Motor and cognitive function in children with neurodevelopmental versus acquired pathology of the cerebellum

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ABSTRACT

This thesis examines the motor and cognitive difficulties that result when the cerebellum is compromised through neurodevelopmental or acquired damage. There is much disagreement over the role that the cerebellum might play in a range of motor, cognitive and socioemotional functions. To address this issue, tests of motor and cognitive function were carried out on two patient populations, one with focal acquired cerebellar excisions (Posterior Fossa Tumours - PFT) and one with relatively subtle neurodevelopmental cerebellar abnormalities (Asperger's Syndrome - AS). The results showed that patients with PFT performed more poorly than controls on almost all tests of motor function, and had particular difficulty with cognitive tests of executive function and reading comprehension. Individuals with AS performed more poorly than controls on a number of tests of motor function, and had difficulties with verbal and spatial working memory, some aspects of attention and with face matching.

MR imaging techniques (conventional clinical imaging and voxel-based morphometry) were used to identify the location and extent of pathology in the patients with PFT and to investigate subtle changes in the density of grey and white matter for both patient groups. Patients with PFT showed a decrease in grey matter near the fourth ventricle. In addition, patients with midline damage showed a decrease in grey matter in the cerebellum; and patients with right hemisphere damage showed a decrease in grey matter in the cerebellum, thalamus, hypothalamus and globus pallidus and a decrease in white matter in frontal, parietal and occipital regions. The patients with AS showed an increase in grey matter in the cerebellum, superior and middle temporal gyri, temporal pole, occipital lobe and in regions close to the amygdala and hippocampus. Finally, the results of diffusion tensor imaging methods showed no abnormalities in the integrity of white matter tracts in either of the patient groups.

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To Dad

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CHAPTER 1: INTRODUCTION

This thesis reports on the motor and cognitive difficulties, and the changes that occur in the brain when the cerebellum is compromised through neurodevelopmental or acquired pathology. The cerebellum has long been known to play an integral role in motor function, but there has recently been increased interest in the additional roles that the cerebellum may play in cognitive function. By investigating syndromes that are associated with cerebellar abnormality, it should be possible to examine both the functions of the cerebellum as well as the more general effects of pathology in the cerebellum on other regions of the brain.

Two patient groups are studied in this thesis. One group has undergone surgery to remove posterior fossa tumours (PFT) located in the cerebellum, and the other group has Asperger's Syndrome (AS), a form of high-functioning autism. In both patient groups there is evidence of cerebellar damage. However, there are a number of important differences between the groups: the patients with PFT have acquired pathology whereas the patients with AS have neurodevelopmental pathology; the patients with PFT have obvious cerebellar abnormalities whereas the patients with AS appear to have more subtle cerebellar abnormalities; and the patients with PFT have pathology that is apparently limited to the cerebellum, whereas in the patients with AS, evidence suggests that the abnormalities in the cerebellum are only part of a more widespread pattern of brain abnormalities. Because there are so many differences between the two patients groups, they are not directly compared with one another, instead, each group is considered separately in relation to its own normal controls. By investigating motor and cognitive function in these patient groups with different types of cerebellar abnormality, it should be possible to uncover some of the functions for which an intact cerebellum is necessary. Neuropsychological investigations and magnetic resonance imaging (MRI) methods are employed in order to gain an understanding of the level of cognitive and motor function in these two patient populations as well as the precise nature and extent of cerebellar and wider brain abnormalities.

This introductory chapter provides an overview of the concepts that underlie the studies carried out in this thesis. The chapter begins with a description of the processes that occur

during normal and abnormal brain development. The structure and anatomical connections of the cerebellum are then detailed, followed by consideration of previous work that has been carried out on the functions of the cerebellum, with particular focus on functional imaging studies and studies of patients with cerebellar damage. Having identified some of the limitations of previous work, the aims and hypotheses of the current study are explained and the methods outlined.

1.1 How the brain develops

The brain is a complex web of highly organized interconnected neural systems spread across a number of different structures and regions. While there is much individual variation in brain organization, there are powerful constraints on the outcomes of development that cause at least some sensory functions (such as vision, audition and olfaction) to always be localized in the same brain regions (Elman et al. 1996).

The roots of the complex organization of the brain are laid down long before birth, so that when infants first encounter the external environment, they already have substrates in place that enable them to carry out basic motor actions, to adapt to their internal physiological requirements appropriately and to selectively orient to environmental stimuli. Studies have shown that newborn babies are actually able to recognize their mother as a person and to imitate facial expressions despite having no previous experience of vision (Meltzoff and Moore, 1977; Bushnell, Sai and Mullin, 1989). This indicates that there may be a neural substrate in place that enables the newborn to identify with and relate to other human beings. Such initial predispositions are on the whole extremely basic and lacking in complexity, which is not surprising given that they exist in the absence of any experience of the external world and thus without any actual experience of learning (Trevarthen et al. 1998). Furthermore, the brain areas now known to be particularly involved in higher-order cognitive and sensorimotor functions (for example the prefrontal cortex) carry out much of their development ex-utero. This means that these regions are only partly formed at birth (Rakic, 1991) and so are not sufficiently developed to be able to function effectively at this point.

1.1.2 Historical perspective on the development of mind and brain

In this section, four prominent theories of changes that occur in the mind and the brain during learning and development are briefly outlined in order to provide a theoretical framework for the studies carried out in this thesis.

A) Piaget's theory (Jean Piaget, 1896-1980)

Piaget's work focused on normal patterns of development of the human mind. He concentrated on cognitive development in particular, and proposed that there are a number of distinct stages of intellectual growth through which all children pass:

(i) **Sensorimotor stage** (birth to 18 months): During the first stage, the basic reflexes present at birth become coherent behavioural patterns (referred to as schemas). This stage ends when the concept of object permanence is grasped.

(ii) **Preoperational stage** (18 months to seven years): This stage involves some early symbolic representational thought, but the child mainly concentrates on physical features of the environment.

(iii) **Concrete operations** (seven to eleven years): In this stage, thought tends to be egocentric and the child relies on concrete reasoning.

(iv) **Formal operations** (eleven years plus): This is the last of Piaget's four stages and is characterized by the emergence of logical reasoning and an adult pattern of thought.

Piaget believed that children are only able to attain these stages of cognitive function by taking an active part in their own development, absorbing external factors and events into their developing schema, and adapting their own behaviour to fit in with the external environment. There is some support for the existence of these stages (e.g. Dasen, 1978; Azzone, 2003). However, in order to understand where the developing brain may fit into this unfolding of the human mind, it is necessary to consider the work of Luria.

B) Luria's theory (Alexander Romanovich Luria, 1902-1977)

Luria was the first to relate the brain and cognition during development. He proposed that there are three units of functional brain systems that show a stage-like development over childhood, essentially mirroring Piaget's stages of intellectual development.

(i) **The "arousal unit":** The arousal unit develops soon after birth, is subserved by the reticular formation and modulates the level of cortical arousal.

(ii) **The "sensory-input unit":** During the next few months, the "sensory-input unit" develops. This unit acquires, processes and stores incoming sensory information in the lateral cortex of the temporal, parietal and occipital lobes.

(iii) **The "organization and planning unit":** From the age of four, the "organization and planning unit" starts to appear. This unit continues to develop right up to adolescence, is subserved by the frontal lobe, and is argued to be involved in more complex behaviours such as programming, checking and controlling behaviours.

Luria proposed that in the adult brain, once these units had all become active, they then worked together in a cooperative manner in order to facilitate high-level cognitive and sensorimotor behaviours.

Luria's theory has provided a useful framework of a hierarchical development of brain function where initial localization of function in the brain during childhood turns into wide-spread activity throughout the whole brain in adults in order to support the most complex levels of thought and action. However, a limitation of Luria's theory is that it does not detail how the brain actually carries out these various activities. In order to understand the dynamic processes that occur during the development of the brain and thought, it is necessary to consider the work of Hebb.

C) Hebb's theory (Donald Olding Hebb, 1904-1985)

Hebb's theory provides a neural account of the internal physiological processes that are involved in learning and development. He believed that learning involves repeated synaptic transfer of information between neurons which results in a permanent facilitation of information transfer along a particular pathway. Hebb argued that interconnected neurons are arranged into large functional groups that he called cell assemblies:

(i) **Cell assemblies**: Cell assemblies are groups of synchronously firing cells that form reverberating circuits. Hebb argued that repetitive and synchronous firing of these cell assemblies can result in structural changes in the brain as the facilitation of information transfer mentioned above requires growth changes in

the pre- and/or post-synaptic cells in order that information transfer can become more automatic. It is important to note that cells involved in cell assemblies are not necessarily situated in the same area of the brain, but can be distributed over multiple cortical regions and even over multiple different brain structures.

(ii) **Phase sequences**: When there is simultaneous activity in multiple cell assemblies, this is called a phase sequence. Hebb considered phase sequences to be the thought process, and argued that associated cell assemblies form after repeated sensory events and that the nature of the thought depends on which particular cell assemblies are involved.

Hebb's theory provides a physiologically-based explanation of the neural mechanisms involved in normal learning, but it does not discuss abnormal development. The final theory to be considered here is that of Lashley, which provides an account of changes that may occur in the brain when development has to occur in the face of pathology.

D) Lashley's theory (Karl Spencer Lashley, 1890-1958)

Lashley was one of the first investigators to search for the specific location of mental faculties within the brain, which he referred to as the engram. He carried out lesions studies on rats where he removed between 10 and 50% of the cerebral cortex and then assessed learning ability using mazes. The results of these investigations led to two important concepts:

(i) **Mass action:** Lashley found that rats showed a gradual loss in the ability to learn as more and more of the cortex was removed. This led him to argue that the amount of brain removed is critical to the level of learning that can be carried out.

(ii) **Equipotentiality**: Lashley found that no area of the cortex was more important than another area and therefore argued that all areas of the cortex play an equal role in learning and are equipotential.

Summary of historical theories of the development of brain and mind

These theories of development are included in order to provide a theoretical framework for the investigations that will be carried out in this thesis. The work of Piaget, Luria and Hebb provide accounts of how normal development and learning occur. Piaget carried out

behavioural observations that led him to argue that the development of cognition is anchored in sensorimotor changes and that all children go through a number of stages of intellectual development. Luria proposed functional brain systems that show a similar stage-like pattern of development, and Hebb provided a physiological explanation for the neural networks that become established during learning and development, both in individual cells, and in groups of functionally related cell assemblies. For abnormal development, Lashley posited the concepts of mass action and equipotentiality which maintain that there is an association between the amount of pathology and behavioural dysfunction, and that all cortical areas are equally able to carry out learning.

On the basis of these theories, as well as some more recent research, an outline of the processes likely to be involved in both normal and abnormal development will now be provided in order to explain the nature of the developmental abnormalities that are likely to be present in individuals who have suffered from brain damage during development.

1.1.3 Normal Development

In normal development, an explosion of novel experience and associated learning commences as soon as an infant is born. Development begins in a relatively linear fashion with basic functions (such as attention and memory) developing in parallel. Once these basic abilities are in place, development starts to take a more modular pathway, whereby complex functions (including language and visual perception) begin to develop (Vargha-Khadem et al. 1994). This modular development relies on the integration of a number of basic functions (Elman et al. 1996) and can therefore not commence until these basic functions are in place (in line with Hebb, more complex functions require the activation of increased numbers of cell assemblies, and development of these functions cannot progress until all of the cell assemblies for the basic functions have been formed). Taking language as an example, this higher-level ability depends on fine motor control of the muscles of the mouth, on good auditory discrimination abilities so that children can hear differences between sounds that they have to imitate, on attention and on memory, so that they can build up a vocabulary and an understanding of grammatical rules. In healthy children, the most complex modular function (executive function) is not fully developed until after the hormonal changes during adolescence (about age 15-17). Although these executive

abilities start to develop at around age 11-12, when children acquire deductive reasoning and lateral thinking (the beginning of Piaget's stage of formal operations), these abilities are not complete until at least four or five years later when children possess the organizational skills needed to bring different functions together.

1.1.4 Abnormal development: When something goes wrong

Having outlined how normal development progresses, it is important to consider what happens when something goes wrong. The development of interconnected networks of neuronal pathways in the brain implies that different brain structures become recruited for multiple networks or pathways, and pathology in one area will therefore have an impact on other brain structures and systems as well. In the presence of brain pathology of developmental origin, two competitive processes are thought to occur: modularization versus compensation:

(i) **Modularisation:** This process is the normal drive to gradually establish specialized, and non-redundant cognitive functions from a variety of lower level skills that gradually develop from birth. If brain pathology occurs early in life, then this is likely to impact not only on the lower level skills supported by the damaged region, but also on the functions of other brain areas with which the damaged region interacts. In line with Hebb's theory, the more complex modular functions depend on the synchronous firing of cells in multiple cell assemblies, and if any of the cell assemblies involved are not fully developed or are abnormally developed, then the phase sequence will not be able to function normally.

(ii) **Compensation:** Brain pathology always incurs a cost and a compromise of function. At the same time, however, early brain pathology unleashes powerful mechanisms of compensation that aim to rescue functions and promote recovery and/or reorganization of compromised abilities. Compensation can occur via recovery, or via reorganization of function, or a mixture of both, depending on the site and extent of brain damage. Compensation via recovery of function is thought to occur when brain damage is less extensive, and when there is recoverable tissue (i.e. the penumbra) beyond the primary site of pathology capable of subserving lost or

compromised functions. An example of such recovery is seen in cases of early stroke where despite an initial interference with speech and language functions during the acute stage, these functions recover and continue to develop within the limits imposed by intellectual capacity (Vargha-Khadem et al., 2000). Compensation via reorganization of function, on the other hand, is though to occur when there is extensive damage such that brain tissue distant from the primary site of pathology needs to be recruited to subserve the skills and functions that have been lost. An example of compensation via reorganization of function comes from cases of hemispherectomized patients in whom basic speech and language functions have been rescued despite the removal of the left hemisphere (Vargha-Khadem and Mishkin, 1997; Vargha-Khadem et al., 1997). The concept of compensatory mechanisms via reorganization is in line with Lashley's theory of equipotentiality, which maintains that different brain regions are equally able to subserve skills and abilities, and it therefore follows that after pathology, different regions of the brain should be able to take over the functions of the damaged area.

The consequences of pathology of the brain that occurs early in life before the basic skills, abilities, and functions have developed fully are likely to differ from those seen after damage sustained later in life, after the cognitive modules and their functions have developed normally (Vargha-Khadem et al. 1994). Once modularization has occurred and specialized functions have developed, the areas subserving these functions are no longer as dependent on other brain regions supporting the basic functions on which these specialized abilities were built. This means that late pathology of the brain tends to result in more selective deficits than early pathology. When pathology of the brain occurs after cognitive systems have developed, then the resultant impairments will be determined by the extent and site of pathology. In contrast, when pathology of the brain occurs before cognitive systems have developed, then the resultant impairments will be widespread, affecting both basic functions and the more specialized abilities which develop through modularization and depend on the interplay of a number of different brain structures.

