically-developing norm sample and the patients in this study, the Processing Speed index was the cognitive measure least strongly associated with academic skill.

5.4.5 Conclusion

The results reported here suggest that academic functioning in this group is strongly associated with the level of cognitive skill. Those children with significantly impaired cognitive skills appear to exhibit deficits in most areas of academic ability. Conversely in participants who do not demonstrate such significant cognitive impairments, academic attainment would seem to be relatively age-appropriate. The main factors in determining this outcome appear to be the prognostic factors discussed in Chapter 3, with children with medulloblastoma, treated with CSI and a younger age at diagnosis being at higher risk of academic impairment. It should also be considered that a more extensive course of treatment and recovery period in these children, in addition to the added brain injury incurred due to radiotherapy, is likely to have resulted in a greater time spent away from school during important primary years. Two interesting cases, P13 and perhaps P07, have arisen as they demonstrate cognitive impairments on both the WISV-IV and the KABC-II but are not significantly impaired on the tests of academic skills. It would be extremely interesting to track their academic development over a longer time period to establish whether the scholastic deficits are in fact downstream effects of a general diminishment in cognitive capacity. In particular, P13 may be considered to be at risk due to diagnosis of ependymoma and treatment with chemotherapy, although P07 also received chemotherapy. These findings, together with the trend towards increasing time post diagnosis leading to a further reduction in standard scores, suggest early cognitive and motor

assessment may be able to flag up children that are likely to experience difficulties at school.

The results reported in this study suggest that the cerebellum may not have a specific role in academic functioning above and beyond its role in the general cognitive skills which underpin scholastic skills. The majority of children who demonstrated impairments in scholastic skill above and beyond their cognitive deficit were those children who suffered more aggressive tumour histologies and were therefore likely to have been affected by additional treatments such as chemotherapy and radiotherapy and longer periods of missed schooling than those with more benign tumours. In addition, these severely affected children demonstrated the greatest motor impairments which may have had an additional negative impact on scholastic functioning. It is possible that the secondary impact of treatment for a tumour on scholastic skills is the result of a downstream effect of a cognitive impairment which prevents the child from attaining the appropriate scholastic skills at the appropriate age. Alternatively, the cerebellum may contribute to a specific process, additionally to the underlying cognitive skills, such as phonological processing or attention skills, which prevents the development of academic skills. This is partly addressed in Chapter 6 which investigated attentional skills in this sample. The finding that some patients in this study did not demonstrate scholastic impairments and were able to read appropriately for their ages speaks against the cerebellar deficit hypothesis of dyslexia. Two children who demonstrated significant discrepancy between their academic and cognitive skills were not treated for medulloblastoma and therefore did not receive radiotherapy. P04 was treated for an astrocytoma with surgery alone; however this 14 year old patient had missed a significant period of schooling, which may contribute to this discrepancy in this instance. In addition P10, treated for ependymoma with chemotherapy, was severely motorically impaired and was unable to regularly attend school.

The results from this study suggest that rehabilitation programmes for children with severe cognitive deficits should focus on remediation in core cognitive skills, which may then impact upon academic functioning. For the children who are less impaired, individual assessment of cognitive and academic skills may help to identify potential areas of weakness, however it appears unlikely from this study that children with a cerebellar injury and no cognitive impairment will develop marked academic difficulties.

6 Impact of cerebellar tumour injury in the preschool years on the development of attentional skills

6.1 Background literature

In the previous chapter it was demonstrated that some of the patients in this study who have a severe and pervasive cognitive impairment also show deficits in scholastic abilities above and beyond that expected, based on their cognitive capacity alone. To understand further why these children appear to be additionally affected in their academic abilities, the attention skills in this sample were investigated. It is possible that the cognitive and academic deficits noted in most of the children in this study are the result of multiple deficits in more basic neurocognitive processes such as attention, working memory and processing speed. It may be hypothesised that the academic difficulties displayed by the severely impaired children in this study, which are more severe than expected, may be the result of additional attention deficits limiting their ability to develop appropriate scholastic skills, particularly in classroom settings. Attention deficits, particularly in conjunction with working memory difficulties, cause disruptions to learning new information and activating and using previous knowledge (e.g. Grossberg, 2005). Attention and working memory deficits together may therefore limit the amount of available knowledge affecting the ability to assimilate new knowledge thereby impairing the rate of learning. The results from Chapter 4 suggested this may be the case as the majority of the sample in this study was cognitively improving at a slower rate than typically-developing children.

The concept of attention as a psychological construct will be investigated and then considered in relation to whether the cerebellum may be implicated in any of the processes.

6.1.1 Attention

Whilst attention was historically viewed as a uniform concept, more recently it has been defined as a broad term covering processes that are used to bring stimuli into conscious awareness by giving precedence to motor actions, consciousness and certain types of memory (Raz & Buhle, 2006). Whilst the study of attention has been a highly investigated topic for many years and a number of varied hypotheses concerning the structure of attention have been proposed, a model positing three fundamental divisions of attention remains extremely influential (Posner & Boies, 1971), despite numerous revisions. These three attentional components, in both children and adults, are believed to function independently (e.g. Rueda et al., 2004) and be subserved by different anatomical regions of the brain (e.g. Fan, McCandliss, Sommer, Raz, & Posner, 2002; Rueda, Posner, & Rothbart, 2004; Raz & Buhle, 2006). In the context of the current research, this reliance on different locations may be particularly pertinent as the patients may show a dissociation of deficits with difficulties in one aspect of attention but not the other. Previous research with this population may help to inform whether or not this is in fact the case. In addition, the use of a multifaceted test of attention in this study will allow any patterns of strengths and weaknesses to be defined in this population. It should be considered that although it has been demonstrated that these attentional networks may work independently, it is likely that cooperation across these different systems occurs and is important for effective functioning (Raz & Buhle, 2006). Therefore disruption to one network may impact on the others.

The three major divisions of attentional capacity are defined as executive attention, alerting and orienting (Fan, Raz, & Posner, 2003; Posner & Petersen, 1990). The executive control of attention is postulated to encompass a variety of skills such as choosing between conflicting actions (conflict resolution), supervisory, selective and focused attention. It is thought that although inhibitory control and emotional regulation continue into adolescence, skills

related to executive attention, the executive attention network may not alter past seven years (Rueda, et al., 2004). The alerting aspect of attention may be conceptualised as sustained attention or vigilance and more specifically refers to the ability to change the internal state in preparation for perceiving a stimulus (Raz, 2004). In contrast to executive attention, alerting is hypothesised to continue developing into adulthood (Rueda et al., 2004). Attentional orienting refers to the selection of information from sensory input usually in the presence of multiple sensory stimuli, and shifting the focus of attention. It is also known as selective attention. The orienting network was not found to alter in a study which included 6-10 year olds and adults, suggesting early development of this network (Rueda, et al., 2004). Given this postulated variation in developmental timeframes it is possible to suggest that this patient group, with a young age at insult, will demonstrate a differential pattern of impairment across the facets of attention. Many studies have suggested that an earlier age at insult results in a poorer developmental outcome (see Chapter 3), due to an inability to acquire new skills. This suggests that those aspects of attention, namely executive attention and attentional orienting, which develop earlier in childhood may be less impaired than inhibitory control and alerting which have a more protracted development.

The anatomical networks subserving these three attentional processes have received substantial experimental examination. For executive attention, the anterior cingulate cortex (ACC) is thought to be an important region (Bush, Luu, & Posner, 2000; Fan et al., 2002) together with the lateral prefrontal cortex (e.g. MacDonald, Cohen, Stenger, & Carter, 2000). The alerting network has been linked to frontal and inferior parietal regions, especially in the right hemisphere (Robertson & Garavan, 2004). Orienting has been associated with the pulvinar, superior colliculus, superior parietal lobe and frontal eye fields with different areas seemingly responsible for different aspects of the orienting process. For example, lesions of the temporal-parietal junction lead to difficulty

in disengaging from a particular location (Friedrich, Egly, Radal & Beck, 1998), the superior parietal cortex is thought to facilitate voluntary covert shifts of attention (Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000) and the superior colliculus and frontal eye fields are associated with eye movements in attentional shift (Corbetta, 1998).

These previous anatomical studies have mainly focused upon cortical networks, although the importance of subcortical circuits, such as the fronto-striato-thalamo-cortical loops has been recognised (Raz & Buhle, 2006). In addition cerebellar vermis activation has been reported for alerting and executive attention but not for orienting in typically-developing individuals (Fan, McCandliss, Fossella, Flimbaum, & Posner, 2005). Imaging evidence for additional cerebellar involvement may also be drawn from atypically developing populations as is discussed below. Demonstration of cerebellar involvement in attention skills may also be gathered from lesion studies and behavioural research with children with developmental disorders. These are explored below.

6.1.2 Cerebellar involvement in attention

The cerebellum has been demonstrated to have highly intricate connections with cortical areas, for example association and paralimbic areas have feedforward projections through nuclei in the basis pontis into the cerebellum in addition to feedback projections from the cerebellum (Middleton & Strick, 1994; Schmahmann, 1996; Schmahmann & Pandya, 1997a, 1997b). Schmahmann has proposed a modular topography hypothesis which suggested that the vermis connects predominantly with the orbitofrontal cortex and the ACC, whilst the cerebellar hemispheres may link with dorsolateral and dorsomedial prefrontal cortex (Schmahmann, 2004; Schmahmann & Sherman, 1998). It has been argued that these connections enable the cerebellum to modulate cognition, attention, emotion and motor behaviour in the same way across all domains (Schmahmann & Pandya, 2008), and that disruption to the

cerebellum, or the neural circuits linking the cerebellum to association and paralimbic cerebral areas, results in a "loss of cerebellumizing" (p. 1054). In this way, patients with cerebellar damage are still able to demonstrate cognitive and motor abilities, but their skills may lack the automatisation and optimisation provided by the cerebellum.

The precise overarching function of the cerebellum in multiple domains has received considerable debate. The cerebellum has been postulated to be a timing system, initially to control and regulate temporal patterns of movement, although this was subsequently extended to encompass a cerebellar implication in higher cognitive processes (e.g. Ivry, 1997). Ivry suggested that the cerebellum may be involved in automatically preparing multiple responses for a given situation, rather than being directly involved in specific processes, such as attention shifting.

Another hypothesis is that the cerebellum has an anticipatory role by learning predictive relationships among series of events so that this knowledge may be employed in analogous situations in the future. This learning feeds into predictions about upcoming events so the cerebellum can prepare the relevant neural systems that will be involved in processing such events to respond appropriately and optimise the signal-to-noise conditions (Courchesne et al., 1994). It is suggested that the cerebellum performs this adjustment of responsiveness for all systems with which it is interconnected, such as motor, attention, memory and sensory systems. It is posited that for this process the cerebellum may bring about precisely timed and selected changes in the pattern or level of neural activity in these diverse networks (Akshoomoff, Courchesne, & Townsend, 1997). Given this central role of the cerebellum in multiple domains, it may therefore by expected that it would be implicated in attentional control.

Behavioural studies also offer support for a more direct role of the cerebellum in attention processes. For example, one study reported that in their sample of 5 children with cerebellar damage due to severe traumatic brain

injury, of the skills measured, the strongest deficit associated with cerebellar damage was a task of sustained attention, despite little evidence of concurrent brainstem damage (Braga, Souza, Najjar, & Dellatolas, 2007).

6.1.2.1 Evidence from paediatric lesion studies

Schmahmann & Pandya (2008) have suggested that one manifestation of cerebellar disorder is attentional control difficulties, with positive symptoms including inattentiveness, distractibility, hyperactivity and compulsive behaviours, and negative symptoms such as perseveration, obsessional thoughts and difficulty shifting attention. Attention impairments have indeed been widely observed following a range of tumours in childhood (Moore, Copeland, Ried & Levy, 1992), including cerebellar lesions (e.g. Riva, Pantaleoni, Milani, & Belani, 1989).

Akshoomoff and Courchesne (1992) found that children with cerebellar damage due to astrocytoma were significantly impaired relative to controls on a task that involved switching attention but were relatively spared for a focused attention task and showed no difficulty in disengaging attention. They suggested that this deficit in shifting attention was not due to motor difficulties as they were able to respond to targets at a comparable rate when there was not an attentional shift involved. In a later paper which combined these results with those of autistic participants, these authors posited that the cerebellum may be involved in coordinating attention and arousal systems, rather than having a direct role in attention (Courchesne et al., 1994). A number of subsequent studies have failed to replicate these results, finding no deficit in shifting attention in adults and children with cerebellar lesions (Helmuth, Ivry & Shimizu, 1997; Ravizza & Ivry, 2001; Schoch et al., 2004). It has been postulated these differences are due to the motor demands of the task as cerebellar patients demonstrated significant improvements when the motor demands of the task were reduced (Ravizza & Ivry, 2001). This was supported by an fMRI study

investigating the role of the cerebellum in attention switching in typically-developing adults, which suggested that the cerebellum was activated when the task demanded a reassignment of motor responses to different stimuli (Bischoff-Grethe, Ivry & Grafton, 2002). When attention was switched between domains without requiring a motor response, there was no corresponding increase in cerebellar activation. A subsequent fMRI study by Courchesne and colleagues however used a visual attention task that did not require any guided motor operations and did find posterior cerebellar activation (Allen et al., 1997). These authors therefore concluded that there is a case for cerebellar involvement in attentional capacity.

The studies previously described were primarily conducted using experimental designs to focus tightly on a specific aspect of attention. In reality, most of the work to investigate attentional skills in children with cerebellar tumours is conducted using standardised assessments, which limit interpretation but are more practical to use with severely impaired children. Many studies have been conducted using a variety of standardised tests to assess attentional capacity in children with both malignant and benign cerebellar tumours. A study which examined the outcome of children with pilocytic astrocytoma, either in the infratentorial, the supratentorial midline or supratentorial hemisphere region reported difficulties for all participants for sustained attention, as measured by the Cancellation test (Aarsen et al., 2009). Given that both infratentorial and supratentorial groups displayed these deficits and some of the sample had received radiotherapy, it was difficult to draw firm conclusions concerning the role of the cerebellum in sustained attention. Furthermore, those children with supratentorial tumours exhibited additional attentional deficits in selective attention and executive functioning which were not observed in those with cerebellar tumours. Another study which investigated developmental outcome in children with benign cerebellar tumours (pilocytic astrocytoma, choroids plexus papilloma, astrocytoma grade II, gangliocyoma & haemangioblasoma) found that

selective, sustained and divided attention were severely impaired using performance on the TAP test (Testbatterie zür Aufmerksamkeitsprüng) as a measure (Steinlin et al., 2003). Given that none of the children in this sample received either chemotherapy or radiotherapy, this study offers clearer evidence that the cerebellum may be involved in some attentional processes. The authors of this study conclude that the concurrent difficulties also found for working memory in this population suggest that the same basic functions are disturbed in these patients as in those with frontal lesions and that this outcome is the result of cerebello-frontal connections (e.g. Leiner, Leiner & Dow, 1995; Schmahmann & Sherman, 1998).

Rønning and colleagues investigated outcome in both medulloblastoma and astrocytoma paediatric sufferers and reported difficulties in both groups for the attention aspect of their study (Rønning et al., 2005). The measures included in this study to assess attention skills were a forward and backward digit span and the Paced Auditory Serial Addition Test (PASAT) for sustained attention. Whilst the children with medulloblastoma were more impaired than those with astrocytoma, presumably reflecting the impact of radiotherapy, both groups were nevertheless significantly lower than the test norm mean. Another study investigating attentional outcome in a group of mixed tumour paediatric patients (medulloblastoma, pilocytic astrocytoma, ependymoma, oligo astrocytoma and choroid plexus papilloma) also used the forwards and backwards digit span and the CPT for sustained attention (Stargatt et al, 2007). The tumour participants were found to perform significantly below the normative sample for the CPT, suggesting impairments in sustained attention which continued to decline across the follow-up period for this study (3 years). Whilst the scores for the digit span test were not reported in relation to the normative sample the results also demonstrated a decline in this ability over time, although the authors suggested the primary attentional deficit is likely to be in sustained attention. Similarly to the findings of Rønning et al., Stargatt and colleagues

reported that those children who had received radiotherapy showed a more severe deficit in sustained attention than those who had not, although children with benign tumours were also impaired in comparison to the normative sample. Whilst this study included several other measures of developmental outcome, no attempt was made to disentangle whether the deficits in basic skills, such as attention and processing speed, may have accounted for the difficulties seen in more complex cognitive tasks.

One study which did examine attentional skills in conjunction with other areas of functioning found that in children with cerebellar tumour (medulloblastoma, astrocytoma & glioma) attention span, as measured by the Rey Auditory Verbal Learning Test (RAVLT), significantly predicted scores on the communication aspect of the Vineland Adaptive Behavior Scale (Papazoglou, King, Morris & Krawiecki, 2008a). Given the design of this study, it was not possible to evaluate whether this relationship was correlational or causal in nature, however these results provided a suggestion attentional capacity may impact on functioning in other domains. The precise aspect of attention tapped by the RAVLT, typically used to assess verbal learning and memory, was unclear and scores on this measure should be interpreted with caution given that performance of the task is likely to depend on additional skills that may also be impaired.

Copeland and colleagues also assessed children with cerebellar tumour (medulloblastoma, astrocytoma and ependymoma) and found impairment in attention skills (as measured by the Trailmaking Test A & B, and the Freedom from Distractibility Deviation Quotient (FDDQ) from the WISC-R) suggesting that the tumour itself may be having a detrimental impact on performance (Copeland et al., 1999). For this study, as with some previously discussed, it is difficult to extract precisely which aspects of attention these participants found most challenging, particularly for the FDDQ, given that it is comprised of the Arithmetic and Digit Span subtests of the WISC, which may involve many other

processes such as short term and working memory and mathematical understanding. In addition, when the children in this study were separated according to whether they had received radiotherapy, those who had not were found to be performing close to the test norm mean whereas those who were irradiated were significantly impaired. Counter to this finding, an earlier study by this group did find evidence of attentional difficulties (Trailmaking Test A & B and FDDQ) in children with posterior fossa astrocytoma at the time of diagnosis prior to any treatment, suggesting that an impact of tumour may be responsible for an attention deficit in this population (Ater et al., 1996).

As highlighted in Chapter 4, the impact of radiotherapy on white matter in children treated for cerebellar tumour is an important consideration when examining developmental outcomes in this population. The studies above have yielded a mixed picture over whether attentional difficulties are seen in children with cerebellar damage but no radiotherapy, or if any deficits recorded are due to radiotherapy alone. Attention skills in 37 children treated for brain tumours with cranial radiotherapy were investigated using the Conners Continuous Performance Test (CPT; Conners 1995) for visual attention (Mulhern, et al., 2004). The results demonstrated that the patients were significantly worse than controls for many of the subtests of the CPT. In addition, the attentional deficits were strongly related to IQ scores as well as to reduced cerebral normal appearing white matter (NAWM). Other studies have also highlighted the interrelation between NAWM, attention, memory IQ and scholastic skills. For example, Reddick et al. (2003) reported that better attentional capacity in children treated for a range of brain tumours was associated with greater NAWM, cognitive skills and academic achievement. This study also employed the CPT which did not allow for the separate components of attention to be studied separately or for any differential impact of these subskills on cognitive and academic functioning to be established. One study which did aim to address these limitations found that specific aspects of the attention test (also the CPT)

were impaired in children with medulloblastoma, including selective attention, slow and inconsistent responding and target discrimination in children treated for medulloblastoma with radiotherapy (Reeves et al., 2006). In turn, these deficits were highly associated with academic achievements as measured by the WIAT.

Although these studies highlighted that attention deficits may be seen following treatment for a cerebellar tumour, the exact pattern of attentional difficulties and the corresponding impact they may have on both cognitive and academic abilities has yet to be fully understood. Conclusions are further confounded by some studies including samples with mixed tumour types, with some participants having received radiotherapy and others treated with surgery alone. A case series approach, as adopted in this thesis may help to disentangle some of these issues.

6.1.2.2 Evidence from developmental disorders

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder of inattention, impulsivity and hyperactivity. Some studies have implicated a link between ADHD and cerebellar development, with several reporting structural abnormalities in children with ADHD. Generally these findings have reflected a decreased cerebellar volume (Castellanos et al., 2002; Mackie et al., 2007), especially in the vermis (Berquin et al., 1998; Castellanos et al., 2001; Hill et al., 2003; Mostofsky, Reiss, Lockhart, & Denckla, 1998). From a behavioural viewpoint, patients with ADHD often demonstrate difficulties with timing information (e.g. Barkley, Koplowitz, Anderson & McMurray, 1997; Smith, Taylor, Rogers, Newman, & Rubia, 2002) which would link to the temporal role proposed for the cerebellum. It has been suggested that these timing deficits, due to impaired fronto-cerebellar neural loops, may result in a failure to appreciate the temporal structure of the environment and therefore underpin many ADHD symptoms (Nigg & Casey, 2005). It is possible that a similar mechanism may account for the attention deficits reported in children with

cerebellar injury particularly those with very early insult, as in this thesis, given the developmental nature of ADHD. A further strand of evidence for a cerebellar involvement in ADHD is that it is often found to coexist with Developmental Coordination Disorder (DCD), speech and language impairments and reading difficulties, in which cerebellar deficits have also been implicated (Cruddace & Riddell, 2006; Zwicker, Missiuna, & Boyd, 2009).

Some studies have suggested that medication typically used for children with ADHD (methylphenidate), may be effective for children with attention difficulties following brain injury after treatment for a tumour (DeLong, Friedman, Friedman, Gustafson & Oakes, 1992; Thompson, Leigh, Christensen et al., 2001). Other studies however have found no improvements in attention using methylphenidate in this population (Torres et al., 1996). Given these mixed results and that these studies investigated highly heterogeneous groups not specifically targeting children with cerebellar injury, further work is required before firm conclusions may be drawn concerning the efficacy of methylphenidate to alleviate attention deficits in these paediatric patients.

Research into attentional deficits in autism, which are highly prevalent in this disorder, have also implicated the cerebellum in attention networks. Many imaging and autopsy studies have demonstrated cerebellar abnormalities in autism (e.g. Bauman & Kemper, 1986; Courchesne, 1995; Hashimoto et al., 1995). An fMRI study which aimed to relate structural irregularities to functional differences reported that the superior posterior cerebellar hemisphere was associated with nonspatial visual selective attention and that the size of the cerebellar hemisphere lobule VIIA in autistic individuals was highly correlated with accuracy on the attention measure (Allen & Courchesne, 2003). Another study examined the attentional aspect of visuospatial processing using late positive event-related potential responses (LPC) and found that the LPC, thought to reflect attention orienting, was delayed or missing in autistic subjects (Townsend et al., 2001). Given that the cerebellum is the most consistently

reported site of structural abnormalities in autism and the association between cerebellar size and speed of orienting, the authors suggested that these results highlight a cerebellar involvement in attention orienting.

6.1.3 Current Study

The purpose of this chapter was to investigate the impact of a cerebellar tumour on attention skills in children with a variety of tumour types, some of whom have received radiotherapy. This study employed both a case-by-case design as well as group analyses to ensure that any individual differences were not obscured by reporting group analyses only. In addition, scores from the tests recorded in the previous chapters were considered in relation to performance on the attention measure to investigate whether deficits in attention skills are related to the impairments seen in other domains (Grossberg, 2005).

6.1.4 Hypotheses

It was possible to highlight some hypotheses based on previous studies.

- The majority of previous research has highlighted impairment in at least one of the attentional networks. The most frequently reported aspect of attention which is impaired would appear to be sustained attention, or alerting, although executive attention and orienting have also been found to be affected. Given the difficulty in accurately defining the attention network being measured in many previous studies, it was not possible to draw any firm hypotheses concerning the nature of an attentional impairment in this population in relation to Posner's three attentional networks. Considering the postulated developmental trajectories for each of the attention networks and the age range at diagnosis in this sample (≤ 5 years) it is possible to suggest that if

the cerebellum contributes to all aspects of attention they should be equally affected in the children in this sample.

- It was hypothesised that those participants in this study who demonstrated the greatest impairments in previous chapters would be similarly the most affected on the attention measure. In particular, of those children who demonstrated a discrepancy between observed and predicted academic skills, those with the largest difference are predicted to have the lowest performance on the attention tasks. If such a relationship is seen, it might suggest that attentional difficulties may be accounting for the scholastic difficulties of these children.
- All of the children in this sample were hypothesised to show at least some measure of deficit on the attention skills, even those treated without radiotherapy. Previous studies suggested that those children who received radiotherapy (i.e. those with medulloblastoma) would perform most poorly. This prediction was also in line with findings in previous chapters, which would support the hypothesis that poor attention skills may underpin low functioning in other domains.
- The imaging studies detailed above made it possible to tentatively form predictions concerning the location of damage and functional outcome. It was hypothesised that damage to the vermis may result in alerting and executive attention deficits. It may not prove possible to determine the validity of this hypothesis given that many of the patients in this sample suffered injury to both vermis and hemisphere regions.
- Few longitudinal studies have investigated the developmental trajectory of attention skills in this population following treatment. One study investigated the impact of time since radiation on attention and found that ability did decrease with time and that the decrease in attentional skills was responsible for a corresponding deficiency in adaptive functioning (Papazoglou, King, Morris, Morris, & Krawiecki, 2008b). It is therefore possible to propose that

for those children who received radiotherapy, a longer time since treatment may lead to poorer attentional performance. For those children who did not receive radiotherapy it is not possible to make such a prediction.