1.2 Introduction to the cerebellum

The cerebellum (literally "small brain") is a delicately convoluted, intricately organized part of the brain that has a uniform structure throughout its entirety. However, despite there being a comprehensive understanding of cerebellar anatomy and of its projections to other parts of the brain, the actual functions of the cerebellum are still a relative mystery. The fact that the cerebellum has strong connections with the motor cortex suggests that it is involved in the coordination and planning of motor actions. The cerebellum has been particularly implicated in skilled, learned movements that become more accurate and automatic with practice, which is in line with clinical observations that, after cerebellar injury, there are often permanent difficulties with skilled movements such as piano playing, despite compensatory mechanisms that enable many other motor functions to be carried out.

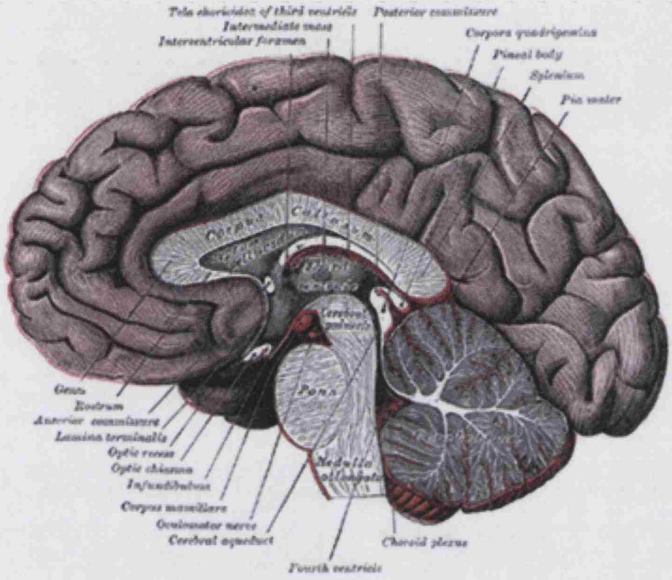
It is important to note that the connections between the cerebellum and the cerebral cortex are almost entirely crossed. The right cerebellar hemisphere is connected to the left motor cortex and the left cerebellar hemisphere is connected to the right motor cortex. This means that whereas the cerebral cortex controls movement of the contralateral side of the body, the fact that there are crossed connections between the cerebellum and the cerebral cortex means that the cerebellum has an influence on motor function of the ipsilateral side of the body. Thus, cerebellar symptoms on the right side of the body are likely to be due to damage to the right side of the cerebellum, and cerebellar symptoms on the left side of the body are likely to be due to damage to the left side of the cerebellum. The crossed cerebellar-cortical connections are considered further in Section 1.3.1.2 below.

In addition to being involved in motor function, the cerebellum has been implicated in a variety of cognitive and emotional behaviours as well (e.g. Leiner et al. 1993; Schmahmann and Sherman, 1998). The various postulated functions of the cerebellum are considered through both functional imaging studies and studies of patients with different types of cerebellar damage in Section 1.4 below. However before this, in the following section, the anatomy of the cerebellum and its connections to other areas of the brain will be described.

1.3 Anatomy of the cerebellum

The cerebellum is situated in the hindbrain, overlying the pons and medulla and is separated from the overlying cerebral cortex by the tentorium cerebelli, an extension of the dura mater. Figure 1.1 shows the position of the cerebellum within the brain.

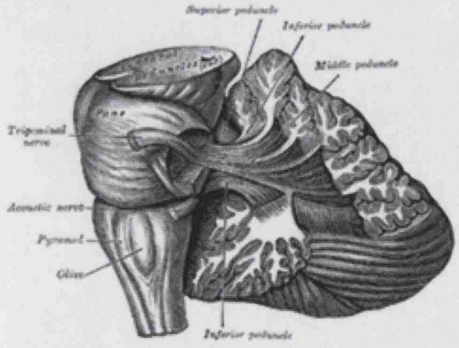
Figure 1.1: The human brain (Fig. 720 from Gray's Anatomy of the Human Body 1918)



The cerebellum is connected to the brain stem and the rest of the nervous system by three clusters of nerve fibres (see Figure 1.2 below) which carry information to and from the brain stem:

(i) **The inferior cerebellar peduncle (the restiform body):** The inferior cerebellar peduncle contains fibers from the spinal cord, the inferior olive and the vestibular nuclei, and also outgoing projections from the cerebellum back to the vestibular nuclei. These fibres principally carry proprioceptive information about widespread areas throughout the body.

Figure 1.2: Position of the cerebellar peduncles (Fig. 705 from Gray's Anatomy of the Human Body 1918)



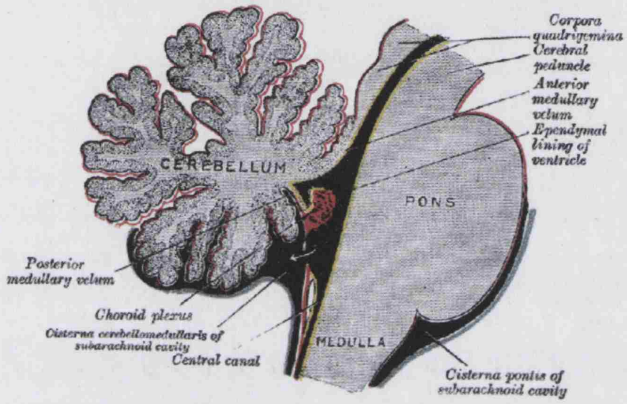
(ii) **The middle cerebellar peduncle (the brachium pontis):** The middle cerebellar peduncle contains fibers from the contralateral and ipsilateral pontine nuclei (Rosina and Provini, 1984), which carry information from diffuse cortical regions including the motor cortex.

(iii) **The superior cerebellar peduncle (the brachium conjunctivum):** The superior cerebellar peduncle principally contains fibers carrying information away from the cerebellum. These

projections pass to the red nucleus and some go on to the thalamus and spinal cord. In addition, there are some incoming fibers in the superior cerebellar peduncle which come from the spinal cord via the spinocerebellar tract and carry proprioceptive information about the body.

A detailed diagram of the position of the cerebellum is shown in Figure 1.3.

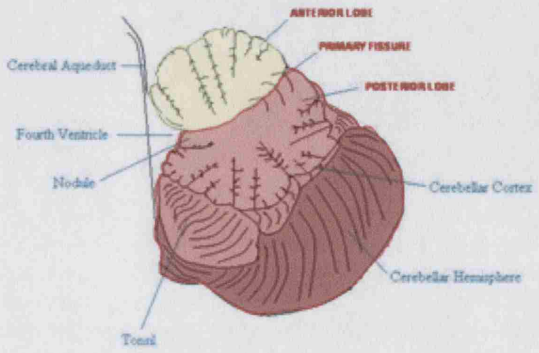
Figure 1.3: Position of the cerebellum (Fig. 708 from Gray's Anatomy of the Human Body 1918)



The crude structure of the cerebellum is very similar to that of the brain as a whole: it has a folded outer layer (cortex) composed of neurons and supporting cells (grey matter) and an internal core of white matter, and it is made up of two distinct hemispheres. Between the two cerebellar hemispheres lies the vermis (Latin for worm) which is the midline structure of the cerebellum. The hemispheres and vermis are separated from one another by the shallow paramedian sulci. The cerebellum has most frequently been subdivided in one of two ways, either into anterior and posterior portions or into medial and lateral portions.

The division of the cerebellum into anterior and posterior lobes results from observations of the prominent primary fissure that splits the cerebellum into two distinct halves (see Figure 1.4). This division is, however, not based on functional differences and for this reason it serves for descriptive purposes only. The medial/lateral distinctions in contrast, are functional distinctions, and stem from Jansen and Brodal's study (1940) of the cerebellar cortico-nuclear projection. On the basis of functional

Figure 1.4: The anterior and posterior lobes of the cerebellum and the primary fissure which separates them
(adapted from the website http://137.222.110.150/calnet/Cereb/image/cerebellum-sagittal%20sec.jpg)



variation, the cerebellum can be divided into three longitudinal zones: the lateral zone, the intermediate zone and the vermis (Kuhlenbeck, 1975; Carpenter, 1976) (see Figure 1.5).

Figure 1.5: The cerebellum (adapted from Mackenna and Callander, 1990 and Kandel et al., 2000)

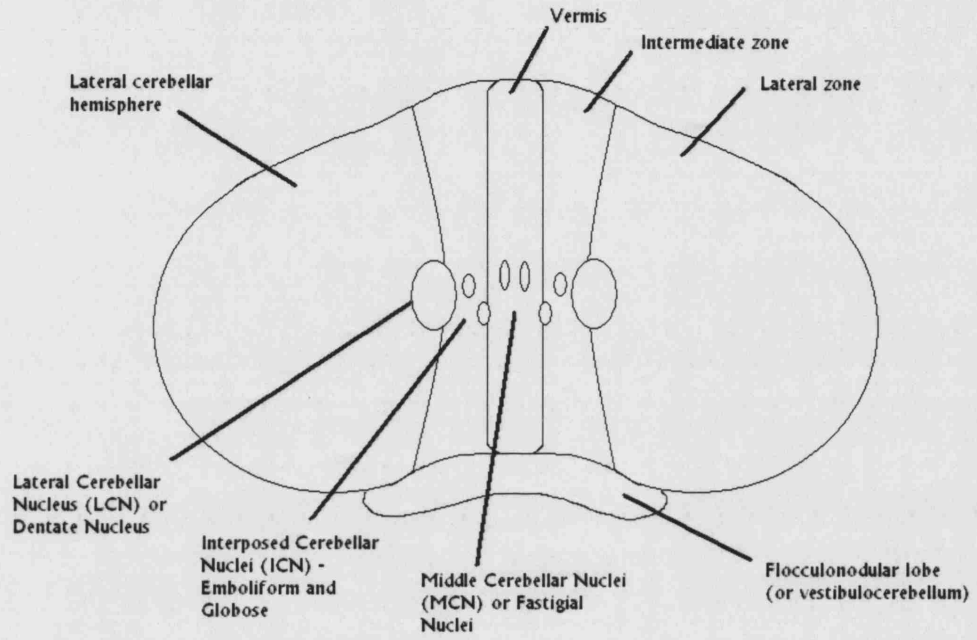
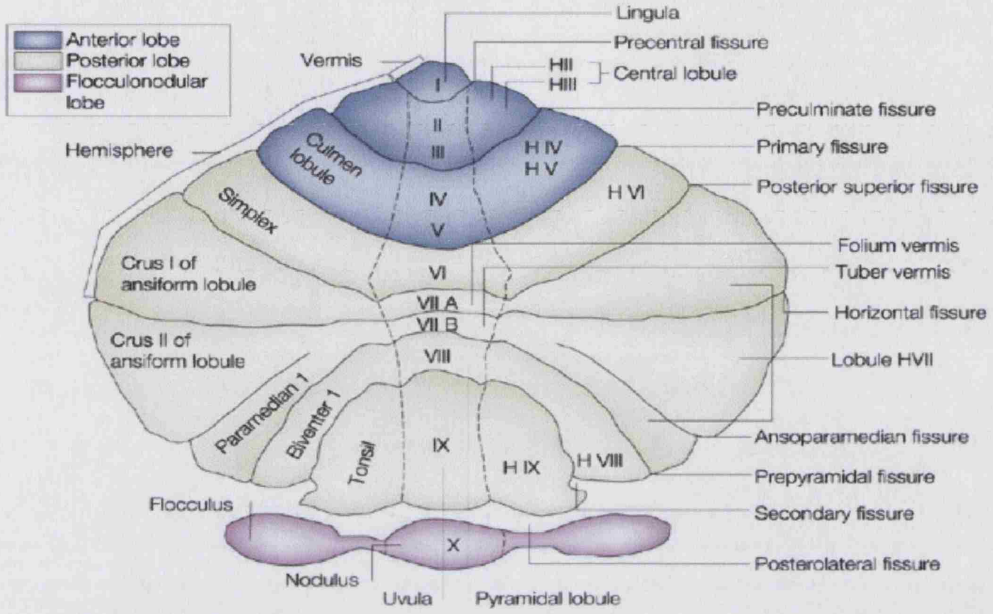


Figure 1.5 also shows that within the white matter of the cerebellar hemispheres lie the major output structures of the cerebellum, four pairs of cerebellar nuclei: the fastigial nuclei, the interposed nuclei (emboliform and globose) and the dentate (or lateral) nuclei. These nuclei and their projections are considered in some detail in Section 1.3.1.

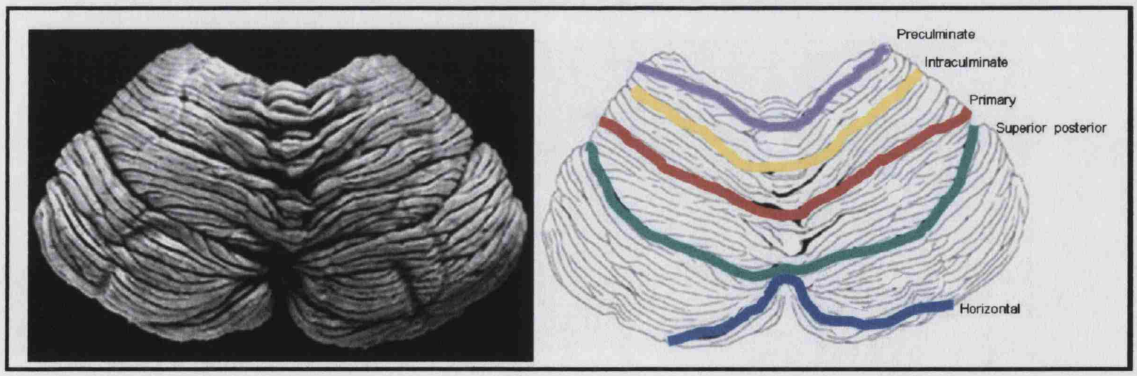
One further important division of the cerebellum is into ten parallel lobules on the basis of the principal fissures present in the cerebellar cortex. There has been much disagreement in the past over which fissures are the most important and thus over exactly where the distinctions between the different lobules should lie. The divisions most widely used today and those that will be used in this thesis (shown in Figure 1.6) are based on the work of Larsell (1947), Jansen and Brodal (1958) and Angevine et al. (1961).

Figure 1.6: Flattened map of the cerebellar cortex showing the lobules and fissures (from Manni and Petrosini, 2004)



In order to gain an understanding of the organization of these fissures in the cerebellum, Figure 1.7 below shows the position of the preculminate, intraculminate, primary, superior posterior and horizontal fissures in a postmortem cerebellum viewed from a posterior position.

Figure 1.7: Position of cerebellar fissures in posterior view of postmortem cerebellum (adapted from the http://www.vh.org/adult/provider/anatomy/BrainAnatomy/Ch3Text/Section01.html website)



Having considered the gross anatomy of the cerebellum, attention will now focus on the structures within the cerebellum and the way in which these are connected to and interact with one another and the rest of the brain.