- Similarly, no studies have directly investigated the impact of age at diagnosis on attentional outcome and so it was not possible to form any hypotheses for this prognostic factor. Using data from other domains and the previous chapters, in which a younger age at diagnosis lead to a poorer outcome, if attention is postulated to support other domains then a similar pattern may be expected for attention scores, particularly if the different systems cooperate to optimise functioning, as suggested earlier.

Further hypotheses concerning the postulated relationship between the separate aspects of attention and the previous standardised measures are outlined in the methods section following a description of the attention test.

6.2 Method

6.2.1 Participant information

Of the 15 children who participated in the initial phase of the study (Chapter 3), 10 children completed this phase of the study. Those children who were lost to follow-up in Chapters 4 and 5 (P08, P12 & P15) did not complete these measures for the same reasons as described previously. In addition, P07 and P09 were unable to participant in this section of the study as they were too young to complete the standardised assessments. For the Conners 3 assessment the parents of P14 were unable to complete the questionnaire so data for this participant was missing. The patient details for inclusion criteria, demographics, tumour and treatment details were the same as reported in Chapter 3.

6.2.2 Procedure

Each child completed the Test of Everyday Attention for Children, TEA-Ch (Manly, Robertson, Anderson, & Nimmo-Smith, 1999), a standardised measure to assess several different types of attention. This measure was administered in a single testing session at the same time as the measures described in Chapter 5. The TEA-Ch was administered first, with a substantial break given before the WISC and WIAT were given. All assessments were conducted in a quiet area in the child's home and breaks were given as necessary.

The Conners 3 Parent questionnaire (Conners, 2008) was also used in this study. This assessment is primarily used as a screen for ADHD, however it includes many valuable measures including inattention, learning problems and executive functioning. For this study the Parent report from was used. This was given to parents during the testing session for the TEA-Ch, WISC-IV and WIAT-II. Parents were asked to complete the form either during the session, in a quiet room away from the testing, or if this was not convenient, in their own time within two weeks following the assessment session.

6.2.3 Assessments

6.2.3.1 Test of Everyday Attention for Children

The TEA-Ch was used to assess attention skills. This is an age-adjusted standardised measure suitable for 6 to16 year olds. Nine subtests are presented as a series of games and standardised scores on these subtests ($\mu = 10$; $\sigma = 3$) are taken to reflect performance on different aspects of attentional control. This measure was used as it was developed using theoretical frameworks of attention and provides a strong measure for researchers to investigate attentional performance in both typical and clinical populations. Good psychometric properties in terms of reliability and construct validity have been demonstrated for this measure (Manly et al., 1999). The structure of the TEA-Ch and brief description of the tests are outlined below.

- *Selective/Focused Attention (Orienting)*

  Two subtests (Sky Search and Map Mission) are used to measure this ability, which is defined as the ability to filter information, detect relevant information and reject or inhibit irrelevant information. Both of these measures involve an element of motor control, and the Sky Search subtest takes into account differences in motor speed by including a motor control task and calculating an attention score. This is not the case for the Map Mission subtest and so results on these subtests should perhaps be considered together.

- *Sustained Attention (Alerting)*

  Four subtests (Score, Score Dual Task (DT), Walk Don't Walk and Code Transmission) are used to assess this factor. As described above, these tasks require the participant to actively maintain attention for a task or goal despite little inherent stimulation or reward for doing so. One difficulty that has been highlighted with these measures is that it can be difficult to establish whether low scores are due to a lack of motivation rather than poor sustained attention (Manly et al., 1999). This is particularly the case for Score and Code Transmission and these subtests should be considered in conjunction with Walk Don't Walk to help establish whether poor scores are reflecting an inability rather than reluctance.

- *Attentional Control/Switching (Executive attention)*

  This is measured by two subtests (Creature Counting & Opposite Worlds). Creature Counting involves switching between counting up and down based on explicit cues (arrows). Of all the subtests this task has previously been found to correlate most highly with measures of IQ, which may make interpretation of these scores particularly challenging in this sample of patients for those who demonstrate impaired cognitive functioning. For Opposite Worlds participants are required to perform a task in a novel way whilst inhibiting more prepotent responses.

The different subtests, the attentional factor they are measuring and brief details of the tasks are summarised in Table 6.1.

Table 6.1 Test structure of the TEA-Ch and subtest details

Attention Factor	Subtest	Task description
Selective/ Focused Attention	Sky Search	Child must circle matching pairs of items on a sheet filled with distractor items. The child must then complete the same task in the absence of distractor items to measure motor speed. This motor score is subtracted from the first score to give a measure free of motor influences.
	Map Mission	Child must circle as many target symbols on a map as possible in a minute.
Sustained Attention	Score	Child must count the number of beeps they hear in a row over an extended time.
	Score Dual Task	Child must count the number of beeps as above, in addition to listening for an animal name in a news report played concurrently.
	Code Transmission	Child must listen to a series of spoken numbers. Every time two fives are spoken together the child must say the number that came immediately before the two fives. This test lasts for 12 minutes continuously.
Sustained/ Response Inhibition	Walk Don't Walk	Child is asked to make steps on a path with a marker every time they hear a tone. A different tone is used to indicate when the child should stop marking. The two tones are similar meaning the child must not lapse into an automatic response.
Sustained/ Divided Attention	Sky Search DT	This subtest combines Sky Search and Score – the child must circle matching items whilst keeping count of beeps.
Attentional Control/ Switching	Creature Counting	The child is asked to count items which are interspersed with occasional arrows telling them to switch between counting down and counting up. The time taken to complete the task and accuracy are measured.
	Opposite Worlds	For the Same Worlds aspect of this task the child must name the digits 1 or 2 aloud when they are randomly placed along a path. For the Opposite Worlds part the child must say the opposite number to that written, i.e. 'one' for 2 and 'two' for 1. The difference in speed of reading for the two conditions is compared.

If limited performance on the cognitive and academic tests reflects an attentional deficit, it is possible that different aspects of attention may differentially impact on scores of the KABC-II, WISC-IV, WIAT-II and BOT-2. Table 6.2 presents hypotheses predicting which attentional networks may impact most on the indices of the cognitive, academic and motor standardised tests. These are based on hypothesised task demands of standardised measures. For those children who demonstrated inconsistent performance on previous measures, such as P10 on the KABC-II indices (score range 62-100), it is possible that certain indices are more reliant on certain aspects of attention than others, leading to a variable pattern of scores. As attention is perceived as a basic underlying ability, the hypotheses proposed here were based on which cognitive, academic and motor scores will be related to certain attention networks. These predictions were drawn after considering the task demands of the cognitive, academic and motor subtests. It should be noted that performance on some of the attention tasks is likely to depend on motor skills to a degree although this is taken into account when scoring where possible, as discussed above. However, for the purposes of these hypotheses only the attentional requirements thought to be important to perform the BOT-2 subtests were considered.

Table 6.2 Predicted impact of attention skills on cognitive, academic and motor standardised indices

TEA-Ch subtests		KABC-II	WISC-IV	WIAT-II	BOT-2
Selective/ focused	Sky Search	Visual Processing Fluid Reasoning	Perceptual Reasoning Processing Speed	Reading Maths Written Language	Fine Manual Control Manual Coordination Body Coordination
	Map Mission	Visual Processing Fluid Reasoning	Perceptual Reasoning Processing Speed	Reading Written Language	Fine Manual Control Manual Coordination Body Coordination
Sustained	Score	Short Term Memory	Working Memory	Reading Maths Oral Language	Fine Manual Control Body Coordination
	Score Dual Task	Short Term Memory Long Term Storage & Retrieval	Verbal Comprehension Working Memory	Reading Maths Oral Language	Fine Manual Control Body Coordination
	Code Transmission	Short Term Memory Long Term Storage & Retrieval	Verbal Comprehension Working Memory	Reading Maths Oral Language	Fine Manual Control Body Coordination
Sustained/ Response Inhibition	Walk Don't Walk	-	Processing Speed	Written Language	Fine Manual Control Manual Coordination
Sustained/ Divided	Sky Search DT	Short Term Memory Visual Processing Fluid Reasoning	Verbal Comprehension Working Memory Perceptual Reasoning Processing Speed	Maths Written Language	Fine Manual Control Manual Coordination
Attentional Control/ Switching	Creature Counting	Short Term Memory Fluid Reasoning	Working Memory Processing Speed	Maths	-
	Opposite Worlds	Short Term Memory Fluid Reasoning	Working Memory Processing Speed	Maths	-
Indices not predicted to be directly related to attention subtests		Crystallised Ability	-	-	Strength & Agility

6.2.3.2 Conners 3 Parent questionnaire

The Conners 3 Parent questionnaire is a standardised measure that was used to complement the results from the TEA-Ch in determining the attentional capacities of the patients in this study. This measure aims to assess functioning in the areas detailed in Table 6.3, which include Content Scales, DSM-IV-TR Symptom Scales, Validity Scales, Conners 3 Indices, Screener Items and Critical Items. Item scores for each of these areas are determined using the responses of the parent on the basis of a 4 point Likert scale (0 = Not at all true, 1 = Just a little true, 2 = Pretty much true, 3 = Very much true). The sum of the item scores for the Content Scales may then be converted into T-scores ($\mu = 50$ $\sigma = 10$) or percentile ranks. T scores greater then 1 standard deviation above the test norm mean are typically interpreted as clinically significant.

For the DSM-IV-TR symptom scales the symptom criteria for ADHD Inattentive and ADHD Hyperactive-Impulsive are assumed to be met if 6 out of 10 item scores are scored as 2 or higher by the parent. ADHD combined symptoms are considered to be met if symptom criteria for both ADHD Inattentive and ADHD Hyperactive-Impulsive are satisfied. The Conners test also provides T-scores for these items to compare performance to the normative sample. The Conners ADHD Index provides a probability score that represents the percentage of time that the score occurred in children with a diagnosis of ADHD as opposed to typically-developing children. A high Conners Global Index, reported as a T-score, suggests that the child may be experiencing some degree of psychological difficulty, whether it is expressed behaviourally, academically, socially or emotionally.

The Positive and Negative Impression scales are used to highlight when parents may be responding with either a positive or negative bias. For example, through denial or lack of awareness, the parent may demonstrate a positive bias assessing the child more highly than the child is functioning. Conversely the parent may respond negatively, detailing significant problems and few strengths

for a variety of reasons, such as having high standards that are impossible for the child to reach. In addition the Inconsistency Index is used to check whether answers may have been given at random.

The parental responses may also be used to indicate whether the child is at risk of depression or anxiety, conduct disorder and oppositional defiant disorder as up to 60% of children with ADHD are believed to have co-occurring diagnoses (e.g. Jensen et al., 2001). Quality of life outcome studies for children with cerebellar tumours have shown that these children are at increased risk for a poor quality of life, scoring lower on all measures than controls including psychological, physical, social, emotional and school-functioning scales (Benesch et al., 2009; Bhat et al., 2005; Bull & Kennedy, 2008; Bull, Spoudeas, Yadegarfar, & Kennedy, 2007; LeBaron et al., 1988). The scores obtained for these scales may also help to provide a basic measure of quality of life in this sample.

This measure was used to further explore attentional difficulties in this population and to highlight any hyperactivity that these children may be displaying, as this may also impact upon performance for the previous indices considered with this sample and is not measured by any of the subtests of the TEA-Ch. Whilst it is a questionnaire parent report form and may therefore be open to bias, this measure is reported to have good internal validity and reliability (Conners, 2008). In addition, few studies have previously used this measure with this population (e.g. Wolfe-Christensen, Mullins, Scott, & McNall-Knapp, 2007).

Table 6.3 Test structure of the Conners 3

Area of functioning		Example question
Conners 3 Content Scales	Inattention	Has trouble staying focused on one thing at a time
	Hyperactivity/Impulsivity	Gets over stimulated
	Learning Problems	Spelling is poor
	Executive Functioning	Has trouble getting started on tasks or projects
	Aggression	Is cold hearted and cruel
	Peer Relations	Does not get invited to play or go out with others
DSM-IV-TR Symptom Scales	ADHD Inattentive	Is forgetful in daily activities
	ADHD Hyperactive-Impulsive	Talks too much
	ADHD Combined	-
	Conduct Disorder	Skips classes
	Oppositional Defiant Disorder	Loses temper
Validity Scales	Positive Impression	Is happy, cheerful, and has a positive attitude
	Negative Impression	Makes mistakes
	Inconsistency Index	-
Indices	Conners 3 ADHD Index	-
	Conners 3 Global Index	Cries often and easily
Screener Items	Anxiety	Worries about many things
	Depression	Feels worthless

6.2.3.3 Statistical analyses

As the sample for this study was small and heterogeneous in terms of prognostic factors, the results for these final standardised measures were investigated in a case-by-case analysis considering each participant's scores for the attention measures in the context of scores for the standard cognitive, academic and motor tests discussed in Chapters 3, 4 and 5. In particular the scores on the Conners 3 were investigated individually as the data from this measure was not easily interpreted in group analyses.

In addition, the following group analyses were conducted:

1) Pearson correlations were conducted to establish whether there was a relationship between scores on the TEA-Ch and the indices of the KABC-II, WISC-IV, WIAT-II and BOT-2. Bonferroni correction was applied yielding a significance level of .004 (the α value of .05 was divided by the maximum number of analyses a value was entered in to, in this instance 13) however the *p* values are reported for each correlation coefficient. Where possible these correlations were compared to those seen in a typically-developing sample, as provided by the TEA-Ch standardising manual. Whilst the standardising sample did not complete exactly the same cognitive and academic measures as the patients in this study, comparisons were made between analogous indices. The standardising sample did not complete a motor measure for comparison to performance on the TEA-Ch. Due to these differences in test completion it was considered inappropriate to apply Fisher's z to test for significant differences in strength of correlations across groups.
2) Prognostic factors were considered in relation to TEA-Ch scores. The impact of Age at Diagnosis and Time Post Treatment were assessed using Pearson correlations with Bonferroni correction (α=.006; .05/9). The effect of Tumour Type/Treatment was assessed using a series of Chi square tests to explore differences between groups, with Bonferroni

correction (α=.0125; .05/4). Tumour Location was similarly assessed using a series of Chi square analyses. The impact of Hydrocephalus on cognitive and academic scores was not assessed in this chapter as it is considered for all measures separately in Chapter 7.

6.3 Results

6.3.1 Individual analyses for the TEA-Ch

Individual scores for each of the patients on the TEA-Ch are presented in Table 6.4. Across all subtests, all of the patients except one (P14) were found to have a significant impairment in at least one aspect of attention. The task with the highest number of children impaired was the Walk Don't Walk subtest for Sustained/Response Inhibition on which 7/10 children were significantly impaired. Impairments were also seen for subtests of Selective/Focused attention and Attentional Control. Interestingly, for the two measures of accuracy (Sky Search correct & Creature Counting correct), only one child (P06) was found to be significantly impaired. An important consideration highlighted by the test authors is that performance on the TEA-Ch should be minimally affected by whether or not the child understands the task instructions. Unimpaired accuracy scores for the majority of the patients suggested that the participants understood the tasks, despite difficulties in execution. The previous measures highlighted that P06 is severely cognitively impaired and he failed to successfully perform many of the subtests of the TEA-Ch due to lack of understanding. For scores based on speed of response 4/10 children were significantly below the test norm mean for Sky Search time score and 5/10 for the Creature Counting time score. Taken together, these results suggested that children are having difficulty with the specific attention aspects of the measures rather than the tasks themselves.

6.3.2 Individual analyses for the Conners 3

The individual results for the Conners 3 parental questionnaire are reported in Tables 6.5 and 6.6 and highlight a clear pattern of deficits across the patient sample. Five of the children (P01, P02, P03, P11 and P13) were reported to have clinically significant elevated scores for most or all of the Content Scales, the DSM-IV-TR Symptom Scales and the Conners 3 Indices. Three of the remaining participants (P04, P06 and P10) were found to have clinically significant elevated scores for the Learning Problems content scale but scores within the normal range for all other aspects of the Content Scales, the DSM-IV-TR Symptom Scales and the Conners 3 Indices. One participant (P05) scored within the normal range for all aspects of the measure. These results suggested a marked division within the sample between those children with a high probability score on the Conners 3 ADHD Index and significantly raised scores on most other aspects measured and those patients for whom low probability scores for ADHD were found and scores were in the typical range for other the majority of the other scales. The screening items for anxiety and depression included in the Conners 3 suggested that all children were reported to have high scores on items related to generalised worrying, and all except P10 were reported to have high scores on items investigating the key clinical presentations of depression. It should be emphasised that these were screener items only and should be used to suggest further investigation in a clinical setting, rather than as a diagnostic tool for either of these illnesses.

Whilst no significant problems were highlighted for the Positive Impression scale or Inconsistency Index, for three of the five children who were reported as scoring significantly differently from the test norm, the Negative Impression (NI) scale was found to be either possibly or probably invalid. The NI scale is drawn from items that describe extreme behaviours and are unlikely to be true all the time. The test manual suggests that a high NI score indicates an overly negative description of the youth's behaviour, although it may actually

be the case that the child does misbehave most of the time. For these participants therefore (P01, P03 & P11) the results from the Conners 3 should be viewed with caution, however as these scores were used to complement interpretation of TEA-Ch scores and not for intervention recommendations, the high NI score did not raise too many difficulties.

Table 6.4 Standard scores for attention measured by the TEA-Ch (test norm μ = 10, σ = 3) * -2SD from the test norm mean

P04 was unable to complete Code transmission due to unforeseen time limitations to the testing session

Child	TEA-Ch												
	Selective/focused				Sustained					Attentional control/switching			
	Sky Search			Map Mission	Score	Score DT	Code Transmission	Sky Search DT	Walk Don't Walk	Creature counting		Opposite worlds	
	Correct	Time	Attention							Correct	Time	Same	Opposite
P01	8	7	10	1*	2*	4*	4*	5	1*	10	7	4*	7
P02	6	4*	4*	5	6	7	8	7	4*	10	5	7	5
P03	9	3*	5	1*	9	4*	1*	2*	1*	10	1*	3*	2*
P04	13	8	9	9	7	5	-	4*	5	8	1*	4*	4*
P05	11	5	6	7	15	12	5	5	8	10	7	6	1*
P06	2*	1*	0*	4*	3*	5	0*	4*	0*	0*	0*	1*	1*
P10	5	5	8	1*	4*	6	1*	1*	1*	6	8	1*	1*
P11	9	3*	3*	1*	9	7	1*	1*	2*	8	3*	4*	3*
P13	7	6	5	8	6	6	4*	5	1*	7	0*	7	5
P14	13	9	10	6	6	9	11	10	8	14	8	10	10

Table 6.5 Standard scores for the Conners 3 Parent Scale (test norm μ = 50, σ = 10) *+1SD from the test norm mean. The parents for P14 were unable to complete the questionnaire.

Child	Content Scales *(T-scores)*						Validity Scales		
	Inattention	Hyperactivity /Impulsivity	Learning Problems	Executive Functioning	Aggression	Peer Relations	Positive Impression	Negative Impression	Inconsistency Index
P01	90*	90*	90*	85*	77*	90*	Probably valid	**Probably Invalid**	Probably valid
P02	75*	62*	66*	80*	90*	90*	Probably valid	Probably valid	Probably valid
P03	89*	90*	87*	56	55	75*	Probably valid	**Possibly Invalid**	Probably valid
P04	52	42	79*	53	46	42	Probably valid	Probably valid	Probably valid
P05	55	40	47	48	41	54	Probably valid	Probably valid	Probably valid
P06	52	44	65*	53	47	58	Probably valid	Probably valid	Probably valid
P10	54	52	67*	45	48	55	Probably valid	Probably valid	Probably valid
P11	90*	90*	92*	85*	90*	90*	Probably valid	**Possibly Invalid**	Probably valid
P13	76*	90*	90*	70*	60	49	Probably valid	Probably valid	Probably valid
P14	-	-	-	-	-	-	-	-	-

Table 6.6 Standard scores for the Conners 3 Parent Scale (test norm μ = 50, σ = 10) *+1SD from the test norm mean. The parents for P14 were unable to complete the questionnaire.

Child	DSM-IV-TR Symptom Scales *(T-scores and symptom counts)*									Conners 3 Indices		Screener Items	
	ADHD IN (T)	ADHD IN Criteria	ADHD HY (T)	ADHD HY Criteria	ADHD combined	CD (T)	CD Criteria	ODD (T)	ODD Criteria	Conners 3 ADHD Index *(% probability)*	Conners 3 Global Index *(T-score)*	Anxiety	Depression
P01	90*	**Probably met**	90*	**Probably met**	**Probably met**	90*	**Probably met**	78*	**Probably met**	99	90*	Endorsed	Endorsed
P02	85*	**Probably met**	59	Probably not met	Probably not met	73*	**Probably met**	90*	**Probably met**	97	82*	Endorsed	Endorsed
P03	70*	**Probably met**	90*	**Probably met**	**Probably met**	55	Probably not met	61*	Probably not met	99	80*	Endorsed	Endorsed
P04	45	Probably not met	42	Probably not met	Probably not met	44	Probably not met	47	Probably not met	11	54	Endorsed	Endorsed
P05	50	Probably not met	40	Probably not met	Probably not met	43	Probably not met	41	Probably not met	41	43	Endorsed	Endorsed
P06	50	Probably not met	44	Probably not met	Probably not met	56	Probably not met	51	Probably not met	11	53	Endorsed	Endorsed
P10	53	Probably not met	48	Probably not met	Probably not met	45	Probably not met	59	Probably not met	29	62*	Endorsed	Not endorsed
P11	90*	**Probably met**	90*	**Probably met**	**Probably met**	90*	**Probably met**	90*	**Probably met**	99	90*	Endorsed	Endorsed
P13	76*	Probably not met	90*	**Probably met**	Probably not met	55	Probably not met	60*	Probably not met	99	85*	Endorsed	Endorsed
P14	-	-	-	-	-	-	-	-	-	-	-	-	-

6.3.3 Case-by-case analyses

Based on the results from the cognitive, academic and motor standard scores in previous chapters and the impact of prognostic factors on these skills, it is possible to order the participants in terms of predicted severity of impairment for attention scores. The results in previous chapters highlighted that those children who suffered an astrocytoma and were treated with surgery alone were the least affected, followed by those who were treated for astrocytoma with surgery and chemotherapy then by children treated for ependymoma with surgery and chemotherapy. Patients who were diagnosed with medulloblastoma were found to perform most poorly and those who received CSI in addition to PF radiotherapy generally achieved the lowest scores. On this basis, for the children who completed the measures of attention, it was possible to suggest that P02, P04, P05, P13 and P14 may have been the least impaired, whilst P01, P03, P06, P10 and P11 were expected show a greater impairment. Comparing children across scores on previous measures suggested that P14 may have been expected to achieve the highest score, followed by P05 and P02. Whilst not as severely affected as the patients with medulloblastoma, P04 (astrocytoma) and P13 (ependymoma) demonstrated more variable patterns of performance, with impairment evident in some domains and spared functioning in others. The other patient with ependymoma (P10) however was found to perform more poorly than P13. Indeed, of those children who were consistently negatively affected (including all those with medulloblastoma), results on the previous standardised measures suggested that P03 and P10 were the most impaired. These predictions of severity in outcome are summarised in Table 6.7.

Table 6.7 Patient rank order of predicted severity of impairment on attention scores from least to most impaired. CT = chemotherapy, RT = radiotherapy, PF = posterior fossa

Patient	Rank order	Tumour Type/Treatment	Composite KABC-II score (FCI)	Composite WISC-IV score (FSIQ)	Composite WIAT-II score (TC)	Composite BOT-2 score (TMC)
P14	1	Fibrillary astrocytoma	104	91	103	36
P05	2	Pilocytic astrocytoma	96	95	96	33
P02	3	Pilocytic astrocytoma	91	83	87	37
P04	4	Pilocytic astrocytoma	78	70	59	35
P13	5	Ependymoma, CT	75	62	71	28
P01	6	Medulloblastoma, CT, whole brain RT followed by boost to PF & spine	76	68	51	26
P06	7	Medulloblastoma, CT, whole brain RT followed by boost to PF & spine	70	56	53	27
P11	8	Medulloblastoma, CT, PF RT	68	57	56	32
P10	9	Ependymoma, CT	65	54	45	20
P03	10	Medulloblastoma, CT, PF RT	65	46	54	29

The patients will be considered individually from least to most impaired on previous measures, summarising their previous results and examining performance on the TEA-Ch and Conners 3, to establish whether a pattern for performance on the attention tasks emerges. Individual scores across each subtest for all standardised measures are presented in Appendix 1.