1.3.1 Cerebellar circuitry

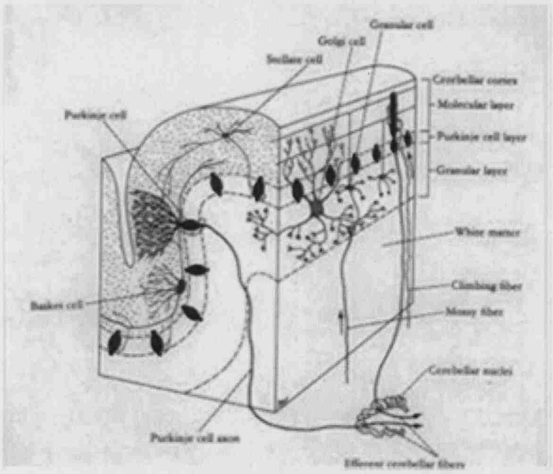
1.3.1.1 Circuitry within the cerebellum

Incoming information to the cerebellum is received by the cerebellar cortex and then passed down to the cerebellar nuclei, which are responsible for the output from the cerebellum. Circuitry within the cerebellum is thus primarily in the form of downward projections from the cortex to the nuclei.

(i) The cerebellar cortex

The cerebellar cortex is folded into numerous tightly packed, almost parallel, fissures of varying depths. In contrast to the cerebral cortex, there is very little regional variation in the microscopic form or structure of the cerebellar cortex (Voogd and Glickstein, 1998). Throughout its entirety, it can be divided into three individual layers: the molecular layer, the Purkinje cell layer and the Golgi granular cell layer. Each of these layers contains varying numbers of five different types of neurons: the inhibitory stellate, basket, Purkinje and Golgi neurons, and the excitatory granule cells (see Figure 1.8).

Figure 1.8: Cross-section of the cerebellar cortex (from the website http://www.hallym.ac.kr/~de1610/nana/8-4.jpg).



The molecular layer: This is the outermost layer of the cerebellar cortex and is made up of the cell bodies of basket and stellate cells, as well as granule cell axons and dendrites of Purkinje neurons.

The Purkinje cell layer: This layer lies directly below the molecular layer and is made up of Purkinje cell bodies. Purkinje cells convey all the output of the cerebellar cortex, sending their axons deep into the white matter where they project to the cerebellar nuclei. This inhibitory cerebellar cortical output is mediated by γ-aminobutyric acid (GABA).

The granular layer: This layer lies beneath the Purkinje cell layer and forms the innermost layer of the cerebellar cortex. It is made up of an extensive number of granule cells, a much smaller number of Golgi cells, as well as the terminals of mossy fibres.

The Golgi, basket and external stellate cells form complex connections within the cerebellar cortex; they are interneurons and are not primarily involved in the transfer of information into or out of the cerebellum.

Figure 1.9: Stained section of the cerebellar cortex (from the website http://www.deltagen.com/target/histologyatlas/atlas_files/nervous/cerebellar_cortex_10x.htm)

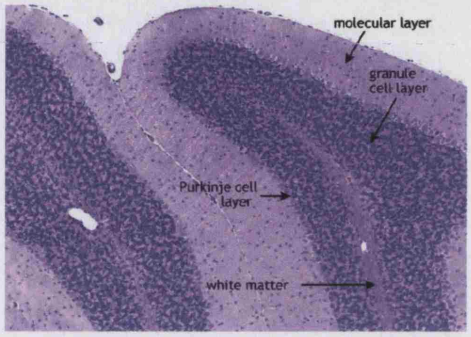


Figure 1.9 shows a stained section of the cerebellar cortex illustrating the positions of the molecular layer, the granule cell layer, the Purkinje cell layer and the white matter.

(ii) The cerebellar nuclei

The different cerebellar nuclei were first distinguished by Stilling in 1864. These nuclei are located deep within the white matter of the cerebellum and are responsible for all of the output of the cerebellum. An overview of the cerebellar nuclei is provided here. Detailed descriptions of the projections of these structures can be found in Section 1.3.1.2, later in this chapter.

a) The fastigial nuclei:

The fastigial nuclei are situated in the vermis. The vermis runs along the midline of the cerebellum and receives inputs from the spinal cord via the spinocerebellar tract; input from the vestibular system via the vestibulocerebellar tract; and visual and auditory information from the tectum by way of the pons. Outgoing signals originate in the Purkinje neurons in the vermis, which send projections to the fastigial nuclei. Fastigial nuclei project to the brain stem reticular formation (which then project to the spinal cord via the reticulospinal tract), and to the lateral vestibular nuclei (which project to the spinal cord via the vestibulospinal tract). The fastigial nuclei also send axons that cross to the contralateral side and project to the primary motor cortex via the ventrolateral nucleus of the thalamus.

b) The interposed nuclei:

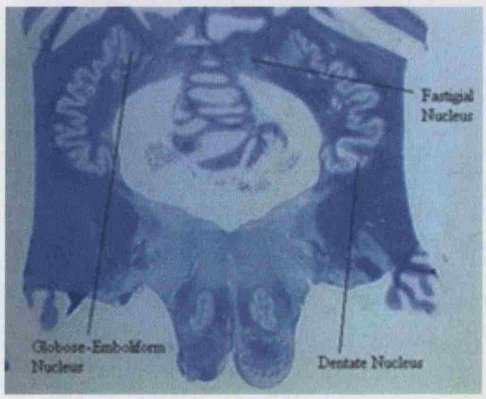
The interposed nuclei include both the emboliform and the globose nuclei. They are situated in the intermediate zone of the cerebellar hemispheres that is adjacent to the vermis. The intermediate zone receives inputs from the spinal cord via the spinocerebellar tract. Outgoing projections pass to the red nucleus, which then projects to the spinal cord (rubrospinal tract); and via the ventrolateral nucleus of the thalamus, to the primary motor cortex, which also projects to the spinal cord (lateral corticospinal tract). Collectively, the corticospinal and rubrospinal tracts are called the lateral descending systems.

c) The dentate nuclei:

The dentate nuclei can be further divided into two parts: the microgyric dentate (dorsomedial and rostral region) and the macrogyric dentate (ventrolateral and caudal region) (Gans, 1924). This division is based on the shape of the convolutions of the nucleus (wider in the ventrolateral and caudal dentate), the size of the cells (generally smaller in the ventrolateral and caudal dentate) and their projections to the thalamus. The dentate nuclei are situated in the lateral zone (cerebrocerebellum) of the cerebellar hemispheres. The lateral zone receives inputs from the cerebral cortex via the corticopontocerebellar tract that passes through the middle cerebellar peduncle. Outgoing projections go to the premotor, motor and prefrontal cortical areas via the ventrolateral nucleus of the thalamus.

Figure 1.10 shows the position of the cerebellar nuclei in a transverse section at the level of the junction between the pons and medulla.

Figure 1.10: The position of the cerebellar Nuclei (from the website http://137.222.110.150/calnet/Cereb/page2.htm)



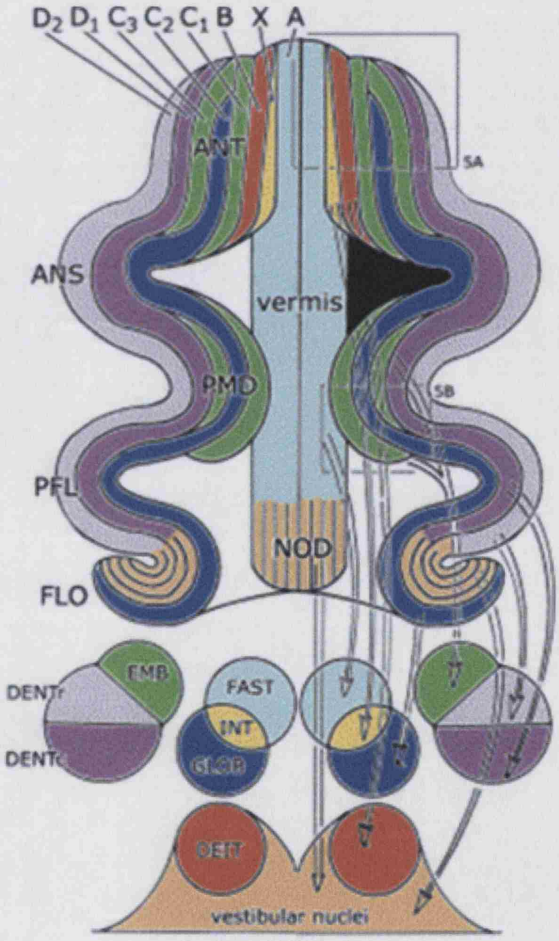
In addition to these cerebellar nuclei, there is one further area of the cerebellum that sends outgoing projections. This is a small portion of the cerebellar cortex called the flocculonodular lobe (or vestibulocerebellum) situated at the base of the cerebellum. The flocculonodular lobe is closely connected to the vestibular system from where it receives projections and to which is sends outputs.

(iii) Cerebellar cortico-nuclear projections

Communication between the cerebellar cortex and the nuclei depends upon the Purkinje cells as these provide the only output of the cerebellar cortex.

Purkinje cells are neatly arranged into a series of parallel zones according to the particular cerebellar or vestibular nucleus to which they project. Altogether, eight parallel zones have been identified (A, X, B, C1, C2, C3, D1, D2) and these tend to be continuous across lobules (see Figure 1.11).

Figure 1.11: Diagram showing the eight parallel zones in the cerebellum
(taken from Voogd 2003)



a) Vermal zones:

The anterior vermis is split into three parallel zones, A, X and B. Zone A projects to the rostral fastigial nucleus, zone X projects to the interstitial cell groups and Zone B projects to Deiters' nucleus (the lateral vestibular nucleus). Zones X and B are not present beyond the lobulus simplex.

b) Intermediate zones:

The intermediate region is split into three parallel zones, C1, C2 and C3. C1 and C3 (which are present in the lobulus simplex, the ansiform lobule and the paramedian lobule but not the paraflocculus), project to the emboliform nucleus (also known as the anterior interpositus nucleus). C2 (which is present throughout the cerebellum) projects to the globose nucleus (also known as the posterior interpositus nucleus).

c) Lateral zones:

The remaining hemisphere makes up the lateral region, which is divided into zones D1 and D2. D1 projects to the caudolateral and rostromedial dentate nucleus whereas D2 projects only to the rostromedial dentate nucleus.

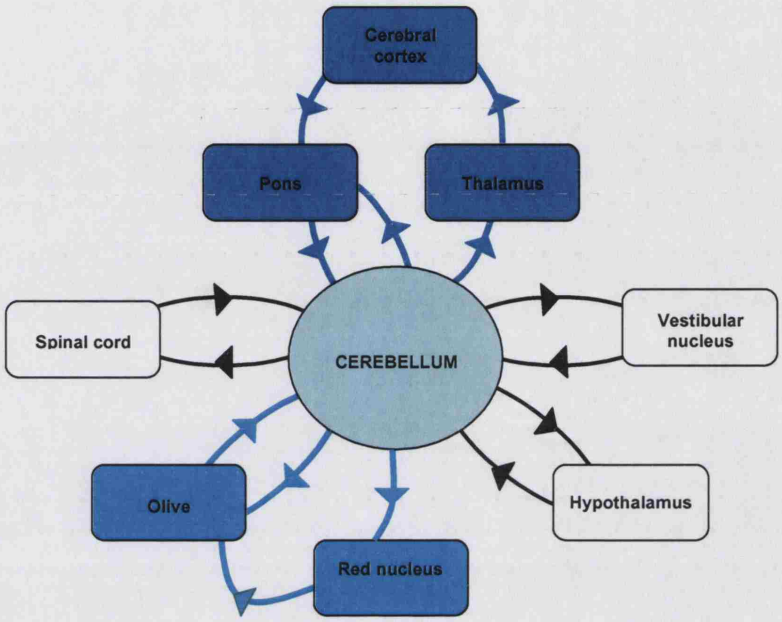
In addition to these parallel pathways, there is also an inhibitory GABA-mediated nucleo-olivary projection connecting the cerebellar nuclei with the contralateral inferior olive, the subnuclei of which give rise to their respective climbing fibres (Kalil, 1979; Mugnaini and Oertel, 1985; Gibson et al., 1987; Ruigrok and Voogd, 1990).

There is only limited direct evidence in support of this zonal arrangement in the human cerebellum as the above-mentioned findings are based on axon-tracing studies carried out in rodents, carnivores and non-human primates. Nevertheless, preliminary developmental studies of human Purkinje cells have shown that even at the foetal stage there are borders between groups of Purkinje cells that are destined for particular cerebellar nuclei (Voogd, 2003), and it is therefore likely that this pattern exists in humans in a similar way to the non-human primates and other vertebrates on which previous research has focused.

1.3.1.2 Circuitry outside the cerebellum

The principal projections to and from the cerebellum are shown in Figure 1.12. There are two main functional circuits in which the cerebellum is involved. The first of these connects the cerebellum to the cerebral cortex by way of the pons (input to the cerebellum) and the thalamus (output from the cerebellum), and the second connects the cerebellum to the inferior olive, both directly and by way of the red nucleus. The characterization of the connections between the cerebellum and the cerebral cortex has been difficult because the connections are not direct, they pass by means of the pons and the thalamus and therefore involve multiple synapses (Ramnani and Miall, 2001). However, using tracers that can cross the synaptic cleft, Middleton and Strick (2001) have found that the cerebellum sends outputs to multiple regions of the dorsal prefrontal cortex (by means of the ventricular and medial dorsal nuclei of the thalamus) and that the regions of the dentate nucleus that project to the prefrontal cortex are spatially separate from the regions that project to the motor cortex.

Figure 1.12: The principal projections to and from the cerebellum (the main functional circuits are shown in shades of blue).



(i) Projections to the cerebellum

The principal projections to the cerebellum come from the cerebral cortex via the corticopontocerebellar tract and from the olivary nucleus in the form of excitatory climbing fibres. In addition, there are important projections to the cerebellum from the spinal cord via the spinocerebellar tract.

A The corticopontocerebellar tract:

There is much variation in the number of projections to the pons from different cortical areas, with some areas projecting heavily and some not at all. Nevertheless, the majority of the projections in the corticopontocerebellar tract arise from cortical regions that are known to be involved in the control of movement (particularly areas 4, 5, 6, 7 and 18 - Glickstein et al., 1985), and it is therefore likely that these tracts carry information related to motor function. There are also some projections from frontal areas rostral to the arcuate sulcus and a limited number of projections from the occipital lobe and the infero-temporal cortex. Examples of cortico-pontine projections include the following:

a) Sensory and motor projections

Projections from sensory and motor cortical regions project to the pons and then on to the cerebellum by means of the middle cerebellar peduncle (Brodal 1968a,b; 1971; 1982; 1987; Glickstein et al., 1971; Glickstein et al., 1972; Baker et al., 1976; Gibson et al., 1978; Mower et al., 1980; Robinson et al., 1984; Glickstein et al., 1985; Glickstein et al., 1994; Glickstein, 1998).

b) Extra-striate visual projections

Visual projections from the cerebral cortex to the pons do not originate in primary visual areas in the occipital lobe, but rather stem from extra-striate visual regions in the parietal lobe, where the cells are responsive to motion and known to be involved in the visual guidance of movement. In monkeys, these extra-striate cortico-pontine projections go to regions in the dorsolateral pons (Glickstein et al. 1985; Stein and Glickstein 1992; Glickstein et al. 1998). These visual projections go on to terminate in vermal lobules IX and VII and in the paraflocculus (Hoddevik, 1977; Burne et al. 1978; Robinson et al. 1984).