- *P14 – Individual analysis (astrocytoma, surgery)*

For the KABC-II, P14 was found to perform consistently close to the test norm mean or above for all of the indices across all time points. For the WISC-IV, again scores were close to the test norm mean with the exception of Processing Speed, for which a significant impairment was recorded. No significant impairments were found for academic skills (WIAT-II) in this patient and scores were found to be equal to, or greater than, those predicted based on WISC-IV achievement. For motor control, P14 scored consistently below the test norm mean although only the score for Strength & Agility at T2 was found to be significantly impaired. In general therefore, this patient may be described as functioning at a typical level for his age in the majority of skills tested.

This relatively high performance was reflected in scores on the TEA-Ch, as P14 was the only patient not found to be significantly impaired on any of the subtests and many of the scores were found to be close to or above the test norm mean. These results indicated that attention skills were typical in this child, and commensurate with scores in the other domains tested. Unfortunately the parents of this child were unable to complete the Conners 3 assessment so performance on the two attention measures cannot be compared in this child. These results agreed with the predictions in Table 6.2 concerning the interrelation of attention skills and other abilities insofar as the deficit in Strength & Agility was not reflected in the scores for the attention subtests. The impairment in Processing Speed however, did not appear to be reflected in the attention scores for this child suggesting that these two areas may not be as closely linked as initially hypothesised.

- *P05 – Individual analysis (astrocytoma)*

Similarly to P14, this patient was not found to be significantly impaired for any of the cognitive indices of the KABC-II. A slightly variable pattern was seen across the indices however, with scores for Visual Processing consistently

lower across the three time points than the other cognitive measures. P05 was again not found to be significantly impaired for any of the WISC-IV indices, although the score for Processing Speed was found to be depressed compared to those for other indices, reflecting a similar pattern to that seen in P14. No significant impairments were found for the academic scores in this participant with scores close to or above the test norm mean and at a level corresponding to achievement on the WISC-IV. Motor scores were below the test norm mean for this child although significant impairments were only seen for Manual Coordination at the T2 and T3.

The scores for P05 on the TEA-Ch demonstrated a significant impairment for only one subtest (Opposite task) which measured attentional control/switching. This deficit was not similarly found for the other measure of attentional control (Creature Counting) suggesting that the particular aspects of the Opposite Worlds task may be particularly demanding. Indeed this task would appear to require a greater inhibition of prepotent responses than the Creature Counting task as it involves saying the opposite number to that printed, whilst the latter would seem to require a higher level of cognitive flexibility. Weakness in this aspect of attentional control did not appear to impact on performance in any of the cognitive or academic domains. The deficit in manual coordination in this child was not reflected in the attention scores highlighting that although attention may be implicated in manual abilities, other functions of the cerebellum are also important for successful motor skills.

For the Conners 3 scales P05 was not found to have significantly elevated scores for any of the Content Scales, DSM-IV-TR Symptom Scales or the Conners 3 Indices. This report supported the findings of the TEA-Ch and further highlighted that functioning across domains is relatively intact in this child.

- *P02 – Individual analysis (astrocytoma)*

P02 was not found to be significantly impaired on any of the cognitive indices of the KABC-II, with performance close to or above the test norm mean for all measures. Similarly, no significant deficits were found for the indices of the WISC-IV or the academic measures of the WIAT-II. In comparison to cognitive ability, performance on the Maths and Written Language indices was at the appropriate level, as the Reading index scores were marginally higher than expected and for Oral Language scores were slightly lower than predicted, although these were not significant. No specific motor difficulties were highlighted using the BOT-2, although as with P14 and P05 performance was well below the test norm mean for all subtests.

Despite apparent intact functioning on the previous standardised measures P02 was generally found to perform more poorly than P14 and P05 on the attention scores. Significant weaknesses were recorded for one measure of Selective/Focused attention (Score) and for the subtest for Sustained/Response Inhibition (Walk Don't Walk) and low performances particularly for the other subtest of Selective/Focused attention (Map Mission) and both measures of Attentional Control/Switching (Creature Counting & Opposite Worlds). Scores were generally found to be higher for the Sustained attention subtests. These attention deficits did not appear to impact on performance in the other domains measured, however the parental report for the Conners 3 suggests that the consequences in this child may be mostly behavioural. For the Conners 3 Content Scales, T-scores were found to be elevated for all of the measures, most particularly for Aggression and Peer Relations. Similarly, the T-scores for the DSM-IV-TR Symptom Scales were high, with the exception of ADHD Hyperactive-Impulsive. The symptom counts were also elevated with the criteria probably met for ADHD Inattentive, Conduct Disorder and Oppositional Defiant Disorder. Similarly the Conners 3 ADHD Index indicated a 97% probability that the responses for this child were very similar to those for a child with ADHD and that

a classification of ADHD is very likely. Unsurprisingly, a high Global Index score was found for this patient.

It may be the case that the attentional difficulties demonstrated by this child are limiting progress in the other cognitive and academic domains considered in previous chapters and that this child had the potential to attain much higher scores than those recorded although this is purely speculative. The behavioural difficulties reported for this child are in line with the cerebellar cognitive affective syndrome that has been reported in adults (Schmahmann & Sherman, 1998) but also in children (Levisohn et al., 2000; Steinlin et al., 2003). In addition, the outcome in this child supports findings that deficits in the regulation of affect may be evident in children with cerebellar tumours treated with surgery but without chemotherapy or radiotherapy (Levisohn et al., 2000).

- *P04 – Individual analysis (astrocytoma)*

For the cognitive indices of the KABC-II P04 was not found to be significantly impaired, although the majority of scores were below the test norm mean, especially for Short Term Memory and Long Term Storage & Retrieval. For the WISC-IV however, significant deficits were recorded for all indices (Verbal Comprehension, Working Memory & Processing Speed) except for Perceptual Reasoning. The impairment on Working Memory supports the low scores for the Short Term Memory index, however the difficulties with the other WISC-IV indices highlight that these standardised measures appear to be tapping different abilities. The importance of using multiple tests for assessment is also emphasised. Similarly, academic skills were found to be limited in this patient with significant impairments found for all indices (Reading, Mathematics & Written Language) except Oral Language, which was relatively spared in most participants. The analyses in Chapter 5 also highlighted that for all academic subtests except Oral Language, P04 was impaired to a greater extent than would

be predicted based on his cognitive skills as measured by the WISC-IV. This discrepancy suggests that a deficit in another domain may be impacting on academic scores in a way that is not present for the previous patients considered. For the motor indices P04 demonstrated a slightly variable performance across time and although his scores were generally not significantly impaired, all were below the test norm mean. Significant impairments were found for Body Coordination and Strength & Agility.

For attentional control, P04 demonstrated variable performance across the subtests and showed greatest difficulty with the measures of Attentional Control/Switching with significantly impaired scores for both Creature Counting and Opposite Worlds. Significant difficulty was found for the Sustained/Divided subtest Sky Search DT. Scores for the other Sustained attention subtests were low but not significantly impaired, whilst the scores for the Selective/Focused subtests were close to the test norm mean. In this patient therefore Selective/Focused attention appears to be relatively unaffected whilst for Sustained attention and Attentional Control/Switching performance is lower than the test norm mean. P04 was reported as having damage to the vermis and these results are therefore in line with the location hypotheses for this study.

In relation to results for the other standardised measures, this pattern of results largely supports the hypotheses made in Table 6.2. It is possible that the deficit in Attentional Control/Switching may account for the additional academic difficulties that are seen in this child.

With the exception of the Learning Problems item of the Content Scales, which was found to be elevated, none of the other items from the Conners 3 Content Scales were reported as significantly raised for P04. The finding of learning difficulties is in line with the results from the previous standardised results. Scores for the DSM-IV-TR symptoms scales were all in the typical range and none of the diagnostic criteria were reached. The Conners 3 ADHD Index suggested only an 11% probability that the responses would be the same as for

a child with ADHD. Whilst this child clearly demonstrated specific attention difficulties, these did not appear to be reflected behaviourally.

- *P13 – Individual analysis (ependymoma, chemotherapy)*

P13 achieved a variable pattern of results which have been interpreted as suggesting that academic difficulties may become more pronounced with increasing time post treatment in this child (see Chapter 5). For the KABC-II P13 was not found to be significantly impaired for any of the cognitive indices, however her results were generally well below the test norm mean. Similarly to P04, P13 showed inconsistent achievements on the WISC-IV with significant deficits found for Verbal Comprehension and Working Memory, and spared performance on Perceptual Reasoning and Processing Speed, although scores were low for these latter indices. On the academic measures P13 was not found to be significantly impaired for any of the indices, however performance was extremely low for this child, bordering on clinical significance for many of the tests. Scholastic scores were found to be significantly lower than predictions based on WISC-IV performance, but only when the Perceptual Reasoning Index was used for comparison. This patient demonstrated significant deficits for Manual Coordination at all time points, and although none of the other indices were significantly below the test norm mean, performance was limited for all measures.

The results from the TEA-Ch for P13 highlighted significant areas of weakness in the Code Transmission and Walk Don't Walk subtests for Sustained attention and for the Creature Counting speed subtest of the Attentional Control/Switching index. Performance on the other subtests was consistently below the test norm mean, although not significantly impaired. Overall these results suggested that Sustained attention was particularly affected in this child, Attentional Control/Switching was impaired and Selective/Focused attention was relatively spared. In relation to the predictions in Table 6.2, these results

suggested that the attentional difficulties in this child may account for the additional academic deficits recorded.

The Content Scales of the Conners 3 highlighted significantly elevated scores for the Inattention, Hyperactivity/Impulsivity, Learning Problems and Executive Functions indices and scores within the normal range for Aggression and Peer Relations. For the DSM-IV-TR Symptom Scales, elevated T scores were found for both ADHD Inattention and ADHD Hyperactivity/Impulsivity scales, although the DSM-IV symptomatic criteria were only met for the latter. This discrepancy for the ADHD Inattention scale highlights that whilst the symptoms are occurring in excess of what is typical for P13's age and gender, insufficient symptoms are reported to meet the criteria. In this instance, given the results from the TEA-Ch, it is possible to suggest that inattention is a significant problem for P13. The criteria for CD and ODD were not met for this participant. The Conners 3 ADHD Index highlighted a 99% probability that the scores for P13 are similar to those for a child with ADHD. This child is demonstrating deficits in multiple aspects of attention which appear to be reflected both cognitively and behaviourally.

- *P01 – Individual analysis (Medulloblastoma, chemotherapy, CSI, PF radiotherapy)*

Despite the prognostic factors for P01 predicting extremely impaired outcome, for the cognitive indices of the KABC-II this participant was not found to show significant impairment. Across all indices and time points scores were generally lowest for Crystallised Ability. For the WISC-IV P01 demonstrated a variable pattern of achievement, with significant deficits found for Verbal Comprehension and Processing Speed, a low score for Working Memory and relatively spared performance for Perceptual Reasoning. For academic skills, P01 was found to be significantly impaired across all abilities, and the discrepancy analyses revealed that this deficit in academic skills was significantly lower than

that predicted based on WISC-IV functioning. For motor functioning, P01 showed a significantly deficit at all time points for Manual Coordination, Body Coordination and Strength & Agility. Fine Manual Control was not significantly impaired but scores were nevertheless substantially lower than the test norm mean.

For the TEA-Ch scores, P01 demonstrated significant deficits in at least one subtest for each broad attentional area measured. All subtests for Sustained attention were significantly impaired, except for Sustained/Divided attention, which was nevertheless substantially lower than the test norm mean. For the Attentional Control/Switching subtests scores were typically within the normal range, although all lower than the test norm mean. The Opposite Worlds Same task was found to be significantly impaired, in agreement with the deficit found for the Processing Speed index of the WISC-IV. For the Selective/Focused subtests the Sky Search score was the same as the test norm mean, however the score for Map Mission was highly significantly lower. This marked difference between the two subtests was also demonstrated by P10 (see below) and suggested that for children with severe attentional difficulties Map Mission may be more difficult than Sky Search, requiring stronger selective attention. On the other hand, as highlighted above, Map Mission fails to take motor skill into consideration whereas Sky Search does. This implied that Selective/Focused attention in both P01 and P10 was relatively unimpaired and the low scores for Map Mission reflected motor difficulties.

P01 therefore demonstrated a deficit on Sustained attention alone. This selective impairment supports the notion of three independent attentional systems. In reference to the hypotheses in Table 6.2, these results suggested that sustained attention may not be closely associated with short and long term memory as these were both spared in this child. In addition, it is possible that sustained attention impairment may account for the academic deficits exceeding cognitive impairment. This is in agreement with the findings from P13.

The Conners 3 results for P01 indicated very elevated T-scores for all aspects of the Content Scales. Similarly very elevated scores were found for the T-scores for the DSM-IV-TR symptom scales for ADHD Inattentive, ADHD Hyperactive/Impulsive, Conduct Disorder and Oppositional Defiant Disorder. The symptom counts were also met for ADHD Inattentive and ADHD Hyperactive/Impulsive indicating a high possibility of ADHD Combined in this child. This was supported by the Conners 3 ADHD Index which suggested a 99% probability that the scores for this child may have come from a child with ADHD rather than the general population. It should be noted that for this child, the Negative Impression Index was found to be probably invalid suggesting that the results may be overly critical and should be interpreted with caution. As with P13 this report supports findings on the TEA-Ch and highlights both cognitive and behavioural difficulties in this child.

- *P06 – Individual analysis (Medulloblastoma, chemotherapy, CSI, PF radiotherapy)*

P06 demonstrated a variable performance on the KABC-II with significant deficits reported for Visual Processing and Fluid Reasoning consistently across time, substantially reduced scores for Crystallised Ability and higher performance for Short Term Memory and Long Term Storage & Retrieval. For the WISC-IV this child was significantly impaired on all indices, with the same pattern seen for the academic scores on the WIAT-II. The discrepancy analysis between observed and predicted scholastic scores for this child revealed that the scores achieved on the WIAT-II were significantly lower than those predicted based on cognitive capacity. P06 was significantly impaired on the Manual Control and Strength & Agility indices of the BOT-2 across all testing points and performance for Fine Manual Control and Body Coordination was substantially below the test norm mean but not significantly impaired.

Scores on the TEA-Ch subtests revealed that P06 performed most poorly across all participants in this study. Significant impairments were found for all subtests with the exception of Score DT, which was also well below the test norm mean. As noted above, the extremely poor scores on the accuracy measures of the Sky Search and Creature Counting subtests suggests that this child was failing the basic requirements of the tasks, and this was observed to be the case during testing. In this instance, it is difficult to disentangle whether the cognitive impairments in this child were limiting completion of the attention subtests. Contrary to this argument however, is the finding from other patients, such as P01, who demonstrated a similar pattern of deficits across the cognitive tests, but who managed to achieve high scores for the accuracy measures of the TEA-Ch, despite struggling with the attentional aspects of the tasks. Even for the most simple subtests on the TEA-Ch such as Score (counting bleeps), P06 demonstrated severe impairments which suggests that he may actually be demonstrating severe attentional difficulties.

Contradicting this conclusion however is the parental report from the Conners 3. With the exception of Learning Problems, which is to be expected based on cognitive scores, all of the Conduct Scales scores were reported to be in the normal range. In addition, all of the DSM-IV-TR Symptom Scales T-scores were in the typical range and none of the symptom criteria were met. The Conners 3 ADHD Index indicated only and 11% probability that the scores for P06 could have come from a child with ADHD. Given the highly impaired nature of P06, it may be possible that parental expectations could have been lowered and therefore behavioural difficulties have not been highlighted in this child.

- *P11 – Individual analysis (Medulloblastoma, chemotherapy, PF radiotherapy)*

For the KABC-II indices P11 was found to be impaired for Visual Processing and Fluid Reasoning at the first testing session. In subsequent sessions none of the scores reached significance for clinical impairment, although

for most indices achievement was well below the test norm mean with the highest scores for Short Term Memory. In contrast, performance on the WISC-IV was found to be significantly impaired for all indices except Processing Speed. All indices of the WIAT-II also showed significant deficits except Oral Language, for which achievement was still substantially below the test norm mean. The discrepancy analysis for the WISC-IV/WIAT-II scores highlighted that achievement on the scholastic tests was significantly below those predicted based on cognitive abilities for all the academic indices. P11 achieved low scores bordering on clinical significance for all the indices of the BOT-2.

The attention scores for the TEA-Ch were generally found to be significantly below the test norm mean for P11. For Selective/Focused attention both subtest attention scores were significantly impaired, although the accuracy score for Sky Search was close to the test norm mean suggesting that the patient understood the tasks but had difficulty with the attentional aspect. For Sustained attention, higher scores were achieved for the Score and Score DT subtests however for Code Transmission, which is a much longer subtest, the score was significantly impaired. Similar impairments were found for the Sustained/Divided and Sustained/Response Inhibition subtests. Finally, both of the attention measures for the Creature Counting and Opposite Worlds subtests for Attentional Control/Switching showed significant deficits, although again the accuracy score for Creature Counting was not impaired. Given the pervasive nature of the attention deficits in this child it is difficult to suggest which aspects of attention may be most likely to be impacting on cognitive and academic scores. The finding of attentional difficulties in a child who demonstrated a cognitive/academic discrepancy is in line with the results from previous participants. Again these results would seem to indicate that attentional problems do not have a demonstrable impact on the scores from the KABC-II.

These attentional deficits are supported by the report from the Conners 3 scales. Elevated T-scores were found for all of the Conduct Scales and DSM-IV-

TR Symptom Scales. Correspondingly, the symptom criteria were satisfied for ADHD Inattention, ADHD Hyperactive/Impulsive and therefore for ADHD Combined, and the Conners 3 ADHD Index suggested a 99% probability that these responses were for a child with ADHD. In addition, the symptom criteria were met for Conduct Disorder and Oppositional Defiant Disorder. Although the analysis indicated that for the NI the scores were possibly invalid, for the attention measures at least this report is corroborated by scores on the TEA-Ch. Considered together, the TEA-Ch and Conners 3 scores suggested that P11 has severe attentional difficulties that are likely to be impacting upon functioning in other domains.

- *P10 – Individual analysis (Ependymoma, chemotherapy)*

P10 demonstrated significant deficits for the Visual Processing and Fluid Reasoning indices across all time points. In contrast, scores for Long Term Storage & Retrieval and Crystallised Ability were close to the test norm mean, with the scores for Short Term Memory reduced but not significantly impaired. This variable pattern of performance was not repeated for the WISC-IV as scores were significantly impaired for all indices. The scholastic scores were similarly affected, with significant deficits recorded for all the academic indices, with scores close to baseline. Despite low scores for the WISC-IV indices, the discrepancy analysis for the WIAT-II scores indicated that the scores P10 achieved for the academic tests were significantly below those expected based on cognitive abilities. P10 demonstrated severe motor impairments, performing close to, or at baseline for the majority of the indices.

The attention scores for P10 highlighted severe difficulties. For Selective/Focused attention the same discrepancy as illustrated by P01 was found, with the score for Map Mission significantly affected whilst the Sky Search score was relatively unimpaired, however this most likely reflects motor limitations. P10 was significantly impaired on all the Sustained attention

subtests except Score DT, although performance for this task was below the test norm mean. It is possible that the patient focused on one aspect of the dual task, and the subsequent high score on this component resulted in a higher score overall. For Attentional Control/Switching severe deficits were found for the Opposite Worlds subtests but not for Creature Counting. Again, this pattern was reflected in other patients' scores and suggests that Opposite Worlds may be more place a greater demand on attentional resources than Creature Counting, requiring a strong element of inhibition due to the highly salient response of saying 'one' and 'two' when reading the opposite numerals, even in young children.

In relation to the other standardised measures this pattern of scores suggested an attention deficit has less impact on short and long term memory and Crystallised Ability than for Visual Processing and Fluid Reasoning whilst a uniform pattern of deficit is seen for the WISC-IV and WIAT-II indices. This is in agreement with the results from other patients.

The scores on the Conners 3 for P10 suggested that ADHD is not likely to be a suitable diagnosis for this child. T-scores for the Content Scale scores were all in the normal range with the exception of Learning Problems, a pattern also seen in other patients. Similarly none of the T-scores for the DSM-IV-TR symptom scales were elevated and none of the symptom criteria were fulfilled. The Conners 3 ADHD Index indicated a 29% probability that these scores were for a child with ADHD. Interestingly however, the Conners 3 Global Index score was elevated reflecting the psychological difficulties experienced by this child, as witnessed by the standardised test scores. As with P04, P10 appeared to demonstrate attentional difficulties that were reflected in his cognitive and academic functioning but not expressed behaviourally. For P04 and P10 therefore, it appears that the manifestation of attentional difficulties is not the same as that seen in children with ADHD. For the other patients with attentional

difficulties, behavioural difficulties are reported, suggesting closer similarities to children with ADHD.

- *P03 – Individual analysis (Medulloblastoma, chemotherapy, CSI, PF radiotherapy)*

The scores for the KABC-II indices suggested that P03 was impaired across most domains, however only Fluid Reasoning was consistently found to show a significant deficit. For the WISC-IV indices, all scores were found to be significantly impaired, with the same pattern seen for the academic indices of the WIAT-II. The WISC-IV/WIAT-II discrepancy analysis demonstrated that the scholastic scores achieved were significantly lower than predicted based on cognitive ability. P03 demonstrated significant motor impairments for all indices except Strength & Agility.

The TEA-Ch scores for P03 reflect severe attentional deficits in all areas measured. The accuracy scores for Sky Search and Creature Counting were close to the test norm, indicating that this patient understood the test instructions, but lacked the attentional capacity to complete the tasks successfully. Two exceptions were seen for the Sky Search and Score subtests, although as discussed above, these tasks appear to be generally less impaired suggesting they demand fewer attentional resources. The pattern of cognitive and academic deficits in relation to the attention scores reflects that seen in other patients, with relative sparing of performance on the KABC-II indices. The higher scored for Strength & Agility appeared to support the predictions made in Table 6.2.

The Conners 3 rating scales demonstrated that P03 had significantly raised T-scores for the Inattention, Hyperactivity/Impulsivity, Learning Problems and Peer Relations Content Scales, whereas scores for Executive Function and Aggression were reported in the normal range. For the DSM-IV-TR symptom scales, elevated T-scores were found for the ADHD Inattention and ADHD

Hyperactivity/Impulsivity scales, with symptom criteria satisfied for both of these diagnoses and consequently for ADHD Combined. The T-score for Conduct Disorder was within the normal range and for Oppositional Defiant Disorder the T-score was slightly elevated, however the symptom criteria were not met suggesting ODD is unlikely to be a suitable diagnosis for this patient. The Conners 3 ADHD Index suggested a 99% probability that the scores for P03 were from a child with ADHD. For this child therefore it is possible that the severe attentional difficulties may be producing a corresponding behavioural impact, although the causal direction of this hypothesis is difficult to disentangle from this study.

These individual analyses are summarised in Tables 6.9, which indicate whether or not a deficit was found across the TEA-Ch and Conners 3 indices for each child in the predicted order of severity as laid out in Table 6.7. These tables indicate that as a general pattern those individuals predicted to have the most severe deficits demonstrated this in their scores for the TEA-Ch (Table 6.9). This is supported by non-parametric (Spearman) correlations between scores for each subtests and the predicted rank for each patient (Table 6.8). These correlations reflect a relatively strong negative correlation between individual scores for most of the subtests and the predicted rank placement of the individual, indicating that those hypothesised to perform most highly did indeed obtain better scores. Not all the coefficients reached significance, particularly for the Score subtest, perhaps further indicating that this test was not as discriminatory, as most patients did not demonstrate an impairment on this measure, as discussed above. For the Conners 3 scores a more variable pattern of difficulty was indicated suggesting that behavioural and social difficulties may not be closely linked to functioning in other domains.

Table 6.8 Spearman rank correlations between predicted patient rank and TEA-Ch subtest scores

TEA-Ch subtest		Correlation	
		r	p
Selective/focused attention	Sky search attention	-.360	.307
	Map Mission	-.738	.015
Sustained attention	Score	-.117	.748
	Score Dual Task	-.632	.050
	Code Transmission	-.860	.003
	Walk Don't Walk	-.858	.001
	Sky Search Dual Task	-.765	.010
Attentional Control/Switching	Creature Counting time	-.514	.128
	Creature Counting total	-.276	.440
	Opposite Words same	-.821	.004
	Opposite Worlds opposite	-.474	.166

Table 6.9 Presence (✓) or absence (x) of a deficit for at least one subtest in each attentional domains of the TEA-Ch and the Conners 3 Parent Scales, with patients ranked according to predicted order of impairment severity from least to most affected (right to left)

	Measure	P14	P05	P02	P04	P13	P01	P06	P11	P10	P03
TEA-Ch	Selective/focused	x	x	✓	x	x	✓	✓	✓	✓	✓
	Sustained	x	x	x	x	✓	✓	✓	✓	✓	✓
	Sustained/Response Inhibition	x	x	✓	x	✓	✓	✓	✓	✓	✓
	Sustained/Divided Attention	x	x	x	✓	x	x	✓	✓	✓	✓
	Attentional Control/Switching	x	✓	x	✓	✓	✓	✓	✓	✓	✓
Conners 3 Parent Scales	Inattention	-	x	✓	x	✓	✓	x	✓	x	✓
	Hyperactivity/Impulsivity	-	x	✓	x	✓	✓	x	✓	x	✓
	Learning Problems	-	x	✓	✓	✓	✓	✓	✓	✓	✓
	Executive Functioning	-	x	✓	x	✓	✓	x	✓	x	x
	Aggression	-	x	✓	x	x	✓	x	✓	x	x
	Peer Relations	-	x	✓	x	x	✓	x	✓	x	✓
	ADHD IN	-	x	✓	x	✓	✓	x	✓	x	✓
	ADHD HY	-	x	x	x	✓	✓	x	✓	x	✓
	CD	-	x	✓	x	x	✓	x	✓	x	x
	ODD	-	x	✓	x	✓	✓	x	✓	x	✓
	ADHD Index	-	x	✓	x	✓	✓	x	✓	✓	✓

6.3.4 Interrelation of attention abilities with cognitive, academic and motor scores

6.3.4.1 Cognitive measures

Inspection of Table 6.10 suggests that significant, positive correlations were found between the KABC-II indices and attention scores, although not all remained significant following Bonferroni correction. Confirming findings from the individual analyses the Visual Processing and Fluid Reasoning indices appeared to be most strongly correlated with the TEA-Ch scores. The Sustained attention subtests demonstrated the strongest relationship with these two indices and also with Crystallised Ability. The scores for the Same Worlds task, which may be considered as a measure of processing speed, was highly related to Visual Processing (r=.924, p<.001) and Fluid Reasoning (r=.871, p=.002). The Opposite Worlds task (Attentional Control/Switching) was correlated with Visual Processing and Fluid Reasoning although this was not maintained following Bonferroni correction. The time aspect of Sky Search (Selective/Focused) was associated with Fluid Reasoning (r=.716, p=.030), however this may be because the Fluid Reasoning subtests are timed tasks, and it was not significant following Bonferroni correction.

Table 6.10 Correlations (r) between scores on the KABC-II indices and the TEA-Ch scores for the cerebellar patients (N=10), after Bonferroni correction α=.004

	Cognitive standardised measures		TEA-Ch												
			Selective/focused				Sustained					Attentional control/switching			
			Sky Search			Map Mission	Score	Score DT	Code Transmission	Sky Search DT	Walk Don't Walk	Creature counting		Opposite worlds	
			Correct	Time	Attention							Correct	Time	Same	Opposite
KABC-II	**Short Term Memory**	r	.002	-.123	-.288	.209	.244	.486	.423	.341	.562	.129	.089	.462	.236
		p	.995	.734	.419	.562	.498	.154	.256	.335	.091	.723	.808	.179	.511
	Visual Processing	r	.626	.590	.344	.605	.238	.489	**.919**	.776	**.911**	.684	.206	**.924**	.732
		p	.053	.072	.330	.064	.507	.151	**<.001**	.008	**<.001**	.029	.568	**<.001**	.016
	Long Term Storage & Retrieval	r	-.070	.074	.049	.189	.056	.610	.551	.541	.500	.090	.576	.263	.058
		p	.848	.839	.894	.601	.878	.061	.160	.106	.141	.804	.081	.463	.874
	Fluid Reasoning	r	.597	.716	.547	.557	.148	.494	**.900**	.772	**.868**	**.707**	.513	**.871**	.756
		p	.090	.030	.128	.119	.705	.176	**.002**	.015	**.002**	**.003**	.158	**.002**	.018
	Crystallised Ability	r	.489	.381	.343	.401	.553	**.825**	.647	**.878**	.434	.539	.629	.518	.109
		p	.151	.277	.332	.251	.097	**.003**	.060	**.001**	.210	.108	.051	.125	.764
	Fluid Crystallised Index	r	.518	.531	.344	.562	.319	**.**738	**.919**	**.891**	**.885**	.621	.498	**.841**	.566
		p	.125	.114	.331	.091	.369	.015	**<.001**	**.001**	**.001**	.056	.143	**.002**	.088

Table 6.11 highlights the correlation coefficients between scores on the WISC-IV and the TEA-Ch. In addition the correlation coefficients between certain subtests of the WISC-IV and the TEA-Ch subtests for the normative sample are included, as reported in the test manual (Manly et al., 1999). These are presented beneath the overall index to which they contribute. For the patient sample significant, positive correlations were found with at least one attention subtest for all indices except for Processing Speed. Unfortunately the normative sample did not complete a measure for Processing Speed so it was not possible to ascertain whether this trend was seen in typically-developing children. Given that the Same Worlds task is purported to be a measure of processing speed (Mulder, Pitchford & Marlow, 2010) the lack of association between this subtest and Processing Speed was surprising. As suggested above, it is possible that the Same Worlds task is a purer measure of processing speed not requiring any additional processes such as working memory.

Following Bonferroni correction significant correlations were only found for Verbal Comprehension and Working Memory and both of these only correlated with measures of Sustained attention. Prior to Bonferroni correction Perceptual Reasoning was the only index to correlate with measures of Selective/Focused attention, more particularly with the timed aspect of Sky Search. As with Fluid Reasoning from the KABC-II this may be due to the timed component of the Perceptual Reasoning subtests. This pattern was supported by results from the normative sample correlations, which reported significant positive correlations for both the Sky Search and Map Mission subtests with the Perceptual Reasoning subtests. In contrast the correlations for the typically-developing sample between attention and verbal measures did not reflect the significant coefficients found for the patient sample. This suggests that in the patient sample low performance in one domain is impacting on ability in another. Whilst correlations do not equate to

causation, it may be possible that the low attention scores in the patient sample may be affecting attainment on the Verbal Comprehension subtests. Similarly to the KABC-II indices, the Same Worlds subtests was related to most of the WISC-IV indices, although not all reached significance, again highlighting a central role of processing speed in performing these subtests.

For both the KABC-II and the WISC-IV performance on the sustained attention subtests was most highly related to cognitive capacity, particularly the more taxing subtests such as Code Transmission and the measures of Sustained/Response Inhibition (Walk Don't Walk) and Sustained/Divided (Sky Search DT). The correlation coefficients were generally found to be higher for the WISC-IV indices, supporting the findings from the individual analyses detailed above.

Table 6.11 Correlations (*r*) between scores on WISC-IV indices (in bold) and TEA-Ch scores for cerebellar patients (N=10) and for the standardising sample (N=160) between subtests of the WISC-III and prorated IQ (not in bold), after Bonferroni correction α=.004

	Cognitive standardised measures		TEA-Ch												
			Selective/focused				Sustained					Attentional control/switching			
			Sky Search			Map Mission	Score	Score DT	Code Transmission	Sky Search DT	Walk Don't Walk	Creature counting		Opposite worlds	
			Correct	Time	Attention							Correct	Time	Same	Opposite
WISC-IV	**Verbal Comprehension**	r	.429	.320	.185	.472	.474	**.890**	.696	**.898**	.678	.418	.531	.615	.256
		p	.216	.368	.610	.168	.166	**.001**	.037	**<.001**	.031	.229	.114	.058	.476
	Vocabulary subtest	r	-	-	.05	.15	.14	.10	.16	.12	.14	**.23**	.12	-	-.002
		p			.530	.058	.077	.208	.043	.131	.077	**.003**	.131		.98
	Similarities subtest	r	-	-	.05	.16	.10	.14	.08	.07	.05	.20	.07	-	.03
		p			.530	.043	.208	.077	.315	.379	.530	.011	.379		.707
	Perceptual Reasoning	r	.578	.777	.598	.641	.049	.383	.818	.697	.764	.496	.362	.653	.645
		p	.080	.008	.068	.046	.893	.275	.007	.025	.010	.145	.304	.041	.044
	Block Design subtest	r	-	-	.15	**.24**	.12	.09	.18	.12	**.24**	**.27**	.01	-	.09
		p			.058	**.002**	.131	.258	.023	.131	**.002**	**<.001**	.900		.258
	Object Assembly subtest	r	-	-	.19	**.27**	.09	.16	.11	.16	**.24**	**.30**	-.05	-	.09
		p			.016	**<.001**	.258	.043	.166	.043	**.002**	**<.001**	.530		.258
	Working Memory	r	.360	.356	.300	.291	.284	.680	**.854**	.802	.765	.623	.652	.673	.429
		p	.306	.313	.400	.415	.427	.031	**.003**	.005	.010	.054	.041	.033	.215
	Processing Speed	r	.131	.141	-.077	.472	.388	.531	.457	.371	.296	.286	.110	.587	.141
		p	.718	.697	.832	.169	.268	.114	.216	.291	.407	.422	.763	.075	.699
	Full Scale IQ	r	.481	.500	.337	.563	.366	.774	**.851**	**.884**	.788	.563	.544	.755	.450
		p	.159	.141	.342	.090	.298	.009	**.004**	**.001**	.007	.090	.104	.012	.192
	Prorated IQ	r	-	-	.14	**.25**	.14	.15	.17	.14	.21	**.31**	-.01	-	.07
		p			.077	**.001**	.077	.058	.032	.077	.008	**<.001**	.900		.379

6.3.4.2 Academic measure

Inspection of table 6.12 suggests that almost all the academic indices were highly related to scores for sustained attention, although many were not significant following Bonferroni correction. This pattern was similarly reflected in the correlation between scores on the Wide Range Achievement Test and attention scores in the normative sample. As with the cognitive measures the Same Worlds task was highly correlated with all the academic indices indicating that processing speed is highly related to scholastic skills.

The normative sample was reported to have significant correlations between academic scores and scores on the Creature Counting subtests of Attentional Control/Switching index, a pattern which was not found in the patient sample. Inspection of the patient scores for Creature Counting task revealed that the spread of patient scores was particularly uneven for this subtest, which may account for the lack of significant correlations. For the patient sample the Reading index was found to significantly correlate with Map Mission from the Selective/Focused attention, although this was not maintained following Bonferroni correction and was not supported by the results from the normative sample. Written Language was found to correlate with most of the Sustained attention subtests, similarly to the other academic measures.

Table 6.12 Correlations (*r*) between scores on WIAT-II indices (in bold) and TEA-Ch scores for cerebellar patients (N=10) and for the standardising sample (N=160) between indices of the Wide Range Achievement Test (not in bold) and the TEA-Ch, after Bonferroni correction α=.004

	Academic standardised measures		TEA-Ch												
			Selective/focused				Sustained					Attentional control/switching			
			Sky Search			Map Mission	Score	Score DT	Code Transmission	Sky Search DT	Walk Don't Walk	Creature counting		Opposite worlds	
			Correct	Time	Attention							Correct	Time	Same	Opposite
WIAT-II	**Reading**	r	.640	.260	.002	.651	.419	.744	.813	.792	.783	.436	.227	.805	.354
		p	.336	.469	.997	.041	.229	.014	.008	.006	.007	.208	.528	.005	.316
	WRAT Reading	r	-	-	.009	.013	.018	.17	.19	.22	**.26**	.14	.17	-	.10
		p			.258	.101	.023	.032	.016	.005	**<.001**	.077	.032		.208
	Mathematics	r	.406	.451	.296	.393	.377	.784	**.888**	.746	.753	.670	.577	**.867**	.527
		p	.244	.191	.407	.261	.283	.007	**.001**	.013	.012	.034	.081	**.001**	.117
	WRAT Arithmetic	r	-	-	.10	.19	**.26**	.16	.18	**.33**	**.28**	**.40**	**.18**	-	.08
		p			.208	.016	**<.001**	.043	.023	**<.001**	**<.001**	**<.001**	**.023**		.315
	Written Language	r	.347	.251	.064	.477	.500	.772	.808	.718	.739	.556	.314	**.833**	.364
		p	.326	.484	.861	.163	.141	.009	.008	.019	.015	.095	.377	**.003**	.301
	WRAT Spelling	r	**-**	-	.13	.06	**.**17	.14	.19	**.17**	**.27**	.16	.22	**-**	.14
		p			.101	.451	.032	.077	.016	**.032**	**<.001**	.043	.005		.077
	Oral Language	r	.714	.575	.357	.603	.392	**.672**	**.853**	**.922**	.792	.630	.317	**.818**	.568
		p	.020	.082	.312	.065	.263	**.003**	**.003**	**<.001**	.006	.051	.372	**.004**	.087
	Total Composite	r	.473	.382	.161	.577	.474	.805	**.870**	**.853**	**.812**	.599	.366	**.881**	.455
		p	.167	.276	.656	.081	.166	.005	**.002**	**.002**	**.004**	.068	.298	**.001**	.186

6.3.4.3 Cognitive/Academic discrepancy

The correlations between the TEA-Ch scores and the discrepancy values between achieved and predicted academic scores (see Chapter 5) reiterated the patterns shown for the WISC-IV and WIAT-II indices. Positive correlations were found between the Code Transmission, Walk Don't Walk and Score DT subtests of the Sustained attention component and the discrepancy values based on the Full Scale IQ score (FSIQ), the Verbal Comprehension Index (VCI) and the Perceptual Reasoning Index (PRI). Although none reached significance after Bonferroni Correction the trend indicated by these results suggested that those children with a lower academic performance than expected demonstrated greater attentional deficits. No striking variation was found for the indices of the WIAT-II (Reading, Maths, Written Language & Oral Language) as the difference values for all the indices were found to correlate with at least one subtest of Sustained attention.

The Same Worlds task was positively correlated with almost all the difference scores across all three comparisons suggesting that processing speed may also be a contributory factor towards academic achievement. Indeed, following Bonferroni correction only the Maths and Oral Language discrepancies based on VCI ability were significantly correlated with the Same Worlds scores.

Table 6.13 Correlations (*r*) between WISC-IV/WIAT-II indices and TEA-Ch scores for cerebellar patients (N=10) after Bonferroni correction α=.004

WISC-IV/WIAT-II Discrepancy			TEA-Ch												
			Selective/focused				Sustained					Attentional control/switching			
			Sky Search			Map Mission	Score	Score DT	Code Transmission	Sky Search DT	Walk Don't Walk	Creature counting		Opposite worlds	
			Correct	Time	Attention							Correct	Time	Same	Opposite
Discrepancy based on FSIQ	Reading	r	.144	-.004	-.286	.580	.366	.547	.602	.535	.599	.231	-.096	.668	.193
		p	.692	.992	.422	.079	.298	.102	.086	.111	.067	.522	.792	.035	.593
	Maths	r	.234	.287	.178	.123	.315	.621	.798	.430	.537	.627	.478	.784	.476
		p	.515	.421	.624	.735	.375	.055	.010	.215	.110	.053	.162	.007	.164
	Written Language	r	.241	.110	-.062	.376	.489	.662	.688	.543	.614	.474	.166	.750	.275
		p	.503	.763	.864	.284	.151	.037	.041	.104	.059	.167	.648	.012	.442
	Oral Language	r	.670	.430	.236	.411	.249	.298	.522	.599	.496	.447	-.042	.566	.478
		p	.034	.215	.512	.237	.487	.402	.149	.067	.145	.196	.908	.088	.163
Discrepancy based on VCI	Reading	r	.192	.147	.148	.643	.287	.469	.712	.533	.682	.342	.060	.763	.340
		p	.595	.686	.682	.045	.422	.172	.031	.113	.030	.333	.868	.010	.336
	Maths	r	.287	.427	.299	.231	.219	.516	.805	.448	.612	.684	.470	**.829**	.585
		p	.421	.219	.402	.522	.543	.127	.009	.194	.060	.029	.171	**.003**	.076
	Written Language	r	.264	.186	.000	.418	.446	.619	.757	.545	.670	.543	.176	**.820**	.364
		p	.462	.606	1.00	.229	.197	.056	.018	.104	.034	.105	.627	**.004**	.301
	Oral Language	r	.762	.635	.407	.512	.146	.154	.735	.585	.606	.627	.059	.728	.701
		p	.010	.049	.243	.130	.687	.671	.024	.076	.063	.052	.871	.017	.024
Discrepancy based on PRI	Reading	r	.142	.039	-.264	.482	.468	.703	.623	.290	.103	.656	.130	.580	.620
		p	.695	.915	.462	.185	.172	.023	.068	.417	.776	.039	.721	.079	.056
	Maths	r	.187	.125	.029	.139	.460	.783	.800	.553	.521	.566	.521	.730	.295
		p	.604	.761	.937	.702	.181	.007	.010	.097	.122	.088	.122	.017	.408
	Written Language	r	.188	.063	-.109	.322	.439	.654	.729	.531	.615	.469	.194	.751	.287
		p	.603	.863	.764	.364	.205	.040	.026	.114	.058	.172	.592	.012	.422
	Oral Language	r	.596	.289	.112	.404	.494	.653	.640	.790	.573	.533	.196	.680	.353
		p	.069	.419	.758	.247	.147	.041	.064	.007	.083	.113	.588	.031	.318

6.3.4.4 Motor measure

The pattern of correlations recorded for the BOT-2 indices was similar to those for the cognitive and academic measures, although generally the coefficients were weaker (Table 6.14) and fewer remained significant following Bonferroni correction. The majority of the correlations were found for the Sustained subtests, including Code Transmission and Sky Search DT. For Code Transmission little coordinated movement was required to perform the task and for Sky Search DT the motor component was taken into account when calculating the scores. Given that no significant correlations were found for the Sky Search task, this suggested that it may be specifically the increased attentional demands in Sky Search DT that are linked to motor skills. The Walk Don't Walk subtest includes a relatively higher motor component in task demands and only Body Coordination was found to be significantly correlated (not following Bonferroni correction) with this test suggesting that it is not purely an overlap in motor abilities driving these correlations. Neither of the Attentional Control/Switching indices were found to correlate with the motor indices. The Map Mission subtest of the Selective/Focused attention component was significantly correlated with Fine Manual Control and Body Coordination, however as stated above this subtest did not include a motor control component when calculating the attention score. The results from the Sky Search subtest, which did partial out motor ability, indicated more strongly that Selective/Focused attention may not be related to motor skills.

As above, processing speed, as assessed by the Same Worlds task, was significantly correlated with Body Coordination and Strength & Agility. For these indices there was a timing component for some of the subtests which was not the case for the Fine Manual Control and Manual Coordination indices, which may explain why these indices were not correlated with processing speed.

Table 6.14 Correlations (*r*) between scores on the BOT-2 indices and the TEA-Ch scores for the cerebellar patients (N=10), after Bonferroni correction α=.004

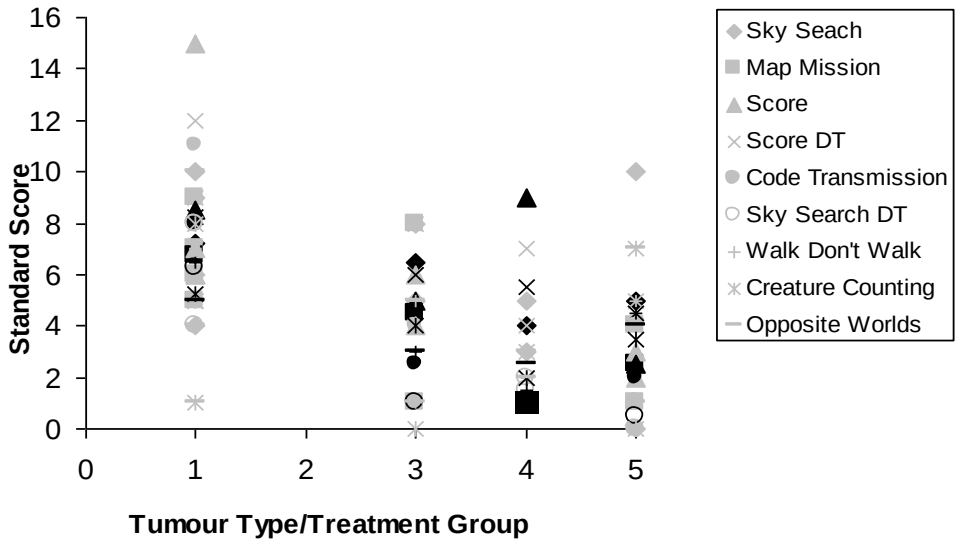
	Motor standardised measures		TEA-Ch												
			Selective/focused				Sustained					Attentional control/switching			
			Sky Search			Map Mission	Score	Score DT	Code Transmission	Sky Search DT	Walk Don't Walk	Creature counting		Opposite worlds	
			Correct	Time	Attention							Correct	Time	Same	Opposite
BOT-2	**Fine Manual Control**	r	.559	.422	.095	**.847**	.297	.323	.703	.630	.599	.280	-.231	.621	.394
		p	.093	.224	.794	**.002**	.405	.363	.035	.051	.067	.433	.521	.055	.259
	Manual Coordination	r	.559	.269	.162	.241	.277	.357	.674	.686	.547	.572	.236	.545	.454
		p	.093	.453	.654	.502	.439	.311	.046	.029	.101	.084	.511	.103	.188
	Body Coordination	r	.308	.111	-.233	.632	.350	.567	.617	.607	.708	.238	-.116	.728	.382
		p	.387	.760	.517	.050	.322	.087	.076	.063	.022	.508	.749	.017	.275
	Strength & Agility	r	.485	.035	-.193	.552	.667	.504	.516	.612	.454	.460	-.183	.662	.183
		p	.156	.923	.593	.121	.035	.138	.155	.060	.187	.181	.613	.037	.612
	Total Motor Composite	r	.601	.269	.026	.551	.440	.439	.710	.719	.600	.524	-.037	.704	.420
		p	.066	.452	.944	.098	.203	.204	.032	.019	.067	.120	.918	.023	.226

6.3.5 Impact of prognostic factors on attention

The statistical results for the relationship between the prognostic factors and the attention scores are detailed in Table 6.15. Significant positive correlations were found between Age at Diagnosis and the Walk Don't Walk subtest (r=.715, p=.020, not significant following Bonferroni correction) and approaching significance for Map Mission (r=.620, p=.056). None of the other subtests were found to be associated with Age at Diagnosis. A mixture of positive and negative correlations between Time Post Treatment and attention scores were found and none reached significance.

As in the previous chapters, tumour histology and treatment received were considered in conjunction as tumour type informs the treatment received. A significant main effect of Tumour/Treatment Type was found for all subtests of the Sustained attention component (max. $\chi^2(3)=21.66$, $p<.001$; min. $\chi^2(3)=8.73$, $p=.033$) except for Score DT ($\chi^2(3)=3.50$, $p=.321$). A significant main effect was also found for Map Mission ($\chi^2(3)=12.17$, $p=.007$). No significant effect of Tumour Type/Treatment was found for either of the Attentional Control/Switching subtests or for the Sky Search task. Subsequent pairwise analyses of the significant main effects revealed that for most subtests, children with astrocytoma and surgery only performed most highly. For Map Mission the children with ependymoma also performed more highly than the children with medulloblastoma and PF radiotherapy (Figure 6.1).

Figure 6.1 Effect of Tumour Type/Treatment (1=astrocytoma, surgery; 3=ependymoma, surgery, chemotherapy; 4=medulloblastoma, surgery, chemotherapy, PF radiation; 5=medulloblastoma, surgery, chemotherapy, PF radiation/CSI) on standard scores achieved on the TEA-Ch subtests, bold points represent group means. 2=astrocytoma, surgery, chemotherapy, however this child (P07) did not complete this task



A significant main effect of Tumour Location was found for three of the Sustained attention subtests, Code Transmission ($\chi^2(2)=10.80$, $p=.005$), Walk Don't Walk ($\chi^2(2)=7.85$, $p=.020$) and Sky Search DT ($\chi^2(2)=8.00$, $p=.018$) and one of the Attentional Control/Switching subtests (Opposite Worlds: $\chi^2(2)=9.68$, $p=.008$) when the participants were divided according to whether the right hemisphere (RH) and vermis, left hemisphere (LH) and vermis or vermis alone were affected. No difference was found between the groups for any of the other subtests. Pairwise analyses revealed that for all the significant subtests the child with LH and vermis involvement scored more highly than the other two groups (Figure 6.2). As discussed in previous chapters, it is possible that this result arises from the left hemisphere and vermis group including one participant only, limiting the spread of the scores.