Thus, anatomical evidence suggests that the information that reaches the cerebellum by way of the corticopontocerebellar tract is principally concerned with motor control.

B Olivo-cerebellar climbing fibres

The olivo-cerebellar climbing fibre projection (the crossed projection from the inferior olive to the Purkinje cells) mirrors the parallel zones of the cortico-nuclear projection in the cerebellum that was described above (see Section 1.3.1.1). Furthermore, the olivocerebellar fibres send out collaterals to the target nucleus of the Purkinje cells to which they project (Ruigrok and Voogd, 2000) and also to the lateral vestibular nucleus (Deiter's nucleus). This structured arrangement is often referred to as modular where a module is made up of one or more Purkinje cell zones, the nucleus to which they project, and the climbing fibre input from the inferior olive. This high level of organisation means that each subnucleus of the inferior olive is able to monitor the output of a particular cerebellar module.

C The spinocerebellar tract:

The spinocerebellar tract is split into dorsal and ventral sections. The dorsospinocerebellar and the ventrospinocerebellar tracts convey different types of proprioceptive information mainly from the legs and lower body. The information from the dorsospinocerebellar tract is transferred to the cerebellum in the inferior cerebellar peduncle, and the information from the spinocerebellar tract is transferred to the cerebellum in the superior cerebellar peduncle.

In addition to these three principal tracts, the cerebellum also receives input from the cuneate nucleus, from the eyes and ears via the tectum, and from the inner ear via the vestibular nucleus.

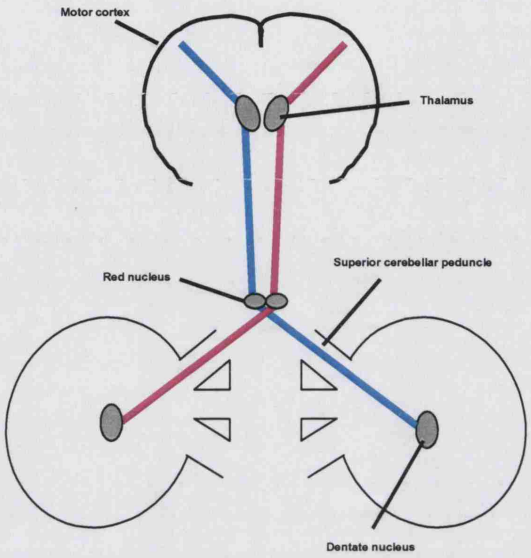
It is important to note that, except for the olivo-cerebellar projection that is made up of climbing fibres, all of the other cerebellar afferents terminate as mossy fibres. The majority of the mossy fibres enter the cerebellum through the middle and inferior cerebellar peduncles. Mossy fibres are excitatory and form synapses with granule cells.

(ii) Projections from the cerebellum

All of the outgoing projections from the cerebellum originate in the cerebellar nuclei. The cerebellar nuclei do not project directly onto motor neurons and their effects on movement are therefore always indirect.

The principal projection from the cerebellum is the dentorubrothalamic tract. This tract projects from the dentate nuclei through the superior cerebellar peduncle, decussates and then enters the red nucleus. From the red nucleus, this tract projects to the thalamus (particularly the ventrolateral nucleus of the thalamus) and thence on to the cerebral cortex. This crossed projection to the contralateral motor cortex (which is shown in Figure 1.13) explains how the cerebellar hemispheres influence motor function on the ipsilateral side of the body.

Figure 1.13: The dentorubrothalamic tract, illustrating the crossed projection from the cerebellum to the contralateral motor cortex



In addition to the dentorubrothalamic tract, there are a number of other projections from the cerebellar nuclei and these projections will now be discussed separately for each pair of nuclei.

a) Fastigial nucleus (MCN)

The principal projections of the fastigial nucleus pass via the inferior cerebellar peduncle to the contralateral pons, reticular formation and spinal cord. The fastigial nucleus also sends a small projection to the thalamus (ventrolateral nucleus and intralaminar nuclei) bilaterally and to the medial accessory olive (the fastigial nucleo-olivary projection is not as well developed as it is for the other cerebellar nuclei). There is a large bilateral projection to the vestibular nuclei and it is in these nuclei that descending pathways originate. Through these descending pathways the A zone (see Section 1.3.1.1) bilaterally influences neurons which innervate truncal, axial and proximal limb muscles (Gray et al. 2000). This is not the same for the B zone, however. The B zone does not project to the fastigial nucleus but instead projects directly to the lateral vestibular nucleus, and so has an ipsilateral influence on the neurons of the same system influenced by the A zone.

b) Emboliform nucleus (ICN):

The emboliform nucleus receives input from the C1 and C3 Purkinje cell zones and projects to the magnocellular red nucleus and to the ventrolateral nucleus of the thalamus. The

magnocellular red nucleus is the origin of the rubrospinal tract, a tract that crosses over in the mesencephalon and terminates on lateral spinal interneurons and motor neurons involved in the innervation of distal limb muscles. The ventrolateral nucleus of the thalamus, on the other hand, projects to the caudal motor cortex and tracts originating in this cortical area go on to terminate on the same lateral spinal interneurons and motor neurons on which the rubrospinal tract terminates.

Thus, through these rubrospinal and corticospinal tracts which share the same spinal terminations, the emboliform nucleus controls ipsilateral limbs. In addition to these projections to the red nucleus and thalamus, the emboliform nucleus also projects to pontine nuclei (the nucleus reticularis tegmenti pontis and the basal pontine nuclei) which give rise to mossy fibres.

c) Globose nucleus (ICN)

The globose nucleus has many projections in common with the fastigial nucleus. There are direct nucleo-olivary projections from the globose nucleus to the rostral medial accessory olive and indirect projections to this same area of the olive which pass via the Darkschewitsch nucleus. The projections to the thalamus from the globose nucleus overlap with those from the fastigial and emboliform nuclei. In addition, the globose nucleus projects to the central grey, the raphe nuclei, the spinal cord and the superior colliculus.

d) Dentate nucleus (LCN)

The dentate nucleus projects principally to ventrolateral thalamic regions by way of the dentorubrothalamic tract described above. These projections overlap with those from the other cerebellar nuclei, but projections from caudal and lateral regions of the dentate extend further into medial regions of the ventrolateral nucleus, regions that project to the premotor area of the frontal lobe. In addition, the dentate nucleus projects to the contralateral oculomotor nucleus and to the contralateral parvicellular red nucleus, thereby influencing the central tegmental tract.

Using McIntyre-B strain of herpes virus (which is transported in a retrograde direction transynaptically), Middleton and Strick (1994, 1997) showed that dorsal regions of the

dentate project to cortical area M1, mid-rostrocaudal regions of the dentate nucleus project to the premotor cortex, and the most caudal third of the dentate nucleus (which is correlated with saccadic eye movements – Van Kan et al. 1993) projects to the frontal eye fields. Projections from the dentate nucleus passing that pass through the thalamus originate in the most ventral part of the dentate, and project to the prefrontal cortex (areas 9 and 46).

Having described the anatomical make-up of the cerebellum, the functions in which the various cerebellar structures and regions have been implicated will now be discussed.

1.4 Functions of the cerebellum

Despite this comprehensive understanding of the structure of the cerebellum, relatively little is known about the role of this brain structure in behaviour and much controversy remains over the functions that it subserves.

The cerebellum was originally thought to be solely involved in motor control and has been implicated in movement planning, execution, timing, learning, co-ordination and fine tuning (see Brooks and Thach, 1981, for a review). Recently, however, evidence has been mounting in support of a role for the cerebellum in a variety of non-motor functions as well.

1.4.1 Models of cerebellar function

In this section, two prominent models of cerebellar function are provided in order to gain an understanding of the way in which the cerebellum may be able to carry out motor and cognitive functions: Stein and Glickstein's model and Schmahmann's model respectively.

(i) Stein and Glickstein's model of cerebellar motor function

Stein and Glickstein (1992) proposed that the principal role of the cerebellar cortex is to produce an internal representation of the body's sensory motor system which it can then use to predict an individual's own pattern of motor actions, to rehearse these and then to optimize them. This is in line with the work of Kawato and Gomi (1992) who argued that the cerebellum is capable of feedback error learning through separate internal representations in the flocculus, the vermis and regions of the cerebellar hemispheres. In addition, this theory has received support from Miall et al. (1993) who proposed that the

cerebellum forms two types of internal model. One provides a prediction of the sensory consequences of each movement (a Smith Predictor). The other models time delays in the control loop, enabling the comparison of a copy of the predicted model with actual sensory feedback from an executed movement. On the basis of this comparison, it is then possible to correct for errors in motor performance, and to improve the original predictive model. This idea that the cerebellum is able to optimize motor functions is derived from the known anatomical connections of the cerebellum. The projections to and from the cerebellum, as well as its regular anatomical structure, mean that the cerebellum is in a position to receive and process information about motor actions from a wide variety of different sources. Stein and Glickstein (1992) argue that the cerebellum is able to use this incoming information to optimize the future performance of a particular movement by appropriately enhancing or depressing Purkinje cell synapses.

(ii) Schmahmann's Dysmetria of Thought model of a cerebellar role in cognitive functions

In Schmahmann's Dysmetria of Thought Hypothesis (Schmahmann 1991), he maintains that in the same way that the cerebellum regulates the force, rhythm and accuracy of motor functions, it may also regulate the rate, consistency and appropriateness of cognitive functions. The cerebellum is thought to be an "oscillation dampener" which regulates behaviours around a baseline level. When the cerebellum is compromised in some way, this oscillation dampener no longer functions, behaviours cannot be smoothed, and they may therefore become inappropriate, inaccurate or unreliable. This hypothesis is in line with previous work which has suggested that the cerebellum is the principal modulator of neurological function (Snider, 1952), that the cerebellum is an emotional pacemaker for the brain (Heath, 1977) and that the cerebellum smoothes out the performance of mental functions (Leiner et al. 1986; Leiner and Leiner, 1997).

In the following section, the possible functions of the cerebellum will be considered. The discussion is subdivided on the basis of the different investigative methods that have been used to elucidate cerebellar function. The two approaches most commonly used to investigate the functions of the cerebellum in humans are functional imaging studies and studies of patients with damage to the cerebellum. The results of each of these methods are now considered, starting with functional imaging studies.

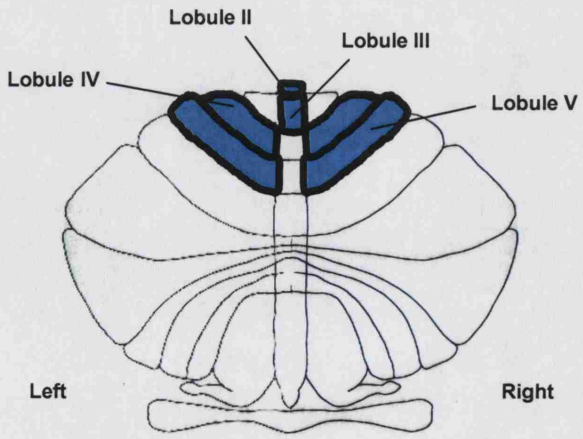
1.4.2 Functional imaging studies of the cerebellum

Functional imaging studies provide a means to carry out in vivo investigations of the brain structures involved in particular behavioural tasks by identifying those areas where there is a haemodynamic change during execution of these tasks. These studies are generally carried out on normal control participants and provide an important approach to investigating the normal functions of different regions of the cerebellum.

(i) Functional imaging studies of the cerebellum during motor function

The first functional imaging study to show focal activation in the cerebellum was a positron emission tomography (PET) study carried out by Fox et al. (1985). They showed that voluntary movement and tactile stimulation of the fingers produced bilateral activation in hemispheric lobule V. Since then, functional imaging studies have revealed activation in the anterior cerebellum during tasks involving finger-tapping (Kuhtz-Buschbeck et al. 2003; Rivkin et al. 2003), particularly in hemispheric lobules IV and V ipsilaterally (Sadato et al. 1996; Blinkenberg et al. 1996), in vermal lobules II and III during wrist and foot movements (Nitschke et al., 1996), and in lateral regions of the right hemisphere during reaching movements with the arm (Inoue et al., 1998). Functional imaging has also been used to show that there is somatotopic representation of hand, foot and tongue movements in the human cerebellum (Nitschke et al., 1996). The localisation of functional activation in the cerebellum during different motor tasks is shown in a flattened map of a single cerebellar hemisphere in Figure 1.14.

Figure 1.14: Regions of functional activation in the cerebellum during motor tasks



This flattened map clearly shows that the regions of the cerebellum that are active during tasks involving motor actions are principally located in the anterior lobe of the cerebellum.

(ii) Functional imaging studies of the cerebellum during cognitive functions

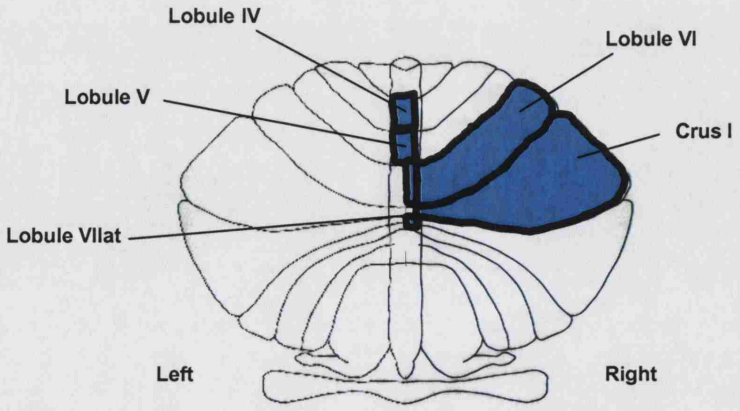
a) Speech and language:

The first functional imaging study to show cerebellar activation during a cognitive task was a verb generation paradigm carried out by Petersen et al., (1988, 1989). Petersen et al. found that the generation of the relevant verb from a noun was associated with activation of right vermal lobule IV and right hemispheric lobule VI. Subsequent functional imaging studies of speech and language have provided further support for a role for the cerebellum in these cognitive functions. The results of these studies are summarized in table 1.1 and the regions of activation can be seen in Figure 1.15.

Table 1.1: Cerebellar regions activated during speech and language tasks

Study	Paradigm	Cerebellar activation
Petersen et al. (1988, 1989; PET)	Verb generation	Right vermal lobule IV and right hemispheric lobule VI
Raichle et al. (1994; PET)	Verb generation	Right intermediate lobule VI
Martin et al. (1995; PET)	Verb generation	Right intermediate and lateral lobule VI
Price et al. (1996; PET)	Single word repetition	Right vermal lobules V and VIIat and left vermal lobule IV
Ackermann et al. (1998; fMRI)	Silent repetition of month names	Right intermediate and lateral lobule VI
Buckner et al. (1995; PET)	Word stem completion	Left paravermian lobule V and right vermal lobule VI
Desmond et al. (1998; PET)	Word stem completion	Right hemispheric lobules VI and Crus I
Mathiak et al. (2002; fMRI)	Speech perception	Right hemisphere lobule Crus I

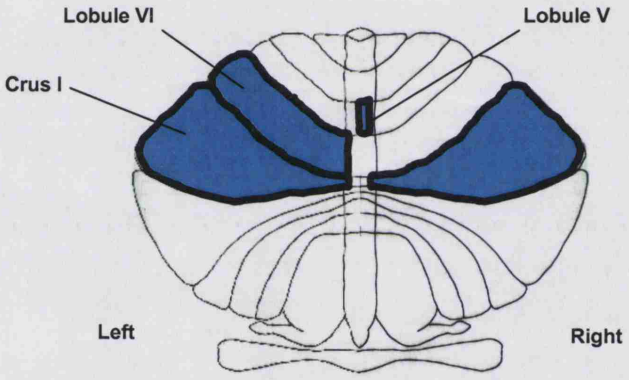
Figure 1.15: Regions of functional activation in the cerebellum during speech and language tasks



b) Attention:

Functional imaging studies have also found activation in the cerebellum during tasks designed to assess attentional abilities. Using shifting attention paradigms, Allen et al. (1997; fMRI) found activation in left hemispheric lobule VI, and Le et al. (1998; fMRI) found bilateral activation in Crus I (with increased activation on the right side). In addition, a study by Rees et al. (1997; PET) found that as they increased the attentional load, there was a proportional increase in activation in lateral regions of left hemispheric lobule VI and in right vermal lobule V. These regions of activation can be seen in Figure 1.16 below.

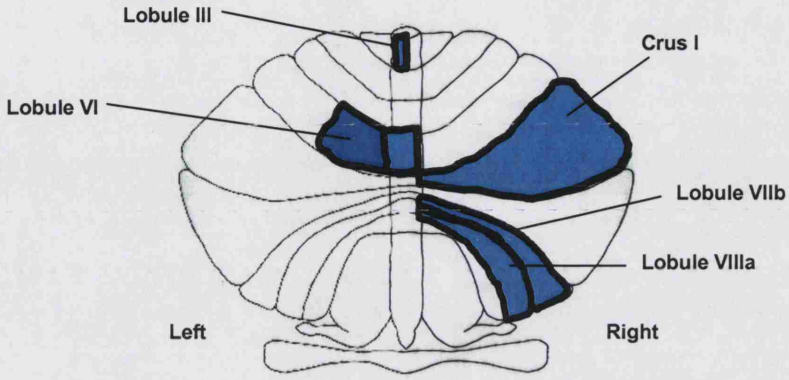
Figure 1.16: Regions of functional activation in the cerebellum during attention tasks



c) Memory:

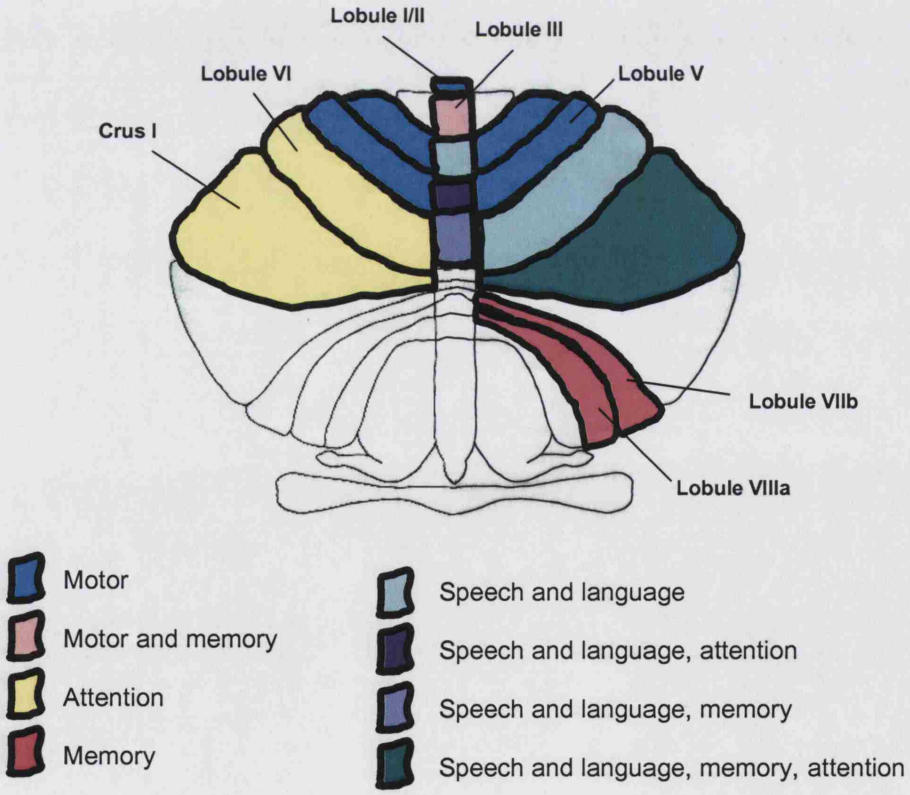
Functional imaging studies of working memory have also shown activation in the cerebellum. Fiez et al. (1996; PET) required participants to remember five verbal stimuli and found cerebellar activation in left vermal lobule III and left intermediate lobule VI. In a slightly more difficult task, Paulesu et al. (1993; PET; 1995; fMRI) required participants to compare verbal and nonverbal stimuli with previously presented stimuli and found cerebellar activation in vermal lobule VI. Desmond et al. (1997) carried out a study where they required participants to remember a number of visually presented letters (either one – low load, or six – high load) over a brief delay. They found cerebellar activation in lateral regions of right hemispheric lobules Crus I, VIIB and VIIIA. In addition, Mathiak et al. (2004) found activation in right hemispheric lobule Crus I during storage and comparison of temporal durations in a non-speech task. These regions of activation can be seen in Figure 1.17 below.

Figure 1.17: Regions of functional activation in the cerebellum during memory tasks



In Figure 1.18 below, all these findings are put together into a single diagram, in order to gain a picture of the pattern of functional localisation within the cerebellum that is emerging from functional imaging studies.

Figure 1.18: Regions of localisation of motor and cognitive function in the cerebellum from functional imaging studies



These findings are in line with the anatomical connections of the cerebellum. As outlined in Section 1.3.1.2, the dentate nucleus (which receives input from the cerebellar

hemispheres) sends projections to the dorsal prefrontal cortex (Middleton and Strick, 2001). The dorsal prefrontal cortex is known to be involved in working memory (Levy and Goldman-Rakic, 2000; Curtis and D'Esposito, 2003) and in attentional selection (one aspect of attention) (Frith et al., 1991; Rowe et al. 2000; Rowe and Passingham, 2001) and the findings that regions of the cerebellar hemispheres are active during tests of working memory and attention suggests that there may be functional circuits involving both the cerebellum and the dorsal prefrontal cortex which subserve these functions. It should be emphasized that both working memory and attention are complex cognitive abilities that can be broken down into a variety of different aspects. Working memory, for example, has phonological, auditory and visuo-spatial aspects, whereas attention has visual and auditory components as well as aspects related to general vigilance and arousal. Therefore it is possible that different areas of the cerebellum may be involved in different aspects of working memory or attention or may be involved to different degrees.

Summary of functional imaging studies

Functional imaging studies of normal control participants have provided evidence that the cerebellum is active during a variety of both motor and cognitive behaviours, indicating that the cerebellum is likely to play a role in these different behaviours. There is evidence for some localisation of function within the cerebellum, most notably, motor functions are principally associated with activation in the anterior lobe (lobules I-V) of the cerebellum. This is in line with early work that found that lesions of the anterior lobe are associated with ataxia, dysmetria and a lack of control of eye movements (Holmes, 1917). For the cognitive functions (speech and language, attention and memory), there is some overlap of functional distribution, with lobules VI and Crus I being involved in multiple functions. This suggests that lobules VI and Crus I may be particularly important for cognitive functions.

It is important to note that an advantage of functional imaging studies is that they provide a means by which to see how the normal brain functions, something that is not possible in the lesion studies that will be considered next. However, a significant limitation of functional imaging is that, although it shows which brain areas are involved in a particular function, it does not show what areas are necessary for that function. In order to discover which brain

areas are necessary for a particular task, studies of patients with damage to the cerebellum are more appropriate. These will now be considered.

1.4.3 Studies of patients with damage to the cerebellum

Cerebellar damage can result from trauma, infection, metabolic problems, the effects of toxins, and inherited cerebellar degenerations. Nevertheless, there are a number of clinical symptoms that are common to most patient groups with cerebellar dysfunction. The clinical features that are most commonly observed in patients with cerebellar syndromes are summarized in table 1.2 below:

Table 1.2: Clinical features of cerebellar syndromes

Hypotonia	Loss of muscle tone
Dysarthria	Inability to correctly articulate words due to problems with weakness or incoordination of speech muscles
Nystagmus	Difficulties stabilizing eye movements
Ataxia	Incoordination of movement
Dysdiadochokinesia	Inability to carry out rapid alternating movements
Intention tremor	A tremor which occurs when carrying out purposeful movements
Dysmetria	Inability to correctly terminate movements

These various clinical features manifest themselves most clearly in cerebellar patients in the form of problems with movement coordination and balance.

In the sections that follow, a number of patient populations with different types of cerebellar damage will be considered. These include cases of cerebellar agenesis and cerebellar hypoplasia (congenital cerebellar damage), patients with different types of acquired lesions of the cerebellum (both focal cerebellar lesions and more slowly developing posterior fossa tumours); and a number of disorders in which the cerebellum has been implicated, all of which have a neurogenetic basis (these include autism and Asperger's syndrome, dyslexia, schizophrenia, bipolar disorder and ADHD).

1.4.3.1 Congenital cerebellar damage

1.4.3.1.1 Cerebellar agenesis

A small number of cases of the rare condition of cerebellar agenesis have been reported in the literature. This is a congenital condition where the cerebellum fails to develop, and

consideration of such cases could facilitate investigation of the functions in which the cerebellum plays a critical role and an increased understanding of the level of plasticity of the brain.

However, cerebellar agenesis rarely occurs in the absence of other malformations and it is therefore difficult to associate behavioural problems with damage to the cerebellum per se. Nevertheless, Glickstein (1994) carried out a review of the literature on cerebellar agenesis and concluded that all patients with near-complete cerebellar agenesis (complete cerebellar agenesis probably does not occur – Boltshauser, 2004) showed considerable motor deficits. This has received support from Timmann et al. (2003) who found that a patient with cerebellar agenesis had ataxia of the upper and lower limbs and of stance and gait, and was unable to acquire conditioned eyeblink responses, indicating that they had an impairment in motor learning. In addition, Glickstein (1994) found that those individuals with cerebellar agenesis who survived beyond infancy also demonstrated dysarthria and cognitive difficulties. This finding is in line with Leestma and Torres's (2000) report of a 38 year-old with cerebellar agenesis who was unemployed and had mental retardation. It should be noted, however, that Sener and Jenkins (1993) reported on a 58 year-old woman with cerebellar agenesis who was apparently asymptomatic.

1.4.3.1.2 Cerebellar hypoplasia

In cases of cerebellar hypoplasia, the cerebellum has a reduced volume, but its shape is broadly normal (Boltshauser, 2004). Cerebellar hypoplasia is a highly heterogeneous condition which has been observed in numerous different cases including individuals who have been subject to prenatal infections, those with metabolic disorders or with chromosomal aberrations or with different types of congenital muscular dystrophies or with complex genetic malformations, or those with isolated cerebellar hypoplasias (Sarnat, 1992; Barth, 1993). Patients with cerebellar hypoplasia demonstrate a variety of motor deficits (including uncoordinated movement and lack of balance) which are particularly prominent in infancy, and also show language and cognitive impairments that become apparent as they grow older (Boltshauser, 2004).

Both cerebellar agenesis and cerebellar hypoplasia are often associated with white matter atrophy, and rarely occur in the absence of any other malformations. For this reason, it is difficult to determine the extent to which any behavioural abnormalities in these patient groups are due to the cerebellum damage rather than to other associated brain abnormalities.

1.4.3.2 Acquired pathology of the cerebellum

Acquired pathology of the cerebellum can be acute (for example as a result of focal head injury) or more slowly developing (for example tumours in the posterior fossa region). Both of these types of lesions can be localised to distinct cerebellar regions, and by looking at the specific behavioural problems of patients with lesions of particular cerebellar areas, it should be possible to gain some understanding of the dysfunction that results from damage to those specific areas, and, by implication, to examine functional localisation in the cerebellum. Furthermore, such studies could potentially shed some light on the level of compensation of function that occurs after damage to particular areas of the brain, especially during development. As was discussed in Section 1.1.4, there is an interplay between compensatory activities and the normal development of modules depending on the age at onset of pathology, and on the region of the brain that is damaged. Studies of behaviour and brain structure in patients who have had pathology of the cerebellum could increase the understanding of the nature of these compensatory mechanisms, and the degree to which they interact with and even over-write normal developmental processes. The effects of time of onset of pathology of the cerebellum on motor and cognitive functions are considered in some detail in chapters 3 and 4 respectively.

In this section, studies of patients with different acquired lesions of the cerebellum will first be discussed, concluding with studies of patients with tumours of the cerebellum. The studies of patients with tumours of the cerebellum are considered in more detail in Chapter 3 (studies of motor functions) and Chapter 4 (studies of cognitive functions).

1.4.3.1.4 Lesions of the cerebellum

(i) Case studies of patients with cerebellar lesions

a) Speech and language

Silveri et al. (1994) reported on a patient with right cerebellar damage who developed a right hemicerebellar syndrome as well as agrammatic speech in the absence of other cognitive impairments. This observation led Silveri et al. (1994) to suggest that "the cerebellum provides the temporal interplay among the neural structures underlying the processes responsible for production of sentences." In 1998, Silveri et al. reported on another individual with cerebellar damage. This patient had a neoplastic cerebellar lesion and had surgery to remove the right hemisphere of the cerebellum. Subsequently the patient performed at normal levels in neuropsychological tests except for a reduction in verbal digit span and a tendency to quickly forget verbal information. These observations led Silveri et al. (1998) to argue that the cerebellum is involved in planning the production of speech "at a level that does not require an overt articulation". Support for a role for the cerebellum in speech also comes from Ackermann et al. (1997) who argue that, as well as acting as an internal clock, the cerebellum is involved in the perception of speech.

b) Visual pursuit

A role for the cerebellum in the initiation of pursuit was put forward by Straube et al. (1997) who examined the abilities of patients with unilateral cerebellar lesions. They found that the lateral cerebellum in particular may be involved in smooth pursuit. These findings are in line with the work of Nawrot and Rizzo (1995) who found that acute midline cerebellar lesions are associated with deficits in motion perception.

(ii) Group studies of patients with cerebellar lesions

A comprehensive study of a group of patients with cerebellar lesions was carried out by Schmahmann and Sherman (1998). They carried out neurological examinations, bedside mental state tests and neuropsychological assessments on 20 patients with acquired lesions confined to the cerebellum and found a consistent pattern of difficulties in four areas:

a) **Executive function:** Problems with planning, changing set, abstract reasoning, verbal fluency, and working memory. These problems with executive function were more evident in patients with lesions that affected the posterior lobe of the cerebellum.

b) **Spatial cognition:** Problems with visuo-spatial organization and memory (for example patients had difficulty with the Rey-Osterrieth Complex Figure). These problems with spatial cognition were more evident in patients with lesions affecting the posterior lobe of the cerebellum.

c) **Changes in personality:** Blunting of affect and/or disinhibited and inappropriate behaviour (this was assessed according to established clinical methods (Weintraub and Mesulam, 1995; Hodges, 1994) where the degree of impairment was recorded using a three-point scale from mild to severe).

d) **Language:** Dysprosodia, agrammatism and mild anomia.