Figure 6.2 Effect of Tumour Location (1=RH, vermis; 2=LH, vermis; 3=vermis) on standard scores achieved on the attention subtests

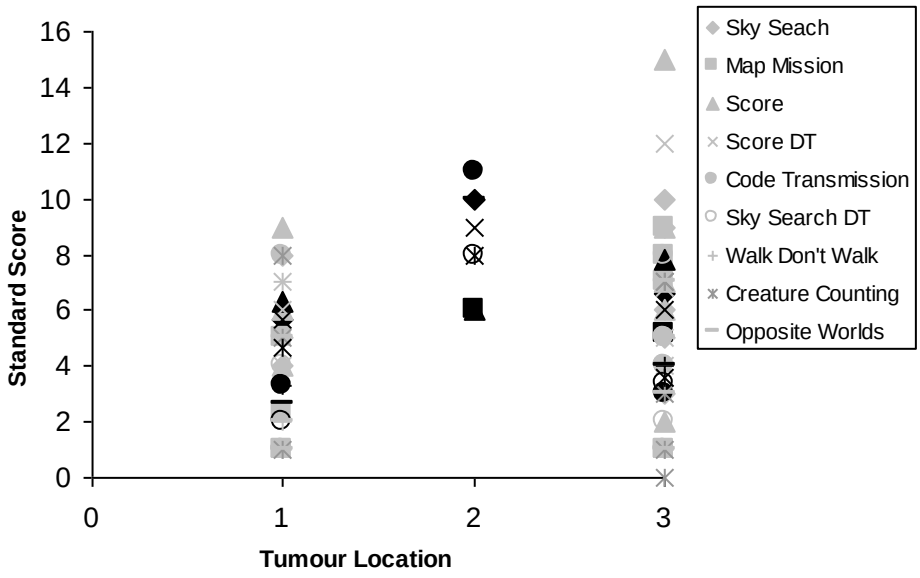


Table 6.15 Correlations (*r*) and differences in performance (χ^2) for the attention subtests in relation to the different potential moderator variables. After Bonferroni correction α=.006 for the correlation analyses

TEA-Ch Subtests		Age at Diagnosis		Time Post Treatment		Tumour Type/ Treatment		Tumour Location	
		r	p	r	p	$\chi^2_{(3)}$	p	$\chi^2_{(2)}$	p
Selective/ Focused	Sky Search	.258	.471	.340	.336	2.79	.425	2.12	.347
	Map Mission	.620	.056	-.362	.304	12.17	.007	4.28	.118
Sustained	Score	-.083	.820	.015	.967	9.64	.022	.760	.684
	Score DT	.366	-.393	-.393	.262	3.50	.321	1.28	.527
	Code Transmission	.533	.140	-.124	.751	20.16	<.001	10.80	.005
Sustained/ Response Inhibition	Walk Don't Walk	.715	.020	-.326	.359	21.66	<.001	7.85	.020
Sustained/ Divided	Sky Search DT	.525	.120	-.022	.952	8.73	.033	8.00	.018
Attentional Control/ Switching	Creature Counting	.217	.547	-.016	.966	3.69	.297	3.68	.159
	Opposite Worlds	.367	.297	.094	.797	2.67	.445	9.68	.008

6.4 Discussion

This chapter examined the impact of early treatment for a cerebellar injury on attentional capacity. The results were considered in the light of previous studies in the area, and in conjunction with the scores from the standardised measures for cognitive, academic and motor functioning reported in the previous chapters.

6.4.1 Individual outcomes

Whilst the case-by-case analysis revealed variable patterns of achievement across the patients, by considering all the profiles together it was possible to draw some conclusions concerning the attentional deficits shown by many of the sample. The first two patients considered, those least impaired (P14 & P05), did not demonstrate ubiquitous attentional difficulties, in fact P14 was not significantly impaired on any of the attention subtests. P05 demonstrated a deficit on one measure of attentional control only, and this appeared to be anomalous in comparison to results for other subtests. This lack of attentional deficits in children with cerebellar damage poses difficulty for the hypothesis that the cerebellum is involved in attention networks. One explanation is that although these children were not significantly impaired, their scores were generally below the test norm mean. It is possible that the potential for high achievement has been limited by cerebellar damage and that more sensitive experimental measures of attention may highlight specific deficits in these two children. Their performance on these tests may have been reduced compared to what may have been expected had they not suffered a cerebellar tumour. This hypothesis is difficult to test given the early age at onset in this patient group, one possible method may be to examine family history to establish whether the patients are functioning at a level that is commensurate with their siblings and/or parents.

The other patient who performed highly on the cognitive and academic measures, P02, demonstrated a more variable pattern of attention skills. The deficits in the Selective/Focused attention and Attentional Control/Switching subtests did not appear to be reflected in the other domains measured, suggesting that sustained attention may be particularly pertinent to cognitive and academic functioning. In addition, the Conners 3 report highlighted behavioural difficulties in this child, with a high probability that a diagnosis of ADHD would be appropriate. This suggested that selective attention and executive attention are more closely linked to the symptoms of ADHD than sustained attention. None of these children (P14, P05 & P02) demonstrated inconsistencies in their academic and cognitive scores.

This hypothesis may be further refined by considering the scores for P04. This child demonstrated difficulties with the Attentional Control/Switching and the Sustained attention subtests whereas selective attention was relatively spared. As this child was not reported as having ADHD tendencies, these results suggest that selective attention may be related to ADHD symptoms rather than executive attention. In addition, this child had difficulty with cognitive and academic scores and demonstrated a discrepancy between predicted and obtained scholastic performance, further supporting the hypothesis that sustained attention is related to these domains. P13 also demonstrated this pattern of performance, with severe sustained attention difficulties and poor cognitive and academic functioning. In addition, P13 had difficulty with Attentional Control/Switching, however unlike P04, the Conners 3 report for this child indicated a high probability of ADHD. These results suggest that it is executive attention that is most closely linked to ADHD. Age at test may be able to account for these opposite findings in P04 and P13. As P04 was 15 years at test and P13 was 6 years, P04 may have developed a greater degree of executive control and may not manifest symptoms of ADHD as obviously as P13. In addition, as discussed in the introduction executive attention is thought to

mature by seven years whereas inhibitory control continues developing into adolescence.

Similarly to P13, the results from P01 would seem to indicate that difficulties in attentional control are linked to a high probability for ADHD. In addition this child showed deficits in sustained attention and corresponding cognitive and academic impairments. P11 and P03 demonstrated pervasive attentional difficulties, had a high probability of ADHD and poor cognitive and academic attainment. Whilst these profiles do not disagree with the hypotheses based on the other patients, it is also not possible to disentangle any particular patterns of functioning based on general limited performance.

The main conclusions from these individual analyses may be summarised as follows:

- Children who have suffered a cerebellar tumour can show deficits in some aspects of attention but not others suggesting that the different attention networks are able to dissociate.
- All three aspects of attention have been demonstrated to be impaired in children with cerebellar tumours.
- Sustained attention appears to be related to both cognitive and academic performance and the discrepancy between the two.
- Difficulties with attentional control and selective attention are both linked to ADHD, but not necessarily sustained attention. Considering all patients, it appears more likely that executive attention is more closely related to the symptoms of ADHD than selective attention.

One child whose profile did not agree with these conclusions is P06 who demonstrated the most severe deficits across all components of attention but was not reported as having a high probability of ADHD. As suggested above, this child was significantly impaired in all domains with severely limited mobility and therefore may have lacked the independence to exhibit behavioural symptoms of ADHD as he was largely dependent upon his parents for most daily

activities. This suggests that the attentional difficulties exhibited by these patients may not automatically be reflected behaviourally, as corroborated by the results for P04 and P10.

Another child with an unusual profile is P02, who was reported as having severe behavioural difficulties but performed within the normal range for most of the standardised measures. Behavioural disturbances in children with cerebellar lesions have been well documented, particularly with reference to poor regulation of affect (Levisohn et al., 2000) and are considered to be analogous to the cerebellar cognitive affective syndrome seen in adults (Schmahmann & Sherman, 1998). In particular this syndrome has been linked to the vermis, which was damaged in P02.

6.4.2 Is sustained attention responsible for deficits in other domains?

The hypothesis that sustained attention has the greatest impact on performance in other domains is supported by the group correlation analyses. Across all the standardised measures previously used, the strongest correlations were recorded for the subtests of sustained attention. In particular Walk Don't Walk, a measure of sustained attention and response inhibition, Sky Search DT, which measured sustained and divided attention, and Code Transmission were found to be strongly correlated with the indices from the previous standardised measures. Score and Score DT (also sustained attention tests) were less strongly associated, suggesting that these measures may have been less demanding on attentional resources. Inspection of the task demands and the results across all subtests (Table 6.4) suggests this may be a feasible explanation. This result in the patient sample was supported by the correlations reported in the TEA-Ch manual for the normative sample. The correlation coefficients were generally lower for the typically-developing group suggesting that in a population with a wider spread of attention scores the relationship with

cognitive and academic scores may be attenuated, although the correlations remained significant.

Similarly, the correlation coefficients indicated a strong relationship between the WISC-IV/WIAT-II discrepancies and attention scores suggesting that the larger the discrepancy between cognitive and academic scores, the lower the attentional capacity. Again, only the Sustained subtests were found to be related to the discrepancy values, emphasising that this aspect of attention is associated with academic skills. This prominence of sustained attention does not appear to be due to a higher proportion of children demonstrating significant impairments in the Sustained subtests compared to the other components of the TEA-Ch.

It has been noted that the relationship between a child's potential and their actual performance is dependent upon attentional capacity and therefore their ability to engage with a task (Gordon, Thompson, & Cooper, 1990). In this way, attention may be viewed as a mediator between cognitive skills and academic achievements. Sustained attention in particular is posited to be important for academic abilities as the capacity to maintain concentration on one or a set of stimuli over a long time period is highly relevant for the problem-solving nature of academic tasks. Work with typically-developing children has demonstrated this (Steinmayr, Ziegler, & Träuble, 2010) and the findings reported here suggest that this relationship is maintained in children with cerebellar injury.

One exception to this overarching influence of sustained attention appears to be the Processing Speed index of the WISC-IV. It is possible that this aspect of the WISC-IV represents an analogous basic cognitive skill that underpins higher cognitive abilities independently to attentional capacity. This is explored further below. This relationship was not investigated in the typically-developing sample so it was not possible to ascertain whether this result was unique to this sample.

6.4.3 The relation of attention networks to other standardised indices

The hypotheses developed in Table 6.2 concerning the relationship of specific indices to the attention subtests may be evaluated using the correlation analyses. As highlighted in the individual case studies, the indices of the KABC-II were not found to be as strongly related to the attention scores as the WISC-IV cognitive indices. For the KABC-II the strongest associations were found for the Visual Processing and Fluid Reasoning scores, with no significant correlations found for either Short Term Memory or Long Term Storage & Retrieval suggesting attentional resources have minimal impact of memory abilities. This is contrary to the predictions made in Table 6.2. In addition Crystallised Ability, which was not predicted to be related to any attentional measures, was found to be significantly correlated to some of the Sustained attention subtests. One of the subtests of this index was the Riddles task in which a child had to assimilate a list of facts to correctly guess the item. It is evident that Sustained attention may be an important mediator in completing this task.

For the WISC-IV indices many of the predictions were accurate, with the exception of those concerning Processing Speed as this was not related to any attention scores. In contrast to the Short Term Memory index from the KABC-II, the Working Memory index was strongly correlated with sustained attention reiterating that these indices may be tapping different capacities. For the WIAT-II, correlations were found between all indices and the measures of sustained/divided attention and response inhibition. For the motor indices the most consistent correlations were found for the Sky Search DT task, a measure of sustained/divided attention, indicating that this aspect of attention is the most associated with both gross and fine motor control. Fine Manual Control was strongly associated with Map Mission, although as discussed the high motor component of this task is not considered when calculating the attention score.

6.4.4 Are attentional capacities responsible for the link between other domains?

Previous chapters have explored the interrelation between cognitive and motor skills in both typically-developing and patient samples (Chapters 2 & 3). The results from these chapters indicated a strong correlation between the two domains that appeared to be driven by an underlying association between Visual Processing and Fine Manual Control. The results of this study have demonstrated that many aspects of both the motor and cognitive measures are highly related to sustained attention. It is therefore possible to suggest that the link between these domains may be mediated by underlying basic processes that influence performance in each, such as sustained attention. The correlation between the KABC-II index Visual Processing and the BOT-2 index Fine Manual Control for the 10 patients who completed this phase of the study was shown to be significant (T2: r=.859, p=.001). Partial correlations were performed between these indices, controlling for the attention subtests demonstrated to be strongly related to all measures; Code Transmission subtest (r=.248, p=.554), Sky Search DT (r=.673, p=.047) and Walk Don't Walk (r=.456, p=.218). The decrease in correlation suggests that sustained attention may at least partially account for the relationship between these domains. Further research with typically-developing children would be required to fully investigate this possibility, however it does appear to be in line with findings from other studies.

Previous results have suggested that the reduction in cognitive and academic achievement in children with cerebellar tumours is due to reduced processing speed, memory difficulties and an inability to sustain attention (Maddrey et al., 2005; Mulhern and Palmer, 2003; Nagel et al., 2006; Palmer, Reddick & Gajjar, 2007; Reeves et al., 2006; Schatz, Kramer, Ablin, & Matthay, 2000). The analyses of this study have suggested that a decline in sustained attention is related to poorer outcome in other domains. As discussed above, some subtests of the TEA-Ch may also be used to assess basic processing speed, namely the Same Worlds task and the motor component of the Sky Search task.

Correlations between Visual Processing and Fine Manual Control controlling for these scores did not indicate a substantial reduction in the correlation coefficient (Same Worlds; r=.840, p.005; Sky Search Motor; r=.777, p=.023). Although these results are based on a small heterogeneous sample, they suggest that sustained attention may be more strongly implicated in the relationship between motor and cognitive skills. In addition, correlations between these measures of processing speed and performance on the cognitive and academic indices did not demonstrate consistent significant associations.

6.4.5 Depression and anxiety

The Conners 3 also highlighted that all the patients for whom it was administered were reported as meeting criteria for anxiety and all except one met the criteria for depression. This result supports previous studies which have found that adolescent survivors of brain tumours are at risk for symptoms of depression, anxiety and diminished social confidence (Mabbott et al., 2005; Shultz et al., 2007). Whilst it is difficult to draw firm conclusions from a parental questionnaire report, these results should be considered when interpreting scores on the other measures as both depression and anxiety have been shown to adversely affect performance on standardised measures in children (e.g. Lundy, Silva, Kaemingk, Goodwin, & Quan, 2010). Given the severity of the deficits many patients demonstrate however, it is unlikely that the impact of depression and anxiety on scores will be significant. Further interpretation of this result is limited with the measures employed in this study, although unlike in previous studies, this finding is not limited simply to those children treated for more aggressive tumours suffering long-term effects of chemotherapy and radiotherapy and warrants further investigation in this population.

6.4.6 Impact of prognostic factors

The impact of prognostic factors on attention scores was similar to the results found in previous chapters, which is unsurprising given the strong association between attention scores and other domains. A younger age at diagnosis, which has consistently been found to result in poorer outcome, was only found to impact on the Walk Don't Walk and Map Mission subtests, however correlations for the remaining attention measures did not even approach significance. Both of these measures include a relatively strong motor element and it is possible that the different components of attention are not affected by age at diagnosis in a sample where this variable is limited to below 5 years of age. Time post treatment was not found to significantly relate to any of the attention subtests suggesting that attention skills do not diminish with time as suggested in some previous studies (e.g. Papazoglou et al., 2008b). A decrease in attention skills would also seem to be counter to the longitudinal results reported in Chapter 4. Again it is likely that the sample size is too limited to fully ascertain any longitudinal changes in attention using a cross-sectional design.

The impact of Tumour Type/Treatment was found for all of the Sustained attention subtests, one of the Selective/Focused subtests and neither of the Attentional Control/Switching subtests. These findings therefore offer further support to the hypothesis that sustained attentional deficits may be related to the volume of normal appearing white matter (e.g. Mulhern et al., 2004). Despite this, impairments were still found in children who did not undergo radiotherapy. A significant effect of tumour location was found, with the child with LH and vermis damage scoring most highly. As in previous chapters however, this finding should be interpreted with caution as only one child was included in this group and mean scores in the group with RH and vermis damage and vermis damage only were very similar.

6.4.7 Conclusion

Damage to the cerebellum due to tumour in early childhood has been demonstrated to result in poor attention skills following treatment. Whilst the analyses revealed that deficits were most pronounced in children who had received radiotherapy, offering support to the hypothesis that white matter mediates this relationship, it is important to note that attention deficits were also found in children who were not treated with radiotherapy. These results, in line with several previous studies suggest that the cerebellum plays a role in attention and that all three attentional components may be affected following cerebellar damage. The limited sample included here does not allow for precise mapping of the location of damage onto functional deficits.

The close relationship between sustained attention and the scores from all other domains highlights the central role this function is likely to perform. Given the widespread deficits demonstrated by this sample, remediation to specifically target sustained attention may be seen to correspondingly impact on performance in other areas. Many of the children in this study were found to exhibit highly similar profiles to those of children with ADHD. In addition to methylphenidate therefore, behavioural strategies that have been employed to help children with ADHD, such as self-monitoring (e.g. Purdie, Hattie, & Carroll, 2002) may be found to have a similar impact in this population.

7 The effect of hydrocephalus following cerebellar tumour: A case-by-case approach

7.1 Background literature

In accordance with previous literature (e.g. Beebe et al., 2005; Scott et al., 2001), the previous chapters have demonstrated motor and cognitive deficits following injury to the cerebellum due to treatment for a tumour in childhood. In addition to the impact of the treatment process (surgery, chemotherapy and/or radiotherapy) other prognostic factors, including age at diagnosis, tumour type/location, and time post onset, have been investigated in relation to developmental progression. Another factor thought to influence outcome is the presence of hydrocephalus. In children with posterior fossa tumours, around 80% are reported as suffering from hydrocephalus (Bognár, Borgulya, Benke, & Madrassy, 2003; Culley, Berger, Shaw, & Geyer, 1994) with treatment for persistent or progressive hydrocephalus necessary post-operatively in 25-30% of patients (Schijman, Peter, Rekate, Sgorous, Wong, 2004) and 7-25% needing a permanent shunt (Mangubat, Chan, Ruland, Roitberg, 2009). Whilst several previous studies have examined the effect of hydrocephalus in children with brain tumours, findings are inconsistent across studies so the consequence of acute hydrocephalus for subsequent development following posterior fossa injury is not clear (Mangubat et al., 2009). Hydrocephalus in the absence of brain tumours across a variety of conditions (e.g. spina bifida and prematurity) has been found to affect several cognitive functions (Anderson et al., 2001; Brookshire et al., 1995; Erickson, Baron, & Fantie, 2001). As a substantial proportion of children with posterior fossa tumours are affected by hydrocephalus, further investigation is warranted towards clarifying the extent of developmental repercussions.

Early investigations suggested that hydrocephalus in children with a posterior fossa brain tumour impacted negatively on cognitive functioning

(Bloom, Wallace, & Henk, 1969; Jannoun & Bloom, 1989), however successive studies present mixed findings. Several studies report that the severity of hydrocephalus at the time of tumour diagnosis is a significant risk factor for subsequent intellectual functioning in patients treated for astrocytoma (Aarsen et al., 2009; Rønning et al., 2005), and of those with hydrocephalus, those who received a ventriculoperitoneal (VP) shunt were found to perform higher than those without a shunt on measures of attention, language and executive functioning (Aarsen et al., 2009). Hydrocephalus following treatment for an ependymoma has also been found to negatively influence IQ scores above and beyond the effects of radiotherapy (Merchant et al., 2004; von Hoff et al., 2008). However, conflicting evidence has been reported concerning the effect of hydrocephalus on patients treated for medulloblastoma. Several studies have reported a negative impact on cognitive functioning (Hardy, Bonner, Willard, Watral, & Gururangan; 2008; Packer et al., 1987) whilst others have found no association between neuropsychological outcome and shunting (Hirsch, Renier, Czernichow, Benveniste, & Pierre-Kahn, 1979; Kao et al., 1994; Rønning et al., 2005). One study reported that children who were given a shunt performed more highly in IQ and achievement tests than those without (Johnson et al., 1994). A study including children with medulloblastoma, astrocytoma or ependymoma reported a higher incidence of postoperative cerebellar syndrome in patients with preoperative hydrocephalus in addition to significantly greater impairment in verbal and performance IQ and fine-motor skills (Grill et al., 2004). Hydrocephalus may also be a risk factor for mutism following posterior fossa tumour treatment, although again this has not been consistently reported (Catsman-Berrevoets et al., 1999; Van Dongen et al., 1994).

Studies have also examined the impact of hydrocephalus following all childhood brain tumours, not restricted to those in the posterior fossa. Again evidence is inconsistent, with some highlighting no effect of hydrocephalus (Mulhern & Kun, 1985; Papazoglou et al., 2008a) and others reporting that

hydrocephalus requiring a shunt is a significant risk factor for adverse neuropsychological outcome (Reimers et al., 2003; Reimers et al., 2007). One study reported no effect of hydrocephalus on academic, language and memory abilities, although children with hydrocephalus performed more poorly on measures of executive function, intelligence, visuo-motor abilities and fine-motor skills (Brookshire, Copeland, Moore, & Ater, 1990). This is somewhat surprising given the interrelation between domains found in earlier chapters. Conversely, another study reported that children with hydrocephalus performed significantly better than those without hydrocephalus on two cognitive measures, at both one and four months post-diagnosis assessments (Ellenberg et al., 1987).

Differences in the classification of hydrocephalus severity, insertion of a shunt resulting in more extensive damage preoperatively, and shunt complications (e.g. infection), may account for some of these discrepancies, as postoperative complications are known to be significant risk factors for subsequent cognitive functioning (Kao et al., 1994). Also the prevalence of hydrocephalus may be higher in younger patients (Chapman et al., 1995) and as younger age at diagnosis often results in poorer developmental outcome (Dennis et al., 1996; George et al., 2003) age may be a confounding factor when studying the impact of hydrocephalus on neurodevelopmental outcome, but very few studies account for this. This highlights the difficulty in performing univariate analyses between cognitive outcome and prognostic and tumour-related factors as risk factors are often associated (Reimers et al., 2003). Although small sample sizes often render multivariate analyses inappropriate, potential interactions between risk factors can nonetheless be considered through a case series approach.

Difficulty with disentangling the impact of prognostic factors on neurodevelopmental outcome arises through the use of group methodology, especially with small and heterogeneous samples. This can result in trends, driven by one or two individuals, which are not representative of all children.

Similarly, group data from heterogeneous samples may yield results that are not reflective of both intra- and inter-individual scatter in performance (Shallice, 1988). This has been illustrated in the preceding chapters with this patient sample. At the group level, a significant effect of hydrocephalus was found for some measures of cognitive functioning, as children most severely affected performed significantly lower than those with moderate hydrocephalus on a measure of Fluid Reasoning. However, there was much individual variation, both across patients on particular measures, and within patients across different tests, suggesting little systematic effect of hydrocephalus on performance. This highlights the need for detailed investigations into the consistency with which hydrocephalus influences developmental progression for a more comprehensive understanding to be gained.

This chapter aims to investigate the extent of variation in the effect of hydrocephalus on performance across the range of standardised measures administered to the patient sample throughout the previous chapters, with examination at both the individual and group level. A benefit of the case-by-case approach employed in this study is that it averts the need for a control group of children with benign conditions associated with hydrocephalus. If substantial intra- and inter-individual variation is shown across performance on different outcome measures, then severity of hydrocephalus will be insufficient to account for differences in developmental outcome in this sample.

7.2 Method

7.2.1 Patient information

This study considers data from all 15 of the patients who participated in the initial phase of this study (Chapter 3). Patient details, including hydrocephalus severity, treatment for hydrocephalus, age at diagnosis, tumour type, time post onset and complications, are described in Table 3.1 (Chapter 3). The severity of hydrocephalus was assessed by a paediatric neurosurgeon from close examination of patient notes, using a 4 point scale; none, mild, moderate and severe hydrocephalus. Of these children, 15 completed an initial session of cognitive (Kaufman Assessment Battery for Children – 2nd edition: KABC-II, Kaufman & Kaufman, 2004) and motor tests (Bruininks-Oseretsky Test of Motor Proficiency – 2nd edition: BOT-2, Bruininks & Bruininks, 2005), 11 completed an additional cognitive measure (Wechsler Intelligence Scale for Children – 4th UK edition: WISC-IV, Wechsler, 2004/Wechsler Pre-school & Primary Scale of Intelligence – 3rd UK edition: WPPSI-III, Wechsler, 2003), 12 completed an academic test (Wechsler Individual Achievement Test -2nd UK edition: WIAT-II, Wechsler, 2005), and 10 completed an attention test (Test of Everyday Attention for Children: TEA-Ch, Manly et al., 1998). Not all participants were able to complete every measure due to patient attrition throughout the testing period as well as some children being too young for some of the standardised measures (see Chapters 4, 5 & 6).

7.2.2 Measures

Patients were given a comprehensive range of standardised neurodevelopmental measures, including intellectual ability (IQ, using the WISC-IV/WPPSI-III), attention (TEA-Ch), language and numerical abilities and literacy skills (WIAT-II) (See previous chapters for test details). These tests were administered in 2-3 sessions, depending on the ability and needs of the child, with each session lasting 2-3 hours. The KABC-II and BOT-2 were completed in

the first session, whilst the WISC-IV/WPPSI-III, TEA-Ch and WIAT-II were given in the second and third sessions. The tests were administered individually in a quiet area in the patient's home with breaks given as necessary.

7.2.3 Statistical analyses

Scores obtained on the standardised measures were investigated individually to assess variation both within and between participants, and across tests and test indices. Group analyses were also conducted using a series of chi-square tests on patients grouped by hydrocephalus severity and shunt placement. Pairwise comparisons were performed to establish where significant differences lay. All analyses were conducted using parametric statistics ($p \leq .05$, two-tailed level of probability) and Bonferroni corrections for pairwise comparisons ($p \leq .0083$) are also reported.

7.3 Results

7.3.1 Individual analyses

Table 7.1 presents standardised scores for all measures for each participant, ordered by increasing hydrocephalus severity group status. Inspection of these scores reveals that many patients have significant impairments across the range of measures used, but there is also substantial intra- and inter-individual variation.

For example, P10 (no hydrocephalus) and P13 (severe hydrocephalus pre-operatively) both suffered ependymoma and were treated with chemotherapy. Whilst both were impaired for the majority of the indices (83%), contrary to expectation, P13 scored higher than P10. Similarly, P01 (mild hydrocephalus pre-op) and P11 (severe hydrocephalus) were both treated for medulloblastoma but P11 performed better than P01 on 61% of the indices despite having more severe hydrocephalus. Contrasts within the same level of hydrocephalus severity demonstrate further inconsistencies. For example, P06

and P14 both had moderate hydrocephalus, but P06 was significantly impaired on 62% of the indices whereas P14 was not impaired on any and was performing close to the norm mean for many of the standardised tests.

Variation in individual performance across indices is also present in some individuals in each of the hydrocephalus severity groups. For example, scores for P10 (no hydrocephalus) were significantly impaired (at least 2 standard deviations below the norm mean) on 81% of the indices but were within the normal range (±1 standard deviation of norm mean) for the remaining 19%. Similarly, P13 (severe hydrocephalus) showed significant impairment on 28% of the indices but performance in the normal range for the remaining 72%.

Table 7.1 Individual standard scores across test indices

Bold scores - 2SD below norm mean, p ≤ .05, at least

		PATIENT																
		None	Mild	Moderate									Severe					
		P10	P01	P02	P09	P04	P06	P05	P14	P15	P08	Mean	P03	P11	P07	P13	P12	Mean
WISC-IV	VC	**61**	**61**	77	-	**67**	**69**	102	98	-	-	82.6	**53**	**63**	90[10]	**59**	-	66.3
	PR	**61**	94	84	-	96	**67**	92	98	-	-	87.4	**55**	**63**	-	79	-	65.7
	WM	**62**	74	107	-	**65**	**59**	102	107	-	-	88	**59**	**56**	-	**52**	-	55.7
	PS	**65**	**65**	94	-	**70**	**56**	85	68	-	-	74.6	**56**	78	75[1]	88	-	74.3
	FSIQ	**54**	**68**	86	-	**70**	**56**	95	91	-	-	79.6	**46**	**57**	82[1]	**62**	-	61.8
WIAT-II	RC	**47**	**44**	101	-	**67**	**63**	96	102	-	-	71.5	**53**	**57**	-	74	-	61.3
	MC	**48**	**66**	84	92	**46**	**40**	94	94	-	-	75	**43**	**57**	78	71	-	62.3
	WLC	**40**	**46**	86	-	**41**	**50**	103	104	-	-	64	**61**	**48**	-	79	-	62.7
	OLC	**60**	**66**	82	91	86	**68**	93	114	-	-	89	**69**	72	82	73	-	74
	TC	**45**	**51**	87	-	**59**	**53**	96	103	-	-	66.3	**54**	**56**	-	71	-	60.3
TEA-Ch	SF[11]	19	26	19	-	39	7	29	38	-	-	26.4	18	16	-	26	-	20
	SA[2]	11	10	21	-	12	8	32	26	-	-	19.8	14	17	-	16	-	15.7
	AC[2]	16	28	27	-	17	2	24	42	-	-	22.4	16	18	-	25	-	19.7
	S/RI	**1**	**1**	**7**	-	**4**	**4**	**5**	10	-	-	6	**2**	**1**	-	**5**	-	2.7
	S/DA	**1**	**1**	**4**	-	**5**	**0**	8	8	-	-	5	**1**	**2**	-	**1**	-	1.3
KABC-II	STM	**68**	97	97	88	77	100	106	97	74	74	89.1	83	91	97	91	83	89
	VP	**50**	71	87	88	80	**64**	84	111	**64**	89	83.4	71	**64**	**61**	80	91	73.4
	LTM	92	75	92	89	78	89	92	97	**58**	84	84.9	75	75	86	75	89	80
	FR	**57**	96	93	-	85	**62**	96	108	**67**	64	82.1	**62**	**67**	-	-	105	78
	CA	92	72	100	93	90	**69**	111	102	77	80	90.3	75	80	90	74	102	84.2
	FCI	**65**	76	91	87	78	**70**	96	104	**60**	73	82.4	**65**	**68**	79	75	92	75.8
BOT-2	FMC	**23**	32	40	52	46	34	39	40	**30**	45	40.8	**30**	34	35	38	39	35.2
	MC	**20**	**29**	39	39	35	26	32	38	**23**	38	33.8	**28**	33	34	**20**	36	30.2
	BC	**20**	**26**	34	41	**30**	32	34	36	35	49	36.4	**26**	31	40	32	45	34.8
	SA	**20**	**27**	45	48	38	31	44	40	**25**	45	39.5	39	38	44	37	53	42.2
	TMC	**20**	**26**	37	42	35	27	33	36	**28**	41	34.9	29	32	34	**28**	39	32.4

[10] Scores obtained from the WPPSI-III.

[11] Derived scores therefore impairment, as measured by SD from norm mean, cannot be reported.

7.3.2 *Group analyses*

Group analyses assessed statistical differences between children based on severity of hydrocephalus. Results for the indices of each of the standardised measures are presented in Figures 7.1-7.4, which plot all patient scores within each severity group.

Figure 7.1 shows a significant effect of hydrocephalus for all indices of the WISC-IV (max. $\chi^2(3)=28.69$, $p<.0001$; min. $\chi^2(3)=12.79$, $p=.05$) except Processing Speed. Pairwise comparisons revealed that for Verbal Comprehension the Moderate group performed higher than all other groups (Moderate>Severe only after Bonferroni correction). For Perceptual Reasoning the Mild and Moderate groups scored higher than the None and Severe groups (all significant following Bonferroni correction). For Working Memory the Moderate group scored higher than all other groups (Moderate>Severe only after Bonferroni correction) and for FSIQ the Moderate group scored higher than the None and Severe groups (both significant after Bonferroni correction).

Figure 7.1 Index scores of the WISC-IV for each participant group by hydrocephalus severity (0=none, 1=mild, 2=moderate, 3=severe)

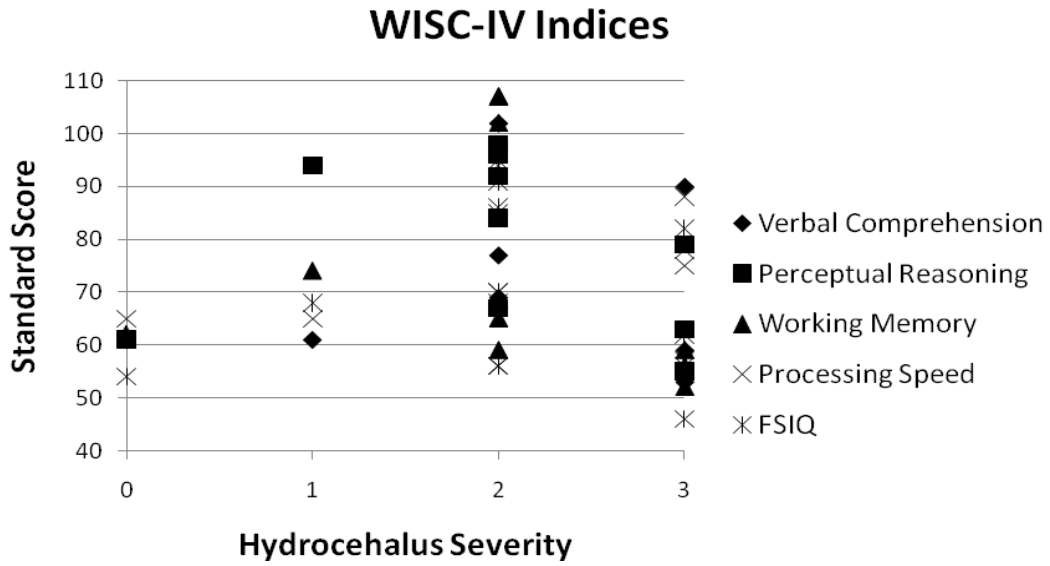


Figure 7.2 shows a significant effect of hydrocephalus for all indices of the WIAT-II (max. $\chi^2(3)=38.03$, $p<.0001$; min. $\chi^2(3)=15.38$, $p=.002$). For Reading the Moderate group scored higher than all other groups (all significant after Bonferroni correction). For Maths the Moderate group performed higher than the None and Severe groups (Moderate>None only after Bonferroni correction). For Written Language the Moderate group scored higher than all other groups, and the Severe group scored higher than the None group (Moderate>None and Mild only after Bonferroni correction). For Oral Language the Moderate group scored higher than all groups (Moderate>None group only after Bonferroni correction). For the Total Composite the Moderate group scored higher than all other groups (all significant after Bonferroni correction).

Figure 7.2 Index scores of the WIAT-II for each participant grouped by hydrocephalus severity (0=none, 1=mild, 2=moderate, 3=severe)

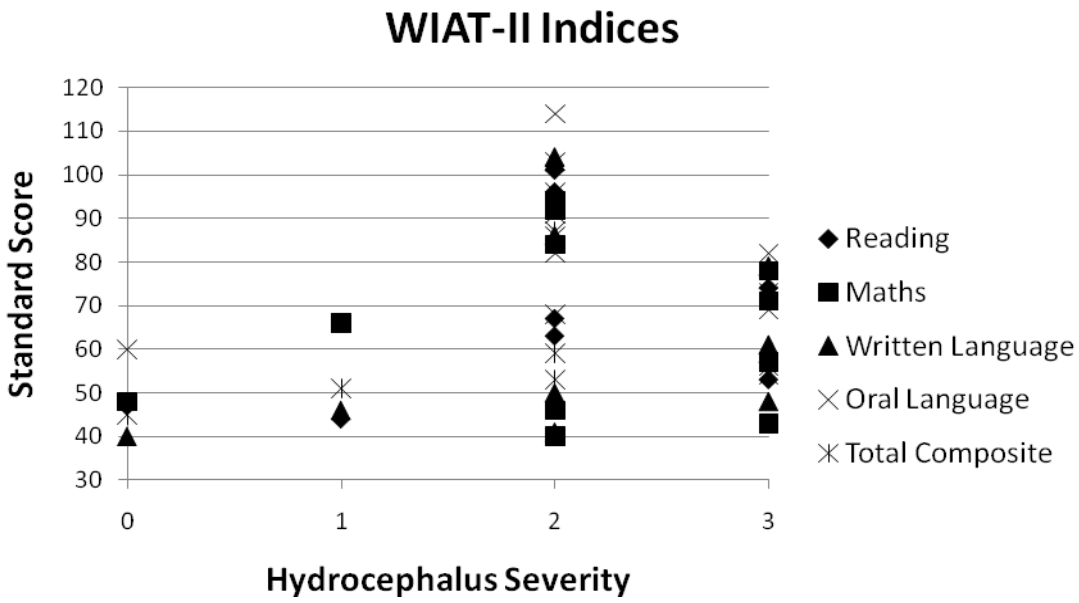


Figure 7.3 shows a significant effect of hydrocephalus on the TEA-Ch for two of the five indices: Sustained-Divided Attention ($\chi^2(3)=11.69$, $p=.009$) and Sustained Attention/Response Inhibition ($\chi^2(3)=10.83$, $p=.01$). For Sustained-Divided Attention the Moderate group performed higher than all other groups (none significant following Bonferroni correction). For Sustained Attention/Response Inhibition the Moderate group scored higher than the Severe group (not significant following Bonferroni correction).

Figure 7.3 Index scores of the TEA-Ch for each participant grouped by hydrocephalus severity (0=none, 1=mild, 2=moderate, 3=severe)

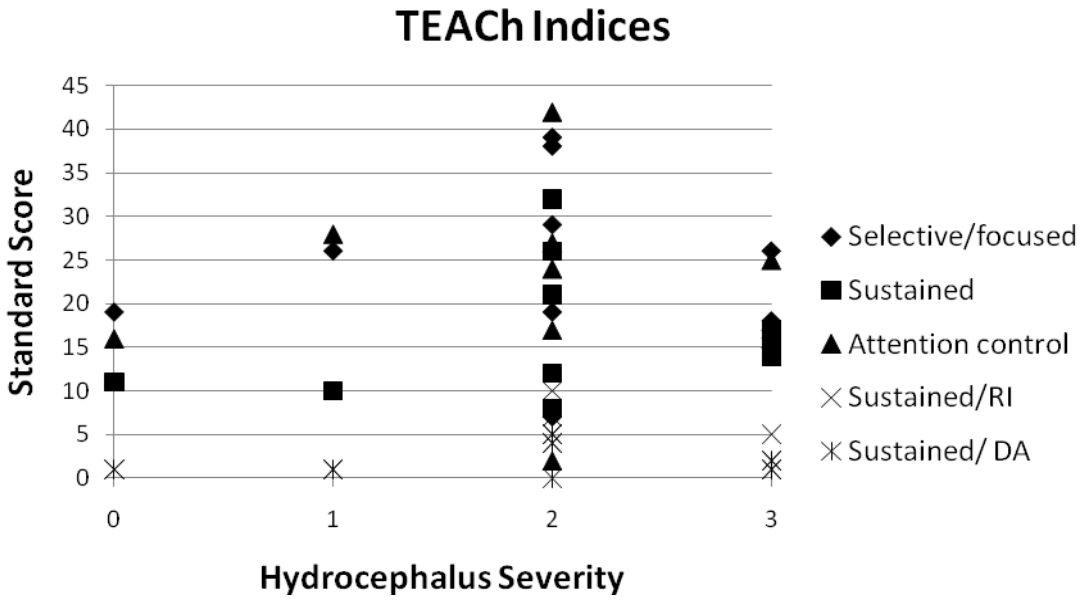
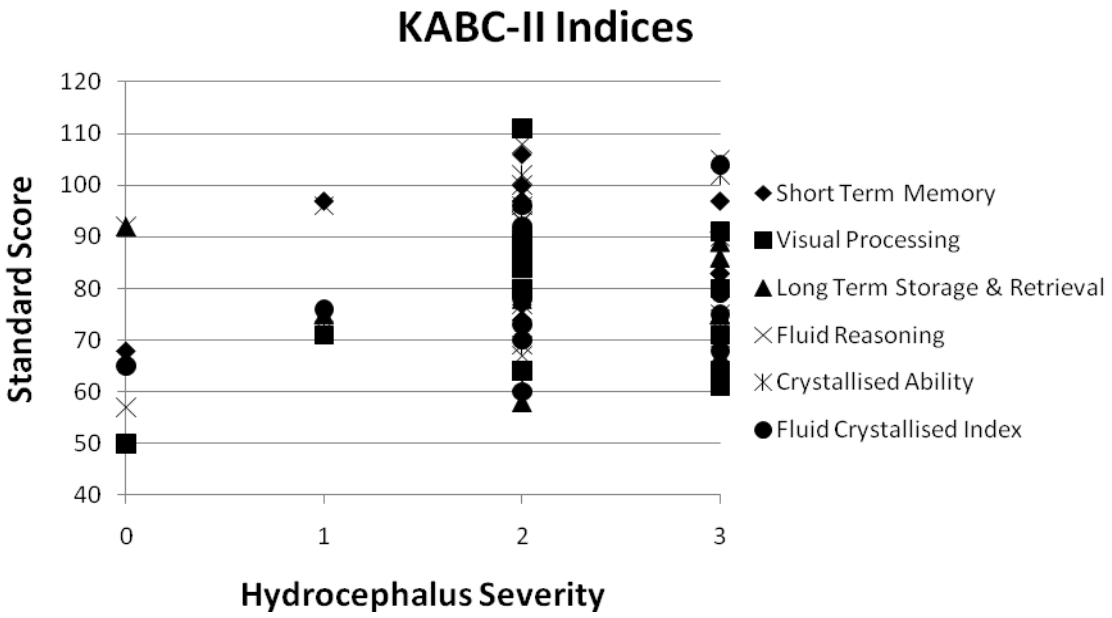


Figure 7.4 shows a significant effect of hydrocephalus for two of the six indices of the KABC-II: Visual Processing ($\chi^2(3)=15.0$, $p=.002$) and Fluid Reasoning ($\chi^2(3)=10.34$, $p=.02$). For Visual Processing, the Moderate and Severe groups performed better than the child with no hydrocephalus and the Moderate group performed higher than the Severe group (Moderate>None only after Bonferroni correction). Similarly for Fluid Reasoning the child without hydrocephalus performed lower than all the other groups (None<Mild and Moderate only after Bonferroni correction).

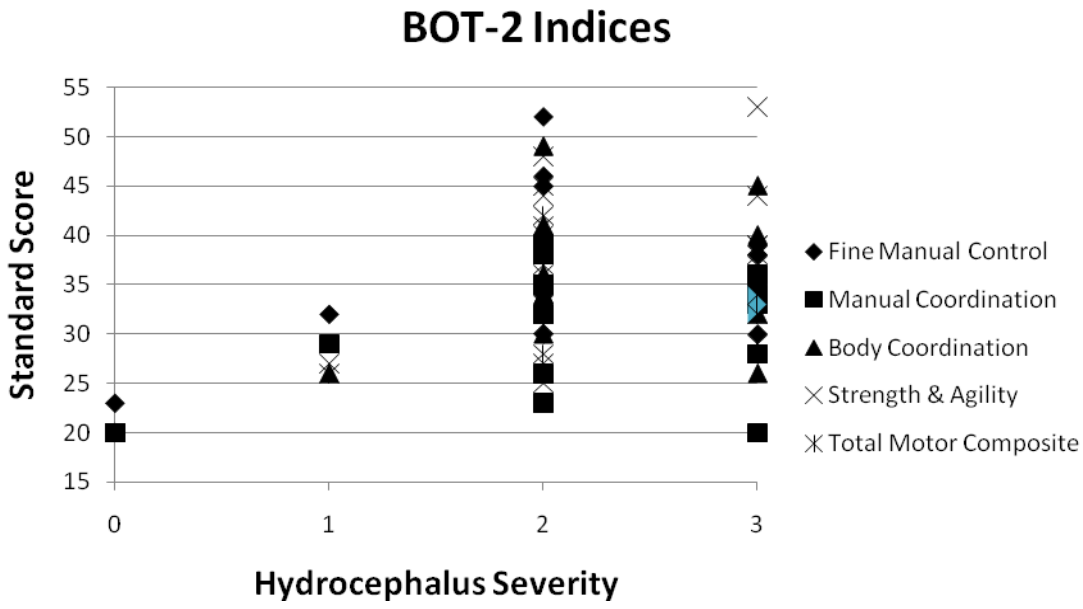
On the BOT-2 a significant effect of hydrocephalus was found for three of the five indices: Fine Manual Control ($\chi^2(3)=9.40$, $p=.02$), Body Coordination ($\chi^2(3)=9.05$, $p=.03$) and Strength & Agility ($\chi^2(3)=12.46$, $p=.006$). The Moderate group scored higher than the child without hydrocephalus for Fine Manual Control (significant after Bonferroni correction) and both the Moderate and Severe groups performed better than the child without hydrocephalus on Body Coordination (neither significant following Bonferroni correction). For Strength & Agility both the Moderate and Severe groups scored higher than the child without hydrocephalus and the Severe group scored higher than the child with Mild hydrocephalus (None<Moderate and Severe only after Bonferroni correction).

Figure 7.4 Index scores of the KABC-II (a) and BOT-2 (b) for each participant grouped by hydrocephalus severity (0=none, 1=mild, 2=moderate, 3=severe)

(a)



(b)



7.3.3 Hydrocephalus treatment

Group analyses on hydrocephalus management compared children who received a shunt or neuroendoscopic third ventriculostomy with children who received no hydrocephalus treatment. For all indices of the WISC-IV, except Working Memory, those with a shunt performed significantly higher than those without shunt placement (max. $\chi^2(1)=9.98$, $p=.002$; min. $\chi^2(1)=4.63$, $p=.031$). For the WIAT-II children with a shunt scored more highly than those without on Reading ($\chi^2(1)=6.16$, $p=.013$), Mathematics ($\chi^2(1)=11.14$, $p=.0008$) and the Total Composite ($\chi^2(1)=4.11$, $p=.043$). For the TEA-Ch no significant differences were found (max. $\chi^2(1)=1.84$, $p=.175$). For the KABC-II the shunted group performed significantly better than the non-shunted group on Short Term Memory ($\chi^2(1)=7.76$, $p=.005$) and Fluid Reasoning ($\chi^2(1)=4.62$, $p=.032$). On the BOT-2 no significant differences were found. Again, a wide spread of scores was seen across groups with significant overlap between groups.

7.4 Discussion

The extent of variation in the effect of hydrocephalus on cognitive, scholastic and motor functioning following injury to the cerebellum due to tumour in the preschool years was investigated in a sample of 15 children. Restricting age at diagnosis to the preschool years minimised the confounding effect of age on predicting the influence of hydrocephalus. This small sample revealed an inconsistent effect of severity of hydrocephalus on neurodevelopmental outcome. Considerable variation in performance was found across individuals on particular tests and within individuals across tests, and the degree of variation was not consistent with severity of hydrocephalus. Specifically, some children with severe hydrocephalus performed at a similar level to those with less severe hydrocephalus, and in general the child with no hydrocephalus performed most poorly of all. Ventriculitis is considered highly detrimental to cognitive outcome (Young, Oakes, & Hatten, 1992) and although

the patient with ventriculitis (P06) performed poorly across most indices his scores were not markedly different from other patients without ventriculitis. Also, P06 was treated for a medulloblastoma with craniospinal irradiation, which also contributes to poor cognitive outcome, so the effect of ventriculitis is not clear.

Similarly, group analyses resulted in little consistent effect of hydrocephalus severity on neurodevelopmental outcome. Children with moderate hydrocephalus were generally least impaired on some, but not all, of the standardised measures administered, but no effect of hydrocephalus severity was found for several indices. Furthermore, Figures 7.1-7.4 clearly show that whilst some children with moderate hydrocephalus achieved higher performance on some measures than children with less or more severe hydrocephalus, the lower scores in each group are comparable and often at baseline. This indicates that severity of hydrocephalus does not discriminate poor performance on these tests. A wider spread of scores is likely with larger sample sizes, so the finding that moderate hydrocephalus resulted in least impairment may be diluted if more children were available for study.

Group analyses based on shunt placement revealed that in general those children who received a shunt performed better than those without a shunt on many of the cognitive, but not motor, tests. This conflicts with some previous findings (Hardy et al., 2008) but agrees with others (Aarsen et al. 2009; Johnson et al., 1994). However, as the majority of children who received a shunt were in the Moderate group and this group was found to be least impaired, shunt placement and severity of hydrocephalus may be confounded. Moreover, the effect of shunt placement on outcome was not pervasive, as no effect of shunt was found for seventeen of the twenty-six indices.