On the basis of these findings, Schmahmann and Sherman proposed that there is a "cerebellar cognitive affective syndrome" which is characterized by impairments in each of the four categories detailed above and which occurs when there is damage to the cerebellum. This syndrome is consistent with Schmahmann's Dysmetria of Thought Hypothesis outlined in Section 1.4.1.

Taken together, the findings from studies of patients with cerebellar damage support the theory that there is functional localization in the cerebellum, as damage to particular areas of the cerebellum results in specific behavioural changes. Furthermore, damage to the cerebellum has been shown to be associated with difficulties in both motor and cognitive function, providing support for the possibility that the cerebellum is not a purely motor structure, but that it plays an important role in cognition as well.

1.4.3.1.5 Tumours of the cerebellum and posterior fossa region

(i) The posterior fossa.

The posterior fossa is the smallest of the three cranial fossa. It is the cavity at the bottom of the skull in which the brain stem and cerebellum are located. The brain stem is the structure that connects the cerebral hemispheres with the spinal cord and it contains the midbrain (the tectum and tegmentum), the pons, the medulla oblongata and numerous small sensory and motor nuclei (the cranial nerve nuclei).

(ii) Tumour types

The two principal types of tumour that occur in the posterior fossa region are astrocytomas

and medulloblastomas. Astrocytomas can be either solid or cystic, and many are of the pilocytic cell type and are thus low-grade gliomas. Although they can be located in the vermis, it is far more common for astrocytomas to be found in the cerebellar hemispheres. These tumours show ringlike growth and often cause both lateral and anterior displacement of the fourth ventricle.

Medulloblastomas, on the other hand, were originally thought to be caused by medulloblast cells (hence their name), but despite many investigations, these medulloblast cells have never been identified (Packer, 2002). Instead, medulloblastomas are now thought to originate from the remains of primitive neuro-ectoderm in the inferior medullary velum (also known as the posterior medullary velum). These tumours are highly malignant and they grow to fill the fourth ventricle, attacking the nearby brain stem and leptomeninges as they increase in size.

(iii) Previous studies of patients with posterior fossa tumours

Despite the fact that half of all brain tumours that occur in children are located in the cerebellum and brainstem, investigations into cerebellar functions through examination of children with tumours in the posterior fossa region have been rare. Studies of motor function in patients with PFT are particularly rare. These cases of individuals with localised damage to the cerebellum are extremely important and provide a promising means by which to gain an understanding of cerebellar function.

Previous studies that have been carried out on patients with PFT have identified a number of difficulties in this patient population. Levisohn et al. (2000) compiled the results of 19 children aged between three and 14 years at age of surgery on a number of neuropsychological tests. They discovered that 14 out of the 19 patients with PFT showed impairment in fine motor coordination. In addition, they found impairments in executive function, visuo-spatial function, expressive language, modulation of affect (particularly associated with vermal damage) and verbal memory in the patients with PFT. Support for these findings come from a study by George et al. (2003) which showed that patients with PFT were impaired on IQ and on verbal and visual memory as assessed by the Wide Range Assessment of Memory and Learning. In addition, Steinlin et al. (2003) administered a

variety of neuropsychological tests to 24 patients with PFT aged between seven and 26 years old and found that they had problems with attention, memory, speed of processing and interference, and a number also had problems with attention. Steinlin et al. (2003) also noted the presence of various psychiatric symptoms, including anorexia, phobia, temper tantrums and addiction problems, and these seemed to be particularly prevalent in patients whose tumour resection had included vermal regions. Thus, in line with Levisohn et al. (2000), Steinlin et al. (2003) also found that there may be localization of function in the cerebellum, with the vermis in particular being involved in the control of emotion or possibly of mental state.

This idea of cerebellar localization of function is in line with the work of Riva & Giorgi (2000). They carried out a number of neuropsychological tests on children who had undergone surgery for posterior fossa tumours. The tests were carried out as soon as possible after surgery and the results showed that damage to the right cerebellum was associated with deficits in auditory sequential memory and language processing, and damage to the left cerebellum was associated with deficits in spatial and visual sequential memory. Furthermore, damage to the vermis led either to mutism or to behavioural disturbances, a finding that is in line with the psychiatric complications after vermal involvement noted by Steinlin et al. (2003), and considered above.

It is important here to mention a number of limitations of these previous studies. One limitation that is particularly relevant for the current study is that the posterior fossa tumours are not always localized within the cerebellum alone. This means that resulting behavioural problems may be associated with damage to areas adjacent to the cerebellum rather than the cerebellum itself. This point was illustrated by Botez-Marquard et al. (2001), who describe a patient with unusual developmental cerebellar agenesis who suffered further unilateral damage to the left cerebellum after a stroke. The behavioural consequences included impairments in verbal and visual memory, in the planning of a sequence of events, in visuo-constructive abilities, and inappropriate jocularity. However, in addition to the cerebellar damage, the lesion also encroached on the pons and there was frontal lobe diaschisis, indicating that these behavioural changes may not be solely related to the cerebellar damage. Thus in previous studies, the areas of the cerebellum investigated are

not always very specific, so any understanding to be gained of functional localization in the cerebellum can only be very limited. This problem will be overcome in the present investigation by identifying, using MRI methods, which particular cerebellar region is damaged and to what extent.

Having considered cases where there is obvious damage to the cerebellum and associated obvious behavioural and psychiatric problems, cases where both the actual cerebellar damage and the resulting behavioural changes are more subtle will now be considered. These are cases with neurodevelopmental brain abnormalities which by their very nature imply that multiple brain systems are involved.

1.4.3.2 Disorders in which the cerebellum has been implicated

The cerebellum has been implicated as playing an important role in a number of different neurodevelopmental and neurogenetic disorders including autism, dyslexia, schizophrenia, bipolar disorder and ADHD. Each of these disorders is discussed below.

1.4.3.2.1 Autism and Asperger's Syndrome

The syndrome in which the cerebellum has received the most attention is autism. Autism is a neurodevelopmental disorder (a disorder of the way the brain develops) characterized by a triad of impairments in social interaction, communication, and restricted and repetitive behaviours and interests, all of which are present from early childhood.

A Social interaction

Impairments in social interaction are the most prominent sign of autism. Individuals live in a world of their own with little interest in social interaction with others. Impairments in social interaction include a relative lack of non-verbal communication mechanisms (eye contact, facial expressions and body language); a lack of understanding of other people's thoughts or feelings; a failure to develop normal relationships with peers, often preferring to spend time with younger children or adults; a lack of spontaneous sharing of activity or interest with others; and inappropriate behaviour in social situations.

B Communication

Impairments in verbal communication vary enormously between individuals with autism, ranging from almost total absence of speech and language to good basic language skills but problems with complex aspects of language such as the use of metaphors, humour, and play on words. There may also be problems with abnormal pitch or rhythm of speech, unusual choice of vocabulary, and a high rate of repetition. In addition to these abnormalities in verbal communication, there are also abnormalities in non-verbal expression such as impoverished use of gesture for communication purposes and poor eye contact and odd body language, which were mentioned in section A above.

C Restricted and repetitive interests and behaviours

The restricted and repetitive interests and behaviours in autism include an obsession with the preservation of sameness (both in routine and in the position of objects); an extraordinary interest and depth of knowledge about one particular topic; and repetitive actions such as hand flapping or twirling.

The first official reports of individuals with autism were those produced by Kanner (1943) and Asperger (1944). Kanner and Asperger described groups of children with overlapping patterns of abnormalities that included repetitive speech, an unusual desire for the preservation of sameness, a lack of imaginative play, a lack of verbal communication and limited awareness of the thoughts or feelings of others. Since this early work, clinical definitions of autism have been produced, based on the investigations of a number of researchers including Wing (1976, 1988, 1996) and Wing and Gould (1979). Autism is now accepted to be a spectrum of behavioural abnormalities that includes very low-functioning individuals with no speech and very little social interaction at one end of the spectrum, ranging up to very able individuals (high-functioning autistics) who have fluent speech but awkward social interaction, at the other end the spectrum (Gillberg, 1991a; Wing, 1996). The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994) and the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) diagnostic criteria for autism can be found in Appendices A and B respectively.

(i) Autism and Asperger's Syndrome: Is Asperger's Syndrome distinct from autism?

Asperger's Syndrome can be defined as a pervasive developmental disorder at the more able end of the autistic spectrum, characterized by a severe impairment in social interaction coupled with an obsessive interest in repetitive behaviours and activities. The DSM-IV and ICD-10 classifications for AS can be found in Appendices C and D respectively. There has been much debate as to whether or not Asperger's Syndrome should be differentiated from high-functioning autism and as such whether it should be considered to be a separate syndrome (Bishop, 1993; Happe, 1994). It has been argued that Asperger's Syndrome can be distinguished from high functioning autism on the basis of language and cognitive function. In his original paper, Asperger (1944) reported that there was no evidence of delay in the development of speech or of cognitive function, and an absence of delay in both language and cognitive function have been incorporated as diagnostic factors for Asperger's Syndrome in both ICD-10 and DSM-IV. However, some investigators claim that, in common with autism, language and cognition can actually be delayed in Asperger's Syndrome (Wing, 1981; Gillberg, 1989; Tantam, 1988). Furthermore, once language skills are in place, the language of individuals with high-functioning autism and those with Asperger's Syndrome shares a number of similarities (Jordan and Powell, 1995; Sigman and Capps, 1997). Language is characteristically stilted, it can be quite pedantic and understanding is very literal, with a relative lack of ability to grasp plays on words or metaphors.

Further similarities between autism and Asperger's Syndrome include the fact that a number of common regions of brain abnormality have been reported (Berthier et al. 1990) and that children often change from being diagnosed with autism at an early age to being labeled with Asperger's Syndrome as they get older, indicating strong links between the two disorders. In addition, there seems to be a genetic aspect in that there is a significantly greater chance that an individual will have autism if they have a sibling with autism or Asperger's Syndrome (Bolton et al. 1994).

The number of similarities between autism and Asperger's Syndrome thus suggests that Asperger's Syndrome should not be considered to be an independent disorder. Instead, this

condition should be considered as part of the broad autistic spectrum of socio-emotional abnormalities. Nevertheless there are a number of behaviours which appear to be particularly obvious in Asperger's Syndrome and these include problems with empathy, unusual clumsiness, a marked preference for the preservation of sameness and oversensitivity to lights and sounds that may not be noticed by other people.

As outlined at the beginning of this chapter, the fact that autism is a neurodevelopmental disorder means that there are likely to be abnormalities in the very earliest neural connections that form during development. It is possible that individuals at different levels of the autistic spectrum differ in the timing and extent of these early abnormalities that have occurred in core regulatory systems of the developing brain (Trevarthen et al. 1998).

(ii) Brain abnormalities in autism

Research into the neural underpinnings of autism point to three main regions of abnormality: the cerebellum, the medial temporal lobes (amygdala and hippocampus) and the frontal lobes. These are considered in some detail below.

a) The cerebellum: The cerebellum has been found to be significantly larger in people with the autistic syndrome (Piven et al. 1997), although this expansion may not be specific to the cerebellum, but may rather be in line with the expansion of the brain as a whole in autism (Lainhart et al. 1997; Hardan et al. 2001; Courchesne et al. 2001; Sparks et al. 2002). It has been hypothesized that this increase in brain size may be due to a failure of the brain to effectively prune synapses over the course of development (Frith, 2003). More detailed studies of the size of groups of cerebellar lobules have produced contradictory results, with some researchers not finding any significant differences in the areas of vermal lobules between autistic subjects and their normal controls (Kleiman et al. 1992; Holttum et al. 1992; Piven et al. 1997), and others like Courchesne et al. (2001) finding that vermal lobules VI and VII are smaller in boys with autism than in controls.

At a cellular level, autopsy studies have reported a significant reduction in either the number of Purkinje cells in the cerebellum of individuals with autism (Bauman and Kemper, 1985, 1986, 1990, 1994; Ritvo et al. 1986; Bailey et al. 1998) or in the size of

their Purkinje cells (Fatemi et al. 2002). This suggests that if there are any differences in the size of the cerebellum, this is likely to be a reflection of a change in its cellular make-up.

On a more global scale, some researchers have argued that it may be the connections of the cerebellum that are disrupted or altered in autism rather than the cerebellum itself. Skoyles (2002), for example, suggested that a disconnection between the cerebellum and the cerebral cortex might be responsible for the autistic symptoms, whereas Muratori et al. (2001) suggested that autism may result from changes in the connections between the neocerebellum (lateral regions of the cerebellar hemispheres) and other areas of the brain.

b) The medial temporal lobes: Two regions of the medial temporal lobes have consistently been found to be abnormal in autism: the amygdala (Abell et al. 1999; Aylward et al. 1999; Howard et al. 2000; Sparks et al. 2002) and the hippocampus (Raymond et al. 1996; Aylward et al. 1999). A study by Salmond et al. (2003) carried out individual voxel-based morphometry (VBM) analyses on the brains of fourteen children with high functioning autism or Asperger's Syndrome. They found that structural abnormalities in the amygdala showed up in half of these patients.

c) The prefrontal cortex: Evidence for abnormalities in the frontal lobe in autism comes from structural and functional imaging studies which have found an increase in the volume of the frontal lobes (Carper and Courchesne 2000) and a delay in the maturation of the frontal lobes (Zilbovicius et al. 1995) in autism; from molecular studies which have found increased cortical thickness, high neuronal density and neuronal disorganization in the frontal lobes in autism (Bailey et al. 1998); and from studies that have found behavioural similarities between patients with frontal lobe pathology and individuals with autism (Hughes et al. 1994).

In addition to these three principal areas, abnormalities have also been found in the thalamus (Tsatsanis et al. 2003), the corpus callosum (Hardan et al. 2000) and the parietal lobes (Courchesne et al. 1993).

It is important to note that these brain areas do not appear to be abnormal in all individuals with autism. A number of studies have found no abnormalities in the cerebellum (Piven et

al. 1998; Sparks et al. 2002); hippocampus (Saitoh et al. 1995; Piven et al. 1998; Haznedar et al. 2000; Howard et al. 2000; Sparks et al. 2002); amygdala (Haznedar et al. 2000) or the frontal lobes (Piven et al. 1998; Carper and Courchesne 2000) in autism. This lack of consistency between different studies may in fact be a reflection of heterogeneities in the study samples. Given that autism is a spectrum of abnormalities, it is possible that different degrees of brain abnormality underlie the problems encountered by individuals at different levels on the spectrum. Whatever the particular behavioural difficulties may be, evidence suggests that damage to one brain system cannot explain all of the features of autism or Asperger's Syndrome.

(iii) Brain abnormalities in individuals with Asperger's Syndrome in particular

A number of studies have been carried out on individuals with Asperger's Syndrome (AS) in particular, and these are considered here because individuals with AS participated in the studies described in the experimental chapters of this thesis.