Seemingly, neither hydrocephalus severity nor shunt placement alone is a strong predictor of developmental outcome. Other prognostic factors, such as age at diagnosis and tumour/treatment type, may be better predictors of

outcome than hydrocephalus, as suggested in previous chapters. These confounding factors may account for inconsistent findings across individual patients and also across previously reported studies. The heterogeneity of scores on the standardised measures both within individuals and between participants is sufficient to highlight, without results from a control group, that hydrocephalus is unable to account for the differential outcomes recorded here.

A limitation of this study is the small number of heterogeneous patients for group analyses. However, the finding that the one child without hydrocephalus generally performed more poorly than all others is firm evidence against the notion that degree of hydrocephalus predicts functional outcome in these patients and supports the need for a case series approach which considers all prognostic factors on an individual basis. Also, hydrocephalus severity was coded using a non-standardised classification based on retrospective examination of patient notes. A greater understanding of the effect of hydrocephalus on neurodevelopmental outcome in this population may be gained by more precise measures of hydrocephalus severity, such as the peak pressure value and duration, although these can be difficult to obtain as children are often only hospitalised for hydrocephalus above a certain level. MRI scans could be employed to assess the ratio between pre- and post-treatment ventricular volumes, however this may still be compounded by ex vacuo increases in cerebrospinal fluid following removal of a large tumour. This highlights the need for clinicians to adopt a standardised protocol of registering hydrocephalus severity, allowing the impact of hydrocephalus to be examined more precisely, in addition to enabling larger, multi-centre studies to be performed encompassing more paediatric patients.

8 General Discussion

This study investigated the developmental outcome of 15 cases of children with cerebellar injury resulting from treatment for tumour sustained in the preschool years. The cognitive, motor, academic and attention skills of this sample were examined in detail using both group and case-by-case analyses. It is important to clarify the profile of deficits seen in this population to enable effective rehabilitation. In addition, as discussed below, examining development in these patients may further clarify the role of the cerebellum in different skills and help to inform theories of development.

8.1 Study aims

8.1.1 Theoretical aims

From a theoretical viewpoint this study first aimed to examine the nature of any underlying link between cognitive and motor skills across middle childhood in typically-developing children. Recently it has been suggested that the divisions typically drawn between different domains are invalid (e.g. Dyck et al., 2009) whilst others have highlighted the possibility that integrated underlying neural networks may be responsible for this lack of distinction between domains (Diamond, 2000). Diamond suggested that as the cerebellum is highly connected to prefrontal regions, it may support cognitive functions more fully than has been previously considered and it is this contribution to multiple skills which brings about any associations seen between domains. This cerebellar role in cognitive abilities is given additional support by a wide base of imaging and tumour studies with both adults (e.g. Schmahmann & Sherman, 1998) and children (e.g. Scott et al., 2001).

Leading from this hypothesis by Diamond, the second aim of this study was to investigate the interrelation of cognitive and motor skills in children who had sustained damage to the cerebellum due to a tumour and subsequent

treatment in the preschool years. This phase of the study aimed to establish whether the link between domains was sensitive to injury of the cerebellum, a brain area hypothesised to be important in supporting this association (Diamond, 2000).

Given the increasing evidence for a cerebellar role in cognition, the third theoretical phase of this study investigated the role of the cerebellum in more scholastic skills, such as reading and mathematics. Again, previous tumour studies with adults and children offer some evidence that the cerebellum may have a function in these abilities, however due to methodological inconsistencies in previous studies it is difficult to establish if academic difficulties are a direct result of cerebellar damage or whether they are due to an overall decline in cognitive functioning. The third component of this study aimed to clarify these opposing hypotheses.

The final theoretical aim of this research was to investigate the impact of cerebellar damage on attention skills. It has previously been noted that attention deficits in paediatric tumour patients have not been well established (Penkman, 2004), with the profile of attentional deficits difficult to establish from previous studies. It was hypothesised that the academic difficulties seen in some patients that are inconsistent with their level of cognitive impairment may be due to a deficit in basic underpinning processes such as attention. It has previously been suggested that the cerebellum may have a role in attentional processing (e.g. Braga et al., 2007) and examining attention skills in children with cerebellar damage aimed to further investigate the nature of this contribution.

8.1.2 Practical aims

This study also had several practical aims to help to clarify the nature of any deficit seen in children who have suffered a cerebellar tumour in the preschool years. In particular, given that previous studies offer contradictory

results concerning developmental outcome, the profile of deficits seen across different patients and across different time points was examined to investigate whether any patterns were evident. The domains investigated included cognitive, motor, academic and attentional skills. This study is one of the first to examine in depth each of these domains within the same children. This approach enabled comparison of deficits in different domains and allowed conclusions to be drawn concerning the nature of development following injury to the cerebellum. Knowledge of areas in which these patients may be expected to show significant weaknesses may enable earlier and more focused remediation. In addition, by studying the impact of a cerebellar tumour on the correlation between domains, this study aimed to distinguish between delayed and deviated functioning (Chapter 3). If the domains are closely linked in early development, it may be expected that damage to the underlying anatomy may result in delayed development, shown through similar correlations to those in the typically-developing sample. If, however, damage to the cerebellum results in atypical development, functioning across the domains may be expected to dissociate resulting in dissimilar correlation coefficients to the typically-developing sample.

In addition, the impact of different prognostic factors was investigated in relation to each skill domain examined and the longitudinal outcome. These included the histology of the tumour and linked to this, the treatment received; the location of the tumour within the cerebellum; the age at diagnosis; time post treatment; the presence of hydrocephalus and mutism. Results from previous studies have not always found consistent results regarding these factors which may be due to inconsistencies in measures used and differences in sample characteristics. This heterogeneous study aimed to clarify the impact of these prognostic factors using both individual and group analyses.

From a practical approach it is also important to clarify both the nature of any deficits or delays in development in children who have suffered a cerebellar

tumour, in addition to clarifying the role of the prognostic factors in order to be able to make better predictions concerning developmental outcome. Few previous studies have been conducted to establish longitudinal change in this population, other than considering time post treatment as a variable. The investigation into the longitudinal outcome in this sample aimed to help clarify whether a decline or improvement over time may be expected in these patients. Previous studies which have conducted longitudinal studies have not offered conclusive evidence to suggest if, and how, impairments may alter across development in these children.

8.2 Study results

The first experimental chapter of this thesis (Chapter 2) examined the interrelation of cognitive and motor skills in typically-developing children aged 4-11 years. The results from this study suggested that the association between the overall gross scores for cognition and motor abilities is underpinned by a close link between visual processing abilities and the ability for fine manual manipulation, a link that appears to be consistent across middle childhood. This stability throughout childhood does not accord with the discontinuous transitions in behaviour predicted by the dynamic systems theory of development (Thelen, 1993). However in line with the embodiment hypothesis (Smith, 2005), a child's dynamic interaction with the environment appears to be important for cognitive development through the close integration of sensory and motor activity.

Chapter 3 investigated the profile of cognitive and motor functioning in 15 tumour patients and compared the correlation between domains with that seen in the typically-developing sample. This study was further developed in Chapter 4 which examined the cognitive and motor interrelation in 12 of the original patients longitudinally. These chapters aimed to clarify between the different hypotheses proposed for the developmental progression seen in the tumour patients, to establish whether development is delayed or deviated. In addition,

the longitudinal aspect was able to distinguish between different models of developmental progression in these patients. The results of Chapters 3 and 4 indicated that the same relationship between cognitive and motor skills is seen in children who have sustained damage to the cerebellum and that this correlation is preserved longitudinally. These results, in accordance with previous theories of cerebellar functioning which suggest that the cerebellum has a 'universal' role in regulating functioning (e.g. Schmahmann, 1998; 2000b), suggested that both cognitive and motor domains appear to be similarly affected. In addition, these results support the hypothesis that there is an association between deficits in different domains which are influenced by the cerebellum (Schmahmann et al., 2002).

The similarities in the correlations between different domains found between the tumour patients and typically-developing children suggested that these children are demonstrating a pattern of developmental delay rather than atypical development. This was further clarified by the longitudinal results from Chapter 4. Contrary to some previous studies (e.g. Beebe et al., 2005), the patients in this study demonstrated developmental progression of cognitive skills at a rate commensurate with those seen in the typically-developing sample, even some of those who have received radiotherapy. The results suggested that in the short-term, following radiotherapy children may demonstrate a decline in cognitive functioning. Those children who received radiotherapy but with a longer time post treatment demonstrated a typical rate of development, despite severe impairments. For the motor skills examined, the raw and standardised scores considered in conjunction suggested that in comparison to the typically-developing group, many patients were developing at a slower rate, with some demonstrating a decline in skills over time.

The results from the academic section of this study (Chapter 5) suggested that patients with severe cognitive impairments demonstrated fairly uniform deficits across the scholastic skills measured. In contrast, those patients with a

more variable pattern of cognitive performance were relatively unimpaired on the academic measures. These results suggested that the scholastic difficulties seen in some patients were the result of a general cognitive delay, rather than a specific profile of deficits due to cerebellar damage. This finding therefore speaks against a specific cerebellar role in academic skills, and suggests that the general cognitive deficits seen as a result of severe cerebellar damage negatively impact upon competence in scholastic areas. Supporting this conclusion is the lack of association between balancing and reading skills in this sample, as this somewhat speaks against the cerebellar deficit hypothesis of dyslexia. In addition, the prognostic factors examined in this study were found to be the main influence on scholastic attainment, highlighting that damage due to more severe treatment results in poorer outcome. The loss of schooling, either due to time spent in hospital or due to other factors following treatment, such as severe residual motor incapacity (P10), appeared to have a strong negative impact on academic skills which was not reflected in the scores on the cognitive measures. This effect of hospitalisation and loss of schooling was not controlled for in this study, and this is further discussed below.

The results from the cognitive, motor and academic measures were drawn together by examining the attention skills in this patient population. The results suggested that the functioning in other domains was most closely related to the capacity for sustained attention, although difficulties with all aspects of attention were found. In addition, the correlation between the visual processing and fine manual control which was recorded in the patient sample, similarly to the typically-developing children, was found to decrease when a partial correlation controlling for sustained ability scores was conducted. This suggests that in this sample the underlying association between domains may be mediated by more basic processes, such as attentional capacity, to which the cerebellum contributes. This is supported by the finding that even some children who did not receive radiotherapy demonstrated attentional difficulties. It is

possible to hypothesise that the impact of cerebellar damage on sustained attention has a corresponding impact on cognitive and motor skills, which in turn impact upon academic achievement. The partial correlation suggested that visual processing and fine motor skills are not independent, even when controlling for sustained attention. This suggests that either other underlying processes, such as processing speed, working memory or other aspects of executive function, may also be contributing to the association, or that the two abilities are inherently linked. Further investigation is necessary to clarify these hypotheses.

8.3 Theoretical implications

The findings from the cross-sectional study of typically-developing children suggested that the association between the overall gross measures of cognitive and motor skills appears to be subserved by the link between visual processing skills and the ability for manual manipulation. Further investigation with the patient sample suggested that a proportion of this association may be accounted for by more underlying capacities, such as sustained attention. This finding offers support to the hypothesis by Dyck et al. (2009) that the distinction between domains may be false as higher order abilities are dependent upon more general processes. Taken together, these results may indicate that sustained attention is most closely related to visual processing and fine manual control of all the cognitive and motor skills assessed, which is why these two subtests appear to underpin the overall association between cognitive and motor skills. The results from Chapter 6 suggested that this is perhaps the case across the motor skills, although with the sample size and heterogeneity of the patient sample this tentative conclusion is difficult to substantiate. Verification in the form of a more comprehensive study with a larger typically-developing sample is required, as discussed below.

This finding may explain why previous studies with typically-developing children have reported such varying results. The different measures chosen in previous studies may differentially tap underlying processes, such as sustained attention, which would result in inconsistent findings regarding the association between the domains. Other general processes, such as processing speed and working memory may also be responsible for the link between different skills and these may also have differing impacts across studies depending on measures chosen. Whilst consistency in choice of measure across studies would enable conclusions to be drawn more easily from a comparison of multiple studies, it is not necessarily feasible within a single study to examine all possible aspects of an area of functioning (e.g. all components of motor skill).

This link between cognitive and motor skills was found to be preserved in children with damage to a postulated important component of the underlying network subserving cognitive and motor skills. In the tumour children, sustained attention was found to be a potentially important mediator in this relationship. Whilst examining whether this link holds in typically-developing children was outside the scope of this study, it is possible that sustained attention may be a general underlying process that affects both cognitive and motor skills and may account for the association seen between domains. The finding that sustained attention also appears to be important in the link between cognitive and academic scores in the patient sample offers further support to this hypothesis.

The consistency between correlations in the patient sample and those found in typically-developing children that are reported throughout this thesis suggest that whilst the patient sample is demonstrating a delay in development, they appear to have a qualitatively typical developmental trajectory. This is the first study to have demonstrated this by examining the association of functioning in patients in comparison to a typically-developing control group. The results suggest that development may be more constrained than proposed by previous hypotheses, such as that of Karmiloff-Smith (1992), as the patients in this

sample do not appear to have deviated development that is following an alternate trajectory. Rather, the results suggest that there is developmental delay, i.e. quantitative difference, with some evidence of catch-up, but that progression is nevertheless qualitatively typical. The results from the older children in this sample suggest that despite this catch-up, the level of functioning may remain lower than that seen in typically-developing children. This suggests that innate brain organisation and connectivity may not be necessarily drastically altered following brain injury. The dynamic systems theory of development (Thelen, 1993) and other hypotheses of brain function such as the free-energy principle (Friston & Stephan, 2007) suggest that the brain aims to optimise functioning. The results of this study support these hypotheses as they suggest that development is not easily perturbed onto a deviated trajectory.

In addition, the impact of the environment on developmental progression has increasingly been recognised as an important factor. It is reasonable to suggest that the environment of cerebellar patients is no different from that for typically-developing children, in that they are required to learn the same basic tasks. If however the tumour and treatment result in severe sensory or motor difficulties, it may be expected that more qualitative differences may be seen in patient development, for example hemiplegia may affect midline reaching or crossing behaviour with subsequent downstream consequences for development. In this sample, P10 exhibited severe motor impairments and it may be that investigation of a larger sample of children with comparable impairments demonstrates deviated, rather than delayed development, that is, the association between different domains may be altered in comparison to typically-developing children.

This finding may also have implications for children with developmental disorders. It is increasingly recognised that a high proportion of children with ADHD have concomitant perceptual and motor difficulties (DCD). In

Scandinavia, these children are classified as suffering from DAMP (deficits in attention, motor control and perception) (Gillberg, 2003). In addition to the difficulties of ADHD and DCD, a high proportion of children with severe DAMP demonstrate autistic features. Given the close interrelation of functioning in different domains, even in children who have suffered early cerebellar damage, in addition to the apparent stability of this relationship across childhood, it is perhaps unsurprising that co-occurrence of deficits is seen in children with developmental disorders. Other researchers (e.g. Kaplan et al., 1998; Pennington, 2006) have suggested that, similarly to the hypothesis of Dyck et al., (2009), developmental disorders are not discrete but are the result of a generalised neurological abnormality, resulting in a deficit in basic functioning which underpins higher order cognitions. The results from the tumour patients in this study offer support to this hypothesis.

In line with increasing evidence for a cerebellar contribution to cognition, the results from the patient sample are suggestive of a cerebellar role in both cognitive and motor processes, as both domains were negatively impacted in these children. In contrast to other hypotheses however (e.g. Nicolson et al., 2001), this study did not report any direct evidence for a specific cerebellar role in reading skills. A deficit in academic functioning above and beyond general cognitive difficulties was only recorded in those children who had received more invasive treatments, indicating that radiotherapy and possibly chemotherapy have a detrimental effect on these skills. As highlighted in Chapter 6, it may be that this effect of radiotherapy on academic skills is indirectly mediated by a negative impact on attention skills.

The results for the typically-developing sample in the patient study proved valuable control data when considering the results from the patients. The comparison between the cognitive and motor correlations for the typically-developing participants and the patients enabled the developmental trajectory of the patient sample to be considered in greater detail. In addition, the

longitudinal change of the patients relative to the controls was a significant extension of previous work, and in particular the importance of examining changes in both raw and standard scores for both groups was particularly informative when considering developmental progression. The later studies examining academic progress and attention skills in the patient group would have benefited from comparison with typically-developing controls similarly assessed, rather than relying on data provided by the test manuals. Whilst this was not feasible in the present study, the benefits of including an appropriate control sample should be considered in future studies examining outcome in children treated for cerebellar tumour.

8.4 Practical implications

From a theoretical viewpoint the impact of general skills, such as sustained attention, on the link between fine manual control and visual processing has yet to be clarified in a typically-developing population. From a practical stance however, the correlation found between domains raises the possibility that intervention in one domain may have a corresponding influence on the other, perhaps by improving the underlying skill which is involved in both domains, such as attention. As discussed in Chapter 2, this has important implications for child-rearing practices, and suggests that a child may benefit from an environment that is highly stimulating to both cognitive and motor skills so as to exploit the association between the two domains and maximise learning.

From a clinical perspective, the longitudinal aspect of this study highlighted that even the most severely impaired patients demonstrated improvements that may have gone undetected by standardised testing alone. It is therefore important for raw scores to be investigated when assessing children in this population. The patients in this study demonstrated variable patterns of development, both within and between individual profiles. This suggests that these children would benefit from a post-treatment assessment, with a view to

tailoring a rehabilitation plan. In line with previous findings, this study highlighted the detrimental effects of treatment for aggressive tumours, however it is important to consider that those children who did not receive chemotherapy or radiotherapy did demonstrate some level of weakness in the skills assessed.

The close link between domains suggests that a multifaceted rehabilitation encompassing several areas of functioning may be most effective. In addition, this study suggests that it is important for any underlying deficits in more basic skills to be identified before a valuable remediation plan may be formulated. The results reported here suggest that in this sample, a deficit in sustained attention is closely related to more severe difficulties with cognitive skills, a specific difficulty with academic measures and some additional difficulties with motor skills. It is therefore possible to suggest that identification of those children with particular attentional difficulties, through early screening with an appropriate assessment, with targeted remediation in this skill may help to ameliorate adverse outcomes in other domains. In addition, this aim may be aided by future study investigating the developmental trajectory of sustained attention in this population to establish whether this capacity develops at a typical rate, exceeds typical development, or reaches a developmental plateau following treatment for a tumour. Given the close association between sustained attention and the other cognitive skills measured, the increase in cognitive skills demonstrated in Chapter 4 may indicate that sustained attention similarly improves with time, although a longitudinal investigation would be necessary. Chapter 6 also indicated that several of the patients in this study met the criteria for ADHD. In addition to skill-targeted remediation programmes, this finding suggests that psychological interventions used with children with ADHD may be beneficial to children following treatment for a cerebellar tumour. The longitudinal results from Chapter 4 suggested that effective remediation may also need to specifically target motor abilities as these were demonstrated to be declining with age in many of the sample.

A final practical implication arising from this study is that concerning the classification of hydrocephalus. The difficulty with consistent classification noted in Chapter 7 suggests that clinicians need to adopt a standardised protocol to enable more direct comparisons to be drawn across different studies.

8.5 Limitations

Several factors concerning the participant samples and measures used may limit the findings of this study and these are discussed below.

8.5.1 Patient sample

Although cerebellar tumours account for a relatively high proportion of childhood brain tumours, incidence is rare, e.g. for ependymoma UK statistics estimate 3 cases a year per million children aged 0-14 years (Parkin et al., 1998). Consequently it was difficult to recruit a large sample of patients who met the inclusion criteria set out in Chapter 3 to participate in this study. The challenge of a small sample size was compounded by the highly heterogeneous nature of this patient group in terms of prognostic factors. There was therefore limited power to observe significant group differences between the patients divided on the various prognostic factors included here, e.g. Tumour Type/Treatment and Hydrocephalus. Despite this, group differences were found in line with previous results, supporting the conclusions from this study. The correlation analyses used for the patient sample throughout often failed to reach significance and this may have been due to the small sample size. Given the similarity between the patient sample correlations and those recorded for typically-developing children in this study, supported by the Fisher's z tests, it is unlikely that this unduly affected the results. However larger sample studies, with greater homogeneity in prognostic factors, are needed to address some of the issues raised by this study. In particular, a group with more focal lesions may enable further examination of functional divisions within the cerebellum, as

has been suggested (e.g. Scott et al., 2001). The finding that one of the children with vermis damage demonstrated emotional and behavioural difficulties (P02) offers support for the hypothesis that this area is important for the modulation of aggression and mood (Riva & Giorgi, 2000). Again however, this finding is limited by the heterogeneity of the sample as few patients had damage which was limited to one cerebellar region.

Where employed, the case-series approach, particularly in Chapters 6 & 7, highlighted the importance of this method when working with a small sample. In addition, whilst group results may enable a clinician to make more accurate prognoses for patients, the case-by-case analyses suggested that an individual approach is vital when approaching rehabilitation to ensure that the patient receives the most appropriate training to maximise potential. This is supported by previous rehabilitation studies which have highlighted the necessity for individualised plans (e.g. Callu et al., 2008).

The retrospective nature of this study does not allow premorbid functioning to be considered as a variable that impacts on functional outcome in this population. A valid prospective study with this population would be challenging as in younger children diagnosis is often not made until the tumour is in an advanced stage (Wilne et al., 2010). Despite this, a measure of pre-treatment functioning may be valuable as although preoperative functioning is likely to be affected by the tumour, such data may help to further disentangle the impact of aggressive treatment regimes from impairment caused by injury to the cerebellum. Given the difficulties of a prospective study another option may be to consider parental levels of education and sibling ability as these may provide a valid proxy for establishing to what extent potential for capacity has been limited due to treatment for a cerebellar tumour.

Whilst all children in this study were diagnosed below five years of age, the impact of hospitalisation on developmental outcome should be considered by including an additional control group for children who have also time spent in

hospital but do not have damage to the cerebellum. For example, children with leukaemia who may have a similar period in hospital but do not receive brain surgery or radiotherapy to the brain. In addition, the time missed in school as a consequence of functional impairment following treatment, as in the case of P10, should be considered as an additional variable which may impact on cognitive, motor, academic and attentional skills.

A final limitation for this study is that with a behavioural approach a wider impact of a cerebellar tumour and treatment on the brain may not be recognised. It had been argued that treatment for cerebellar tumour may result in damage to regions outside the cerebellum, either due to treatments, such as chemotherapy and radiotherapy, or due to diaschisis (Glickstein, 2006; 2007). The finding that some of the children who suffered an astrocytoma in these studies demonstrated cognitive difficulties suggest that this is not the case, and highlights that the cerebellum may play a more fundamental role in cognition than suggested by Glickstein. To further examine the impact of diaschisis on subsequent development, structural and functional imaging is required as future work as discussed below.

8.5.2 Typically-developing sample

To enable a wide section of childhood to be investigated, the study with typically-developing children employed a cross-sectional design with a post-hoc additional longitudinal aspect for children between 5 and 8 years. A large longitudinal study following children across childhood would enable a clear picture of any alterations in the interrelation of cognitive and motor skills to be drawn that may be less affected by sample effects.

8.5.3 Standardised measures

This study employed a number of standardised measures to assess various aspects of functioning. These tests were carefully selected from a broad range

of standardised measures to ensure that they were suitable for the whole sample. The standardised measures used in this study were chosen as they are considered the 'gold standard' for the domains assessed. Standardised measures were used as they enabled accurate comparison across age groups and the patient and typically-developing samples. Use of standardised tests provided a standardised administration procedure with objective scoring. There are a number of limitations related to using standardised measures. The use of standardised tests limits the range of abilities that are measured, with constraints placed upon interpretation due to the theoretical premise for the test construction. In addition, performance on these measures, particularly for the cognitive and academic tests, may be influenced by factors other than innate ability, such as time spent in school (e.g. Webster, McInnis & Craver, 1986) and cultural background (e.g. Gullo, 2005). Of particular note in this study was the use of the KABC-II and the BOT-2 which are standardised using a sample from the USA. For the BOT-2, the longitudinal outcomes explored in Chapter 4 highlighted that the typically-developing sample did not progress at the same rate as the standardising sample, suggesting that the standardising outcome may be slightly different for children in the UK. For the KABC-II, a few items on the Verbal Knowledge subtest of the Crystallised Ability subtest were considered to be culturally specific. As all children in this sample were from the UK however, these items would have affected all children uniformly.

A further difficulty with standardised measures related to the difficulty with assessing one domain only per task as many involve multiple areas of skill in addition to several domains. This was highlighted in Chapter 5, in which the working memory subtest of the WISC-IV, Letter-Number Sequencing, was postulated to be more strongly correlated with academic achievement than the working memory subtests from the KABC-II. Whilst it is not necessarily feasible to create tests which tap a single skill only, it is possible to limit the motor input needed to complete cognitive tasks. Where this is not possible tests should

include a motor control, as in the Sky Search subtest of the TEA-Ch, which subtracts the motor component of the task with the aim of establishing the cognitive requirements of the task.

8.6 Future work

Several directions for future investigation arising from the results of this study have been mentioned in this discussion. The results from the patient sample indicating the influence of sustained attention as a potential mediator between cognitive and motor skills, suggest that this additional factor should be examined in a typically-developing population to establish whether this pattern in the tumour patients reflects that in control participants. In addition, as discussed, other additional general capacities, such as processing speed and working memory may have a similar contribution to the underlying link between domains and should be similarly examined.

In addition to a longitudinal study with typically-developing children to encompass these additional basic skills and to establish if the seven-year old difference found in this study is a sample effect, a microgenetic study may help to address the correlational nature of these findings. In this study, one group of typically-developing children could receive training designed to target the types of tasks which constitute the Visual Processing element of the KABC-II, e.g. constructing designs from pieces to match a diagram, perhaps electronically to reduce manual manipulation. Another group should receive training in fine motor skills. The effect of training in one domain on functioning in the other could then be examined. Given the findings from the patient sample, a final group could be given training designed to improve sustained attention to investigate the effect on both cognitive and motor skills. Attention training is an area that is increasingly under investigation, with the development of a children's version of the Attention Process Training material (Sohlberg & Mateem 1987), Pay Attention! recently developed (Thomson, Kerns, Steidenstrang,

Sohlberg, & Mateer 2001). Previous studies have suggested that Pay Attention! and other cognitive remediation programmes targeting attention skills are effective in cases of childhood cancers (Butler, 1998; Butler & Copeland, 2002; Hardy, Willard & Bonner, 2010; Penkman, 2004). In light of the findings in Chapter 6, future studies may specifically target the use of the Pay Attention! materials in children who have suffered a cerebellar tumour to investigate whether training and improvement in attention skills produces corresponding increments in other areas of functioning.

One example where training in one skill appears to positively affect other domains is that of the Interactive Metronome® (IM; Cassily, 1996), which involves the trainee listening to a beat and tapping either hand or foot in time whilst receiving computerised feedback. It has been suggested that in addition to improving timing and rhythm, this training enables the trainee to become focused for longer periods of time, ostensibly therefore increasing the capacity for sustained attention. Results have indicated that considerable improvements have been found in several domains, for example learning and attentional problems and academic achievement, in a variety of populations (e.g. Kuhlman & Schweinhart, 1999). One study involving boys with ADHD reported that those who undertook the training demonstrated significantly higher improvements in attention, motor control, language processing, reading and the ability to regulate aggression than those in the control condition (Shaffer et al., 2001). One application of this training may be to measure its effectiveness in children who have suffered a cerebellar tumour, as the timing and error detection aspect of the training would seem to be related to proposed cerebellar functioning. Given the results from the typically-developing children, it is possible to suggest that the gains seen by Shaffer et al. are due to improvements in fine motor skill and timing capacity which in turn influence cognitive and academic skills. The microgenetic study described above examining training on domains separately

may be an effective way to unpick the cause of the improvements noted following the IM training.

Conducting an fMRI study in which to compare the tumour patients with typically-developing children on cognitive measures may aid investigation into the extent of plasticity that is seen in this population following treatment. This may further distinguish between the maturational and constructivist approaches to brain injury laid out in the introduction. A maturational viewpoint would suggest that the same anatomical locations would be implicated in the same skills in both typically-developing and patient samples, whereas a more constructivist approach may say that through plasticity different areas may be producing the same functional picture. The functional similarities demonstrated by commensurate associations between the different domains in the tumour and typically-developing groups suggests that the end-state of the tumour patients may be similar to those with typical development. Functional imaging would enable a more direct comparison between the two groups by comparing the anatomical regions thought to subserve different skills. In addition, an imaging approach may help to clarify the nature of diaschisis following treatment and may highlight whether damage to other brain regions may be responsible for the deficits found.

8.7 Conclusion

In conclusion, this study has demonstrated that children who have suffered a cerebellar tumour in the preschool years may demonstrate considerable intra- and inter-individual variation in their profile of functioning. The correlation between cognitive and motor skills found in the tumour patients suggested that there is some evidence for Schmahmann's proposal of the 'universal cerebellar transform' (Schmahmann, 2000b), as it highlighted that different domains appeared to be similarly affected. The progression of the study suggested that the severity of deficit in cognitive, academic and motor skills was related to the

level of sustained attention capacity. In addition these studies highlighted that whilst, similarly to previous findings, those children with aggressive tumours treated with radiotherapy and chemotherapy were generally more severely impaired, some patients treated for astrocytomas demonstrated a level of impairment. These findings should inform more accurate prognoses and emphasise the importance of individualised, tailored rehabilitation programmes for all children who have suffered a cerebellar tumour.

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Appendix 1

Individual summaries of scores on each standardised measure for each patient

For KABC-II and BOT-2, Time 1 scores only included

Patient 01

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	97	BOT-2	Fine Manual Control	32	TEA-Ch	Sky Search correct	8
	Visual Processing	71		Manual Coordination	29*		Sky Search time	7
	Long Term Storage	75		Body Coordination	26*		Sky Search attention	10
	Fluid Reasoning	96		Strength & Agility	27*		Map Mission	1*
	Crystallised Ability	72		Total Motor Composite	26*		Score	2*
	Fluid Crystallised Index	76	Conners 3 Parent Scales	Inattention	90*		Score DT	4*
WISC-IV/WPPSI-III	Verbal Comprehension	61*		Hyperactivity/ Impulsivity	90*		Code Transmission	4*
	Perceptual Reasoning	94		Learning Problems	90*		Sky Search DT	5
	Working Memory	74		Executive Functioning	85*		Walk, Don't Walk	1*
	Processing Speed	65*		Aggression	77*		Creature Counting correct	10
	Full Scale IQ	68*		Peer Relations	90*		Creature Counting time	7
WIAT-II	Reading	44*		ADHD Inattention	90*		Opposite Worlds same	4*
	Mathematics	66*		ADHD Hyperactivity	90*		Opposite Worlds opposite	7
	Written Language	46*		Conduct Disorder	90*			
	Oral Language	66*		Oppositional Defiant Disorder	78*			
	Total Composite	51*		ADHD Index (Probability %)	99			

Patient 02

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	97	BOT-2	Fine Manual Control	40	TEA-Ch	Sky Search correct	6
	Visual Processing	87		Manual Coordination	39		Sky Search time	4*
	Long Term Storage	92		Body Coordination	34		Sky Search attention	4*
	Fluid Reasoning	93		Strength & Agility	45		Map Mission	5
	Crystallised Ability	100		Total Motor Composite	37		Score	6
	Fluid Crystallised Index	91	Conners 3 Parent Scales	Inattention	75*		Score DT	7
WISC-IV/WPPSI-III	Verbal Comprehension	77		Hyperactivity/ Impulsivity	62*		Code Transmission	8
	Perceptual Reasoning	84		Learning Problems	66*		Sky Search DT	7
	Working Memory	107		Executive Functioning	80*		Walk, Don't Walk	4*
	Processing Speed	94		Aggression	90*		Creature Counting correct	10
	Full Scale IQ	86		Peer Relations	90		Creature Counting time	5
WIAT-II	Reading	101		ADHD Inattention	85*		Opposite Worlds same	7
	Mathematics	84		ADHD Hyperactivity	59		Opposite Worlds opposite	5
	Written Language	86		Conduct Disorder	73*			
	Oral Language	82		Oppositional Defiant Disorder	90*			
	Total Composite	87		ADHD Index (Probability %)	97			

Patient 03

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	83	BOT-2	Fine Manual Control	30*	TEA-Ch	Sky Search correct	9
	Visual Processing	71		Manual Coordination	28*		Sky Search time	3*
	Long Term Storage	75		Body Coordination	26*		Sky Search attention	5
	Fluid Reasoning	62*		Strength & Agility	39		Map Mission	1*
	Crystallised Ability	75		Total Motor Composite	29*		Score	9
	Fluid Crystallised Index	65*	Conners 3 Parent Scales	Inattention	89*		Score DT	4*
WISC-IV/WPPSI-III	Verbal Comprehension	53*		Hyperactivity/ Impulsivity	90*		Code Transmission	1*
	Perceptual Reasoning	55*		Learning Problems	87*		Sky Search DT	2*
	Working Memory	59*		Executive Functioning	56		Walk, Don't Walk	1*
	Processing Speed	56*		Aggression	55		Creature Counting correct	10
	Full Scale IQ	46*		Peer Relations	75*		Creature Counting time	1*
WIAT-II	Reading	53*		ADHD Inattention	70*		Opposite Worlds same	3*
	Mathematics	43*		ADHD Hyperactivity	90*		Opposite Worlds opposite	2*
	Written Language	61*		Conduct Disorder	55			
	Oral Language	69*		Oppositional Defiant Disorder	61*			
	Total Composite	54*		ADHD Index (Probability %)	99			

Patient 04

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	77	BOT-2	Fine Manual Control	46	TEA-Ch	Sky Search correct	13
	Visual Processing	80		Manual Coordination	35		Sky Search time	8
	Long Term Storage	78		Body Coordination	30*		Sky Search attention	9
	Fluid Reasoning	85		Strength & Agility	38		Map Mission	9
	Crystallised Ability	90		Total Motor Composite	35		Score	7
	Fluid Crystallised Index	78	Conners 3 Parent Scales	Inattention	52		Score DT	5
WISC-IV/WPPSI-III	Verbal Comprehension	67*		Hyperactivity/ Impulsivity	42		Code Transmission	-
	Perceptual Reasoning	96		Learning Problems	79*		Sky Search DT	4*
	Working Memory	65*		Executive Functioning	53		Walk, Don't Walk	5
	Processing Speed	70*		Aggression	46		Creature Counting correct	8
	Full Scale IQ	70*		Peer Relations	42		Creature Counting time	1*
WIAT-II	Reading	67*		ADHD Inattention	45		Opposite Worlds same	4*
	Mathematics	46*		ADHD Hyperactivity	42		Opposite Worlds opposite	4*
	Written Language	41*		Conduct Disorder	44			
	Oral Language	86		Oppositional Defiant Disorder	47			
	Total Composite	59*		ADHD Index (Probability %)	11			

Patient 05

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	106	BOT-2	Fine Manual Control	39	TEA-Ch	Sky Search correct	11
	Visual Processing	84		Manual Coordination	32		Sky Search time	5
	Long Term Storage	92		Body Coordination	34		Sky Search attention	6
	Fluid Reasoning	96		Strength & Agility	44		Map Mission	7
	Crystallised Ability	111		Total Motor Composite	33		Score	15
	Fluid Crystallised Index	96	Conners 3 Parent Scales	Inattention	55		Score DT	12
WISC-IV/WPPSI-III	Verbal Comprehension	102		Hyperactivity/ Impulsivity	40		Code Transmission	5
	Perceptual Reasoning	92		Learning Problems	47		Sky Search DT	5
	Working Memory	102		Executive Functioning	48		Walk, Don't Walk	8
	Processing Speed	85		Aggression	41		Creature Counting correct	10
	Full Scale IQ	95		Peer Relations	54		Creature Counting time	7
WIAT-II	Reading	96		ADHD Inattention	50		Opposite Worlds same	6
	Mathematics	94		ADHD Hyperactivity	40		Opposite Worlds opposite	1*
	Written Language	103		Conduct Disorder	43			
	Oral Language	93		Oppositional Defiant Disorder	41			
	Total Composite	96		ADHD Index (Probability %)	41			

Patient 06

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	100	BOT-2	Fine Manual Control	34	TEA-Ch	Sky Search correct	2*
	Visual Processing	64*		Manual Coordination	26*		Sky Search time	1*
	Long Term Storage	89		Body Coordination	32		Sky Search attention	0*
	Fluid Reasoning	62*		Strength & Agility	31		Map Mission	4*
	Crystallised Ability	69*		Total Motor Composite	27*		Score	3*
	Fluid Crystallised Index	70*	Conners 3 Parent Scales	Inattention	52		Score DT	5
WISC-IV/WPPSI-III	Verbal Comprehension	69*		Hyperactivity/ Impulsivity	44		Code Transmission	0*
	Perceptual Reasoning	67*		Learning Problems	65*		Sky Search DT	4*
	Working Memory	59*		Executive Functioning	53		Walk, Don't Walk	0*
	Processing Speed	56*		Aggression	47		Creature Counting correct	0*
	Full Scale IQ	56*		Peer Relations	58		Creature Counting time	0*
WIAT-II	Reading	63*		ADHD Inattention	50		Opposite Worlds same	1*
	Mathematics	40*		ADHD Hyperactivity	44		Opposite Worlds opposite	1*
	Written Language	50*		Conduct Disorder	56			
	Oral Language	68*		Oppositional Defiant Disorder	51			
	Total Composite	53*		ADHD Index (Probability %)	11			

Patient 07

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	97	BOT-2	Fine Manual Control	35	TEA-Ch	Sky Search correct	-
	Visual Processing	61*		Manual Coordination	34		Sky Search time	-
	Long Term Storage	86		Body Coordination	40		Sky Search attention	-
	Fluid Reasoning	-		Strength & Agility	44		Map Mission	-
	Crystallised Ability	90		Total Motor Composite	34		Score	-
	Fluid Crystallised Index	79	Conners 3 Parent Scales	Inattention	-		Score DT	-
WISC-IV/WPPSI-III	Verbal Comprehension	90		Hyperactivity/ Impulsivity	-		Code Transmission	-
	Perceptual Reasoning	93		Learning Problems	-		Sky Search DT	-
	Working Memory	-		Executive Functioning	-		Walk, Don't Walk	-
	Processing Speed	75		Aggression	-		Creature Counting correct	-
	Full Scale IQ	82		Peer Relations	-		Creature Counting time	-
WIAT-II	Reading	-		ADHD Inattention	-		Opposite Worlds same	-
	Mathematics	78		ADHD Hyperactivity	-		Opposite Worlds opposite	-
	Written Language	-		Conduct Disorder	-			
	Oral Language	82		Oppositional Defiant Disorder	-			
	Total Composite	-		ADHD Index (Probability %)	-			

Patient 08

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	74	BOT-2	Fine Manual Control	45	TEA-Ch	Sky Search correct	-
	Visual Processing	89		Manual Coordination	38		Sky Search time	-
	Long Term Storage	75		Body Coordination	49		Sky Search attention	-
	Fluid Reasoning	64*		Strength & Agility	45		Map Mission	-
	Crystallised Ability	80		Total Motor Composite	41		Score	-
	Fluid Crystallised Index	73	Conners 3 Parent Scales	Inattention	-		Score DT	-
WISC-IV/WPPSI-III	Verbal Comprehension	-		Hyperactivity/ Impulsivity	-		Code Transmission	-
	Perceptual Reasoning	-		Learning Problems	-		Sky Search DT	-
	Working Memory	-		Executive Functioning	-		Walk, Don't Walk	-
	Processing Speed	-		Aggression	-		Creature Counting correct	-
	Full Scale IQ	-		Peer Relations	-		Creature Counting time	-
WIAT-II	Reading	-		ADHD Inattention	-		Opposite Worlds same	-
	Mathematics	-		ADHD Hyperactivity	-		Opposite Worlds opposite	-
	Written Language	-		Conduct Disorder	-			
	Oral Language	-		Oppositional Defiant Disorder	-			
	Total Composite	-		ADHD Index (Probability %)	-			

Patient 09

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	88	BOT-2	Fine Manual Control	52	TEA-Ch	Sky Search correct	-
	Visual Processing	88		Manual Coordination	39		Sky Search time	-
	Long Term Storage	89		Body Coordination	41		Sky Search attention	-
	Fluid Reasoning	-		Strength & Agility	48		Map Mission	-
	Crystallised Ability	93		Total Motor Composite	42		Score	-
	Fluid Crystallised Index	87	Conners 3 Parent Scales	Inattention	-		Score DT	-
WISC-IV/WPPSI-III	Verbal Comprehension	-		Hyperactivity/ Impulsivity	-		Code Transmission	-
	Perceptual Reasoning	-		Learning Problems	-		Sky Search DT	-
	Working Memory	-		Executive Functioning	-		Walk, Don't Walk	-
	Processing Speed	-		Aggression	-		Creature Counting correct	-
	Full Scale IQ	-		Peer Relations	-		Creature Counting time	-
WIAT-II	Reading	-		ADHD Inattention	-		Opposite Worlds same	-
	Mathematics	92		ADHD Hyperactivity	-		Opposite Worlds opposite	-
	Written Language	-		Conduct Disorder	-			
	Oral Language	91		Oppositional Defiant Disorder	-			
	Total Composite	-		ADHD Index (Probability %)	-			

Patient 10

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	68*	BOT-2	Fine Manual Control	23*	TEA-Ch	Sky Search correct	5
	Visual Processing	50*		Manual Coordination	20*		Sky Search time	5
	Long Term Storage	92		Body Coordination	20*		Sky Search attention	8
	Fluid Reasoning	57*		Strength & Agility	20*		Map Mission	1*
	Crystallised Ability	92		Total Motor Composite	20*		Score	4*
	Fluid Crystallised Index	65*	Conners 3 Parent Scales	Inattention	54		Score DT	6
WISC-IV/WPPSI-III	Verbal Comprehension	61*		Hyperactivity/ Impulsivity	52		Code Transmission	1*
	Perceptual Reasoning	61*		Learning Problems	67*		Sky Search DT	1*
	Working Memory	62*		Executive Functioning	45		Walk, Don't Walk	1*
	Processing Speed	65*		Aggression	48		Creature Counting correct	6
	Full Scale IQ	54*		Peer Relations	55		Creature Counting time	/
WIAT-II	Reading	47*		ADHD Inattention	53		Opposite Worlds same	1*
	Mathematics	48*		ADHD Hyperactivity	48		Opposite Worlds opposite	1*
	Written Language	40*		Conduct Disorder	45			
	Oral Language	60*		Oppositional Defiant Disorder	59			
	Total Composite	45*		ADHD Index (Probability %)	29			

Patient 11

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	91	BOT-2	Fine Manual Control	34	TEA-Ch	Sky Search correct	9
	Visual Processing	64*		Manual Coordination	33		Sky Search time	3*
	Long Term Storage	75		Body Coordination	31		Sky Search attention	3*
	Fluid Reasoning	67*		Strength & Agility	38		Map Mission	1*
	Crystallised Ability	80		Total Motor Composite	32		Score	9
	Fluid Crystallised Index	68*	Conners 3 Parent Scales	Inattention	90*		Score DT	7
WISC-IV/WPPSI-III	Verbal Comprehension	63*		Hyperactivity/ Impulsivity	90*		Code Transmission	1*
	Perceptual Reasoning	63*		Learning Problems	92*		Sky Search DT	1*
	Working Memory	56*		Executive Functioning	85*		Walk, Don't Walk	2*
	Processing Speed	78		Aggression	90*		Creature Counting correct	8
	Full Scale IQ	57*		Peer Relations	90*		Creature Counting time	3*
WIAT-II	Reading	57*		ADHD Inattention	90*		Opposite Worlds same	4*
	Mathematics	57*		ADHD Hyperactivity	90*		Opposite Worlds opposite	3*
	Written Language	48*		Conduct Disorder	90*			
	Oral Language	72		Oppositional Defiant Disorder	90*			
	Total Composite	56*		ADHD Index (Probability %)	99			

Patient 12

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	83	BOT-2	Fine Manual Control	39	TEA-Ch	Sky Search correct	-
	Visual Processing	91		Manual Coordination	36		Sky Search time	-
	Long Term Storage	89		Body Coordination	45		Sky Search attention	-
	Fluid Reasoning	105		Strength & Agility	53		Map Mission	-
	Crystallised Ability	102		Total Motor Composite	39		Score	-
	Fluid Crystallised Index	92	Conners 3 Parent Scales	Inattention	-		Score DT	-
WISC-IV/WPPSI-III	Verbal Comprehension	-		Hyperactivity/ Impulsivity	-		Code Transmission	-
	Perceptual Reasoning	-		Learning Problems	-		Sky Search DT	-
	Working Memory	-		Executive Functioning	-		Walk, Don't Walk	-
	Processing Speed	-		Aggression	-		Creature Counting correct	-
	Full Scale IQ	-		Peer Relations	-		Creature Counting time	-
WIAT-II	Reading	-		ADHD Inattention	-		Opposite Worlds same	-
	Mathematics	-		ADHD Hyperactivity	-		Opposite Worlds opposite	-
	Written Language	-		Conduct Disorder	-			
	Oral Language	-		Oppositional Defiant Disorder	-			
	Total Composite	-		ADHD Index (Probability %)	-			

Patient 13

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	91	BOT-2	Fine Manual Control	38	TEA-Ch	Sky Search correct	7
	Visual Processing	80		Manual Coordination	20*		Sky Search time	6
	Long Term Storage	75		Body Coordination	32		Sky Search attention	5
	Fluid Reasoning	-		Strength & Agility	37		Map Mission	8
	Crystallised Ability	74		Total Motor Composite	28*		Score	6
	Fluid Crystallised Index	75	Conners 3 Parent Scales	Inattention	76*		Score DT	6
WISC-IV/WPPSI-III	Verbal Comprehension	59*		Hyperactivity/ Impulsivity	90*		Code Transmission	4*
	Perceptual Reasoning	79		Learning Problems	90*		Sky Search DT	5
	Working Memory	52*		Executive Functioning	70*		Walk, Don't Walk	1*
	Processing Speed	88		Aggression	60		Creature Counting correct	7
	Full Scale IQ	92*		Peer Relations	49		Creature Counting time	0*
WIAT-II	Reading	74		ADHD Inattention	76*		Opposite Worlds same	7
	Mathematics	71		ADHD Hyperactivity	90*		Opposite Worlds opposite	5
	Written Language	79		Conduct Disorder	55			
	Oral Language	73		Oppositional Defiant Disorder	60*			
	Total Composite	71		ADHD Index (Probability %)	99			

Patient 14

Standardised Test		Score	Standardised Test		Score	Standardised Test		Score
KABC-II	Short-Term Memory	97	BOT-2	Fine Manual Control	40	TEA-Ch	Sky Search correct	13
	Visual Processing	111		Manual Coordination	38		Sky Search time	9
	Long Term Storage	97		Body Coordination	36		Sky Search attention	10
	Fluid Reasoning	108		Strength & Agility	40		Map Mission	6
	Crystallised Ability	102		Total Motor Composite	36		Score	6
	Fluid Crystallised Index	104	Conners 3 Parent Scales	Inattention	-		Score DT	9
WISC-IV/WPPSI-III	Verbal Comprehension	98		Hyperactivity/ Impulsivity	-		Code Transmission	11
	Perceptual Reasoning	98		Learning Problems	-		Sky Search DT	10
	Working Memory	107		Executive Functioning	-		Walk, Don't Walk	8
	Processing Speed	68*		Aggression	-		Creature Counting correct	14
	Full Scale IQ	91		Peer Relations	-		Creature Counting time	8
WIAT-II	Reading	102		ADHD Inattention	-		Opposite Worlds same	10
	Mathematics	94		ADHD Hyperactivity	-		Opposite Worlds opposite	10
	Written Language	104		Conduct Disorder	-			
	Oral Language	114		Oppositional Defiant Disorder	-			
	Total Composite	103		ADHD Index (Probability %)	-			

Patient 15

	Standardised Test	Score		Standardised Test	Score		Standardised Test	Score
KABC-II	Short-Term Memory	74	BOT-2	Fine Manual Control	30*	TEA-Ch	Sky Search correct	-
	Visual Processing	64*		Manual Coordination	23*		Sky Search time	-
	Long Term Storage	58*		Body Coordination	35		Sky Search attention	-
	Fluid Reasoning	67*		Strength & Agility	25*		Map Mission	-
	Crystallised Ability	77		Total Motor Composite	28*		Score	-
	Fluid Crystallised Index	60*	Conners 3 Parent Scales	Inattention	-		Score DT	-
WISC-IV/WPPSI-III	Verbal Comprehension	-		Hyperactivity/ Impulsivity	-		Code Transmission	-
	Perceptual Reasoning	-		Learning Problems	-		Sky Search DT	-
	Working Memory	-		Executive Functioning	-		Walk, Don't Walk	-
	Processing Speed	-		Aggression	-		Creature Counting correct	-
	Full Scale IQ	-		Peer Relations	-		Creature Counting time	-
WIAT-II	Reading	-		ADHD Inattention	-		Opposite Worlds same	-
	Mathematics	-		ADHD Hyperactivity	-		Opposite Worlds opposite	-
	Written Language	-		Conduct Disorder	-			
	Oral Language	-		Oppositional Defiant Disorder	-			
	Total Composite	-		ADHD Index (Probability %)	-			

Appendix 2

Ethics letters of approval