A study by Abell et al. (1999) found that adults with AS had decreases in grey matter in the right paracingulate sulcus and in the left inferior frontal gyrus and increases in grey matter in the amygdala, the middle temporal gyrus, the inferior temporal gyrus and in the cerebellum. Salmond et al. (2003) found significant increases in grey matter density in the orbitofrontal cortex, the superior temporal gyrus and the cerebellum in individuals with AS. They found some evidence for increases in grey matter density in the amygdala and hippocampus, but this was only found in half of the participants with AS. A study by Nieminen-von Wendt et al. (2002) found a reduction in the size of the mesencephalon in children and adolescents with AS, but no other focal brain abnormalities.

A study which looked at differences in both grey and white matter density was carried out by McAlonan et al. (2002). They found that compared to normal controls, adults with AS had significantly less grey matter in the medial frontal lobe and cingulate, the basal ganglia, thalamus and ventral striatum and in the cerebellum, but found no regions of increased grey matter in patients with AS. Significant decreases in white matter were found predominantly in the left hemisphere in fronto-temporal regions, possibly within the inferior and superior longitudinal fasciculi and the occipitofrontal fasciculus fibre tracts.

Decreases in white matter were also found in the left cerebellum and in the pons. Increases in white matter in AS patients were found bilaterally in the region including the basal ganglia and the external capsule.

Furthermore, Murphy et al. (2002) carried out a proton magnetic resonance spectroscopy study of the brain in Asperger's Syndrome, and found abnormalities in the neuronal integrity of the prefrontal lobe (significantly higher concentrations of N-acetylaspartate (NAA) and choline) that were associated with the level of severity of clinical symptoms.

Functional imaging studies have revealed a bilateral reduction in resting blood flow in the medial temporal cortex in individuals with autism, compared to healthy controls (Ohnishi et al. 2000, Zilbovicius et al. 2000). In addition, a functional imaging study by Oktem et al. (2001) found differences in the level of frontal activation between people with Asperger's Syndrome and healthy controls during a task involving social judgment.

Thus, previous work on Asperger's Syndrome suggests that this condition may be associated with abnormalities in a number of brain regions, one of which is the cerebellum.

(iv) Theories of autism:

A number of theories have been put forward with the aim of explaining the behavioural manifestations of this spectrum of disorders. The three most widely accepted are described below:

a) Failure to acquire a theory of mind

Theory of mind is the ability to infer mental states including beliefs, desires, intentions, imagination and emotions (Baron-Cohen et al. 1994). It has been hypothesized that impairments in the acquisition of a theory of mind may underlie the social and communication difficulties observed in individuals with autism (e.g. Baron-Cohen et al. 1985).

b) Weak central coherence

Central coherence is the ability to put together incoming information into a coherent whole in order that it can be processed for higher level interpretation of meaning (Hill and Frith,

2003). It has been hypothesized that there is weak central coherence in individuals with autism because their brains have poor levels of connectivity between regions of basic perceptual processing and regions of higher-level processing (see Frith 1989; Happe 1999). This means that rather than considering objects as coherent wholes, individuals with autism will tend to focus all their attention on the local aspects.

c) Executive dysfunction

Executive functions are higher-level brain functions that depend on the ability to hold information in mind and integrate relevant aspects for the successful completion of a given task (examples include set-shifting, planning and the inhibition of responses). The theory of executive dysfunction in autism maintains that executive functions are impaired due to a lack of initiation of novel actions and a reluctance to move from a given task set. These impairments are similar to those observed in patients with frontal-lobe lesions (Garth et al., 1997; Levin et al. 1997; 2001) and in clinical disorders such as attention deficit hyperactivity disorder, obsessive-compulsive disorder and schizophrenia, all of which are thought to involve abnormalities in the frontal lobe (Hill and Frith, 2003).

1.4.3.2.2 Dyslexia

Dyslexia is a specific learning disability which is characterized by difficulties in expressive or receptive oral or written language. Three main theories have been put forward to account for the difficulties encountered by individuals with dyslexia:

(i) **The phonological deficit account** (Bradley and Bryant, 1983; Shankweiler et al. 1995; Stanovich 1988): This theory argues that the reading problems in dyslexia are due to an inability to break down spoken words into their constituent sounds.

(ii) **The magnocellular deficit account** (Tallal et al. 1993; Eden et al. 1996; Stein and Walsh, 1997): This theory argues that the reading problems in dyslexia are due to abnormalities in auditory and/or visual magnocellular pathways which result in impaired sensory processing.

(iii) **The cerebellar deficit hypothesis (Nicolson et al. 2001):** This theory is based on the fact that in addition to their language problems, individuals with dyslexia also tend to have impairments in automatic skill performance, a function known to rely on an intact cerebellum. The cerebellar deficit hypothesis therefore

maintains that abnormalities in the development of the cerebellum are the cause of the impairments in reading and writing seen in individuals with dyslexia.

Given the focus of this thesis, the third hypothesis is of particular interest. Numerous studies have recently been carried out to investigate the possibility that there are cerebellar abnormalities in individuals with dyslexia.

Behavioural studies have produced somewhat inconsistent results on tasks known to involve the cerebellum. Nicolson and Fawcett (1993), for example, found that individuals with dyslexia show a deficit in time estimation (a function known to be subserved by the cerebellum) and therefore argued that this finding supported the idea that cerebellar abnormalities are involved in dyslexia. However a study by Ramus et al. (2003) found no evidence for a deficit in time estimation in individuals with dyslexia, thus it is at present unclear whether or not individuals with dyslexia have difficulties with this aspect of cerebellar function.

Neuroimaging studies have provided more consistent findings in support of cerebellar abnormalities in individuals with dyslexia. In an MRI study, Rae et al. (2002) found that the normal asymmetry in cerebellar grey matter in controls (more grey matter in the right than in the left cerebellum) was not present in individuals with dyslexia. Instead, individuals with dyslexia had similar levels of grey matter in both of the cerebellar hemispheres. Furthermore, Brown et al. (2001) found that in individuals with dyslexia the cerebellum was one of the brain regions to show a decrease in grey matter.

A study by Eckert et al. (2003) measured the posterior temporal lobe, inferior frontal gyrus, cerebellum and whole brain on MRI scans and found that in individuals with dyslexia, the anterior lobes of the cerebellum, the pars triangularis of the frontal lobe and whole brain volume were all significantly smaller than those of the controls. These results support the idea that abnormalities in cerebellar-frontal connections are associated with dyslexic difficulties. Functional imaging studies (PET) have found a decrease in activation in the left cerebellum in individuals with dyslexia during tasks requiring phonological processing (McCrory et al. 2000). In addition, a postmortem study was carried out by Finch et al.

(2002) on four dyslexic brains and four normal brains. They found that the mean area of the cells in the medial posterior cerebellar cortex was significantly larger in the dyslexic brains than in the controls. These results should however be treated with caution given the small numbers and given that the subjects were not age-matched.

Thus there is mounting evidence for a variety of cerebellar abnormalities in individuals with dyslexia. However, abnormalities have also been found in a number of other brain regions and it is therefore important not to assume that dyslexic difficulties can be completely accounted for by abnormalities in the cerebellum. Furthermore, dyslexia is a neurodevelopmental disorder which means that brain abnormalities are present from the beginning of development and therefore it is very unlikely that abnormalities are limited to individual brain regions, rather it is probable that systems of interconnected brain structures will show abnormalities (see Section 1.14).

1.4.3.2.3 Schizophrenia

Schizophrenia is a neurodegenerative disorder generally occurring in adulthood. Studies of the cerebellum in schizophrenia have found that compared to normal controls, schizophrenic patients have an increased vermis volume, a greater asymmetry in the volumes of the cerebellar hemispheres, and a high correlation between increases in cerebellar white matter volume and increases in the severity of symptoms (Levitt et al., 1999). These findings led Levitt et al. (1999) to suggest that vermal abnormality may be associated with the pathophysiology of schizophrenia.

However, the cerebellum is by no means the only brain area affected in schizophrenia. Other brain abnormalities reported include increases in neuronal density in prefrontal (Selemon et al. 1998) and temporal (Pakkenberg, 1993) cortical areas; a significant reduction in bilateral cortical folding (Sallet et al. 2003); decreased perfusion in prefrontal, inferior temporal and parietal cortex and increased perfusion in the thalamus and cingulate cortex (Andreasen et al. 1997); and abnormalities in synapses of the striatum indexed by a reduction in the size of striatal spines (Roberts et al. 1996). Thus although the cerebellum may be abnormal in schizophrenia, it is clear that it is only one of a number of brain regions showing abnormality and it is therefore difficult to determine what the particular

behavioural implications of the cerebellar abnormalities might be.

1.4.3.2.4 Bipolar disorder and ADHD

Vermal abnormality has also been observed in bipolar disorder and in attention-deficit hyperactivity disorder (ADHD). DelBello et al. (1999) carried out MRI measurements of a number of cerebellar areas in patients with bipolar disorder, and found that vermal lobules VIII-X were significantly reduced in size in "multi-episode patients" compared to "first-episode patients" or normal controls. Berquin et al. (1998), who looked at cerebellum size in ADHD, found that subjects with ADHD have significantly smaller vermal lobules VIII-X, but normal sized vermal lobules VI-VII. These findings were supported by Hill et al. (2003) who found vermal lobules VIII-X to be significantly smaller in individuals with ADHD and also found vermal lobules I-V to be reduced in size in these patients. Thus there seems to be an overlap between the particular vermal regions argued to be reduced in size in both bipolar disorder and ADHD (vermal lobules VIII-X). Future work should aim to determine what the particular functions of these lobules are, either through fMRI studies or through comparisons between bipolar disorder and ADHD, to investigate any shared abnormalities in behaviour.

As was the case for schizophrenia, it is important to note that the cerebellum is not the only abnormal brain region in bipolar disorder or ADHD. For bipolar disorder, there have been reports of an increase in the size of the left amygdala (Brambilla et al. 2003) and of an increase in the activity of a frontal cortical-subcortical neural system that includes the anterior cingulate and caudate (Blumberg et al. 2000). In addition, Bertolino et al. (2003) found indications of malfunction of the hippocampus implicated by a reduction of N-acetylaspartate (NAA) relative signals (NAA is a marker of neuronal integrity).

For ADHD, reductions in the size of the whole brain (Castellanos et al., 1996; Hill et al., 2003), the prefrontal cortex (Castellanos et al., 1996; Hill et al., 2003), the corpus callosum (Semrud-Clikeman et al., 1994; Lyoo et al. 1996; Hill et al. 2003), the splenium (Hill et al. 2003), and the right globus pallidus (Castellanos et al. 1996) have been reported. In addition, Mataro et al. (1997) found an increase in the size of the caudate nucleus in ADHD.

1.4.3.3 Summary of the functions of the cerebellum

Consideration of functional imaging studies and studies of patients with damage to the cerebellum has shown that both of these approaches provide useful means by which to learn about cerebellar functions. While functional imaging methods can be used to determine what are the functions of the cerebellum in a normal brain, patient studies can show for which functions the cerebellum is actually necessary and in which functions the cerebellum serves an integral role. Thus a combination of these methods is important to enhance our understanding of what the functions of the cerebellum might be.

Summary

Considerable attention has been paid to the anatomy of the cerebellum resulting in a comprehensive understanding of its structural make-up. The associated functions of the cerebellum, however, are far less well understood. Although the cerebellum has long been known to play an integral role in motor function, there have recently been strong indications that it also plays a role in cognition. This evidence comes from both functional imaging studies and from studies of patients with cerebellar damage.

1.5 Aims and plan of studies

The aims of the studies carried out in this thesis are to investigate the functions in which the cerebellum may play an integral role and to investigate the more general effects of pathology in the cerebellum on the rest of the brain and on behaviour. Two groups of patients with different types of cerebellar abnormality are considered. One group has acquired pathology (patients with posterior fossa tumours) and one has neurodevelopmental pathology (Asperger's Syndrome) of the brain. Experimental and standardized neuropsychological tests will be used to assess a range of cognitive and motor functions in the two patient populations and in their matched controls. Magnetic resonance imaging techniques will also be used in order to determine the extent of abnormalities in the cerebellum and its associated brain regions. These techniques include conventional clinical imaging as well as voxel-based morphometric (VBM) analyses of 3D T1-weighted data sets and of diffusion tensor images in order to look at subtle differences in grey or white matter densities and in white matter tracts.

1.6 Structure of thesis

This thesis is divided into seven chapters. The first chapter has provided an introduction to the anatomical structure, circuitry and postulated functions of the cerebellum as well as previous studies that have been carried out on patients with different types of cerebellar abnormalities. The next chapter (Chapter 2) provides a detailed characterization of the study sample including individual case histories, parental reports of any motor or cognitive difficulties, family histories and measures of intellectual function. Neuropsychological investigations are described in the next two chapters. Experimental and standardized measures of motor function (uni-manual and bi-manual tests of fine motor ability and tests of motor learning) are presented in Chapter 3. Investigations of cognitive function (numeracy and literacy skills, attention, working memory, visual perception, copying and drawing, and executive function) are presented in Chapter 4. The following two chapters detail the methods and results of the neuroimaging investigations. Chapter 5 describes the MR characteristics of the patients with PFT, including the identification of the precise location of the tumours and the particular cerebellar lobules affected by surgery. In Chapter 6, abnormalities in grey and white matter densities and white matter tracts in each of the two patient groups are reported and correlations between grey matter abnormalities and performance on behavioural tests are described. The final chapter (Chapter 7) provides a discussion of all the findings from this thesis as well as final conclusions.

CHAPTER 2: CHARACTERIZATION OF THE STUDY SAMPLE

In this chapter, the characteristics and selection criteria for the individuals who participated in this study are described and the results from baseline neuropsychological tests of intellectual function are reported.

2.1 Characterization

Two patient groups participated in this study. One group had received treatment for posterior fossa tumours (PFT) and the other consisted of individuals with Asperger's Syndrome (AS). Patients with PFT have acquired pathology that is apparently limited to the cerebellum. These patients have not always had abnormal brains, they started life with the potential to develop normal neural networks and normal cognitive and behavioural functions. The patients with AS, on the other hand, are believed to have neurodevelopmental abnormalities in the cerebellum, but these abnormalities are only part of a more widespread pattern of brain pathology in these patients. Patients with AS are thought to have had abnormal brain development right from the very beginning. By carrying out neuropsychological and neuroimaging investigations on individuals from these two patient populations it is anticipated that it will be possible to investigate in which motor and cognitive functions the cerebellum plays an integral role, and also to examine the more widespread effects on the rest of the brain of neurodevelopmental versus acquired damage of the cerebellum.

Before describing the characteristics of each of these two patient groups, the screening protocol and the methods for the baseline neuropsychological measures of intellectual function will first be detailed.

2.2 Methods

The screening protocol administered in this study includes a developmental questionnaire (see Appendices E and F) as well as measures of intellectual function. The main purpose of the screen was firstly to control and match for IQ levels between patients and control

groups, and secondly to exclude any individuals with developmental problems.

2.2.1 Developmental questionnaire

In order to gain an understanding of the characteristics of each of the patients who participated in the study, parental interviews were carried out by a clinical neuropsychologist (Professor Vargha-Khadem). The parental interview involved the completion of the developmental questionnaires that can be found in Appendix E (patients with PFT) and Appendix F (patients with AS and control participants), and the results of these questionnaires are presented below. For patients with AS, an additional questionnaire (the Australian Scale for Asperger's Syndrome – ASAS) was administered both to confirm the diagnosis of AS and to ensure that behaviours characteristic of AS were shown by the individuals with AS who participated in this study. The ASAS (which can be found in Appendix G) is described in some detail in Section 2.3.4 below. Parental questionnaires are subject to bias due to the tendency of individuals to acquiesce or to provide socially desirable responses (Barker et al., 2002) and the results of the questionnaires included in this study will therefore be interpreted with caution. Nevertheless, it was important to administer these questionnaires as they were the most reliable means by which it was possible to gain an understanding of the early patterns of development of the participants.

2.2.2 Measures of intellectual function

The age-appropriate Wechsler Intelligence Scale (WISC-III, Wechsler, 1992; WAIS-R, Wechsler, 1986) was administered to determine full-scale (FIQ), verbal (VIQ) and performance (PIQ) IQs of each of the patients and the controls. These assessments comprise the following subtests: picture completion, information, coding, similarities, picture arrangement, arithmetic, block design, vocabulary, object assembly, comprehension, symbol search and digit span. In addition, the mazes subtest from the WISC-III was administered to all participants and the matrices subtest of the WAIS was administered to all those participants over 17 years of age. Descriptions of the subtests of the WISC and WAIS can be found in Appendix H.

2.2.3 Statistical analyses

In order to investigate whether there were any significant differences between the mean scores of each of the patient groups and their controls on the measures of intellectual function, independent sample t-tests were carried out between patients with PFT and their matched controls and between patients with AS and their matched controls.

In order to investigate whether there were any within-group differences in the patients with PFT related to the location of the tumour (left hemisphere, right hemisphere or midline tumour), within-subject analyses were carried out. ANOVAs with repeated measures design were computed for all those tasks with repeated conditions and one-way ANOVAs were computed for the remaining single-condition tasks. Any significant interactions were investigated post-hoc using Tukey's test.

Finally, in order to determine whether there were any effects of age at pathology or time since pathology, correlation analyses (Pearson's) were carried out separately between each of these measures and each of the measures of intellectual function for the patient group with PFT.

Both simple t-tests and ANOVAs assume that the data are normally distributed and that there is homogeneity of variance. These assumptions were checked using the Shapiro-Wilcox test for normality and Levine's test of homogeneity of variance. If either assumption was violated on a particular test, then the data were log transformed ($\log_n$) and the assumptions re-checked. If there were still violations, then non-parametric (Mann-Whitney U) tests were carried out.

Interpretation

The nature of this study is such that many statistical analyses were carried out, testing a large number of predictions, and using small sample sizes. Multiple comparison adjustment was not performed. Instead, a cut-off of $p<0.05$ was chosen as a mechanism for flagging potential problematic motor and cognitive functions in the patient groups which will require further investigation in future studies. Any significant findings at this level (p-values <0.05)

will be interpreted with caution. Where there were strong expectations of effects, p values in the range 0.05 - 0.1 will also be commented upon.

2.2.4 Ethical approval

Ethical approval for this project was sought from the Great Ormond Street Hospital/Institute of Child Health Ethics Committee and this was granted on 5th August 2002. The ethics committee required consent forms to be produced both for the parents of the children participating in the project and for the children and adolescents themselves (these can be found in Appendices E and F). These were presented to the participants and their parents at the beginning of their visit when the project was being described, and the consent forms were completed before any testing was carried out in order to ensure that both the parents and the participants knew exactly what their ethical rights were.

Given that the project involves the use of personal data, it was also registered with the Great Ormond Street Hospital (GOSH) data protection officer who provided details of the GOSH data protection guidelines. In line with these guidelines, the personal data were coded using unique identifiers so that the data remained anonymous and participants could not be identified. The key to these data was kept in a password-protected computer to which only one person (Bryony Whiting) had access.

Having described the methods used to gain information about the characteristics of individuals in each of the patient groups and their matched control groups, these characteristics will now be reported. The characteristics (including the levels of intellectual function) of the patients with PFT and their controls will first be reported and then the characteristics of the patients with AS and their controls will be detailed. The chapter will end with a discussion and a summary of the findings.

2.3 Results

2.3.1 Patients with PFT

Fifteen children and adolescents who had been treated for posterior fossa tumours (PFT) participated in this study. There were eight females and seven males ranging in age from 8-

20 years at the time of testing (see table 2.1). All of the participants had been treated for cerebellar astrocytomas at Great Ormond Street Hospital in London between the years 1986 to 2001. Participation was voluntary and individuals were excluded if they had undergone any chemotherapy or radiation treatment, if they had any abnormal development prior to the symptoms of the tumour (determined by looking at medical records and from the parental questionnaire that is described below), if they had any additional neurological or psychiatric diagnosis (including epilepsy, attention deficit hyperactivity disorder (ADHD) and autism) and if their tumours, and post-surgical brain abnormalities, were not limited to the cerebellum alone. In addition, patients were recruited at least two (and up to 16) years post-surgery to ensure that the short and medium-term effects of the tumour and surgery had dissipated.

Altogether thirty patients were approached to enquire whether they would be willing to participate in the study. They were each sent an information sheet (see Appendix K) to give them details about what the study would involve. These thirty patients were selected from the hospital records of over 100 children who had undergone surgery for posterior fossa tumours from 1986 to 2001. They were selected on the basis of the criteria outlined above. Out of these thirty patients, fifteen individuals agreed to take part in the study.

The patients with posterior fossa tumours can be broken down into three sub-groups on the basis of the location of their cerebellar pathology (left hemisphere, midline or right hemisphere) and details of all of these patients can be found in Table 2.1 below. It is important to note that some of the patients had pathology that overlapped both hemisphere and midline and these are indicated with a * in Table 2.1. The criterion for allocating individuals to the tumour location subgroups which will be used throughout this thesis is that patients were allocated to the midline pathology group only if they had damage limited to the midline alone. If there was any pathology of either of the cerebellar hemispheres, then patients were allocated to the relevant hemisphere pathology subgroup.

Table 2.1: Details of the patients with PFT

ID	Tumour location	Handedness	Gender	Age at surgery	Age at assessment	Time since surgery	FSIQ	VIQ	PIQ
PFT1	Left hemisphere	Right	Female	12y 11m	17y 6m	4y 6m	86	81	94
PFT2	Left* hemisphere	Right	Female	7y 3m	11y 6m	4y 2m	66	72	66
PFT3	Left hemisphere	Right	Female	5y 6m	13y 9m	8y 3m	104	100	109
PFT4	Left hemisphere	Right	Male	5y 6m	13y 8m	8y 1m	100	104	94
PFT5	Left hemisphere	Right	Male	7y 7m	9y 11m	2y 3m	92	90	96
PFT6	Midline	Right	Female	15y 2m	18y 10m	3y 8m	103	101	105
PFT7	Midline	Right	Female	2y 9m	19y 6m	16y 9m	94	95	91
PFT8	Midline	Right	Female	4y 7m	12y 11m	8y 4m	120	131	101
PFT9	Midline	Left	Female	11y 10m	20y 0m	8y 1m	80	85	78
PFT10	Midline	Left	Male	11y 2m	13y 3m	2y 1m	85	88	85
PFT11	Right* hemisphere	Right	Female	6y 3m	8y 8m	2y 5m	125	129	112
PFT12	Right hemisphere	Right	Male	2y 2m	12y 9m	10y 7m	89	89	92
PFT13	Right hemisphere	Right	Male	1y 9m	8y 10m	7y 1m	123	140	110
PFT14	Right hemisphere	Left	Male	11y 7m	15y 0m	3y 5m	104	109	96
PFT15	Right* hemisphere	Left	Male	4y 2m	14y 8m	10y 6m	91	103	78

Results of the Developmental Questionnaire from the parental interview for patients with PFT

The developmental questionnaire was completed during the parental interview carried out by a clinical neuropsychologist (Professor Vargha-Khadem), and the results of this questionnaire are divided into three sections. The first section provides a summary of the symptoms experienced prior to surgery and the subsequent presentation following surgery for each of the patients with PFT. The information provided in this section is a compilation of the results from Sections 1 (School and Education), 2 (Developmental milestones) and 4 (Medical) of the questionnaire as well as details from the hospital medical records for each of the patients. The second section examines parental reports of motor and cognitive function from Sections 1 (School and Education), and 3 (motor abilities) of the

questionnaire. The third and final section summarizes the results of Section 6 (Family), detailing which patients had a family history of psychiatric disorders, neurological problems, learning difficulties or any speech, language or motor difficulties.

1. Symptoms prior to surgery and presentation since surgery

Table 2.2 provides a summary of the neurological and medical, motor, affective (changes in temperament) and behavioural symptoms that were reported in each of the patients with PFT before surgery.

Table 2.2: Symptoms of patients with PFT before surgery

ID	Neurological/medical	Motor	Affective/other
PFT1	Headaches, vomiting, double vision	Bumped into objects	
PFT2	Headaches and vomiting		
PFT3	Headaches and vomiting in morning	Poor balance when walking	Poor concentration
PFT4	Headaches, vomiting in morning, nausea all day	Clumsiness	Tearful, annoyed
PFT5	Increasingly bad headaches, associated vomiting in morning		
PFT6	Headaches, sickness in morning, vomiting most days		
PFT7	Headaches and some vomiting	Ataxia	
PFT8	Woke up early every morning to vomit	Poor balance + coordination	
PFT9	Three months of headaches, fatigue, vomiting		
PFT10	Headaches all day. Sickness in morning with projectile vomiting. Diplopia + papilloedema		
PFT11	Headaches and vomiting in morning	Poor balance (fell off bike); writing became very small	
PFT12	Headaches and vomiting in morning	Tremor, unable to stand	
PFT13	No vomiting	Unsteady on feet, eventually unable to walk	
PFT14	Mild headaches which were long lasting		
PFT15	Headaches all day, vomiting in morning.	Balance problems, poor motor actions (couldn't hold pencil, run or jump).	

This table shows that headaches and vomiting, particularly in the morning, are common symptoms in almost all of the patients with PFT. In addition, nine patients showed motor problems prior to surgery, one patient showed changes in affect and one showed poor concentration skills.

Table 2.3 provides a summary of the presentation of patients with PFT after surgery in terms of any neurological or medical, motor, memory, language, affective or temperament problems that were reported.

Table 2.3: Presentation of patients with PFT since surgery

ID	Neurological/medical	Motor	Memory and language	Affective/other
PFT1		No longer bumps into objects		Lack of confidence; depressed; loses temper quickly + for no reason; no control of mood swings, remorseful + upset after
PFT2		Less clumsy		Was quiet and withdrawn but happier since surgery
PFT3		Movement good, but pencil grip is awkward. She is county tennis player.	Problems with word-finding and expressing herself. Lazy speech	Loses temper for no reason (but temper tantrums stopped since surgery). Problems with logic (e.g. maths – used to be very good, now has severe problems)
PFT4				Mood swings – improving gradually
PFT5		Unclear whether right or left handed before surgery. Now hardly uses left hand	Short-term memory problems	Withdrawn; frustrated during following year and would lose temper for no reason. Started sleep walking and has "night terror"
PFT6	Nausea, vomits most mornings	Unsteady gait	Word-finding problems	Lack of control of temper
PFT7	Rickham's reservoir in situ	Initially couldn't use right hand and compensated with left; balance problems; odd pencil grip	Problems with speech – received speech therapy for some years	
PFT8	Double vision for ten days; unable to read stationary stimuli when she is moving (e.g. road signs from moving car)	Serious tremor in right hand. Bad at catching and kicking		Lack of empathy and bad at predicting other people's reactions. Lack of motivation
PFT9	Changed handedness (was right, now left); Mild nystagmus, now resolved; bad circulation; migraines	Poor movement of right hand + leg. Leg improved, hand still very weak. Poor coordination	Short-term memory problems	Episode of extreme anxiety post-surgery. Withdrawn and less "bubbly" than before surgery.
PFT10			Memory problems	Better mood; improved temper
PFT11	Headaches once a month	Problems with balance, coordination and clumsiness		Period of intense anger for 10-12 months post-surgery; very serious pre-surgery, now less tense+happier.
PFT12	Nausea in the morning	Tremor stopped immediately after surgery and balance came back; right side of body is weaker	Pre-surgery could put four or five words together, post-surgery only two or three	Loses temper quickly – aware of this but unable to control it
PFT13		Had to learn to walk again. Problems with coordination		More angry since surgery
PFT14	No problems			
PFT15	Changed handedness (was right, now left)	Slight hand tremor; balance problems; problems holding pencil and using knife and fork		Very bad-tempered, frustrated and self-critical after surgery at age 5-6, now improved.

This table shows that the headaches and associated vomiting dissipated in most of the patients after surgery. Motor problems, although many of these are different from those reported before surgery, are still present in 10 out of the 15 patients. The most striking difference between the presentation of the patients before and after surgery, however, is in affective problems. There were only two reports of affective problems prior to surgery; however after surgery, problems with affect are reported in 12 out of the 15 patients. These problems are most commonly in the form of shortness of temper which individuals are aware of but cannot seem to control. Patients report that they lose their temper over very trivial matters, that they know when it is going to happen, but that they are unable to do anything about it.

2. Parental reports of motor and cognitive function

a) Cognitive function

Five of the patients with PFT (patients PFT3, PFT5, PFT9, PFT10, PFT12) were reported by their parents to have problems with memory, particularly with short-term memory. Only one of the patients with PFT (patient PFT3) was reported by their parents to have problems with language. This suggests that at least some patients with PFT may have particular difficulties with the tests of memory that will be administered in this study.

b) Motor function

Table 2.4 shows which patients were reported by their parents to have problems with a number of different motor functions either before (√pre) or after (√post) surgery (an **X** indicates that no problems were reported either before or after surgery; tumour locations are abbreviated as follows: LH = left hemisphere, V = vermis (midline), RH = right hemisphere).

Table 2.4: Parental reports of types of motor problems in patients with PFT

ID	Tumour location	writing	climbing	catching	kicking	hopping	buttons	Shoe laces	clumsiness
PFT1	LH	X	X	X	X	X	X	X	X
PFT2	LH	√pre	√pre	X	X	X	X	X	√pre+post
PFT3	LH	X	X	X	X	X	X	X	X
PFT4	LH	X	X	X	X	X	X	X	√pre
PFT5	LH	√pre	X	√pre	X	X	X	X	√pre
PFT6	V	√post	X	√post	X	√post	X	X	√post
PFT7	V	X	√post	X	X	√post	X	X	√post
PFT8	V	√post	X	√post	√post	√post	X	X	√pre+post
PFT9	V	√post	√post	√post	√post	√post	√post	√post	√post
PFT10	V	X	X	X	X	X	X	X	X
PFT11	RH	√ post	X	√ post	√ post	√ post	X	X	√post
PFT12	RH	√post	√pre	X	√post	√post	√post	√post	X
PFT13	RH	X	X	X	X	X	X	X	X
PFT14	RH	X	X	X	X	X	X	X	X
PFT15	RH	√post	√post	X	X	√post	√post	√post	X

The table shows that before surgery, out of fifteen patients with PFT, two were reported to have problems with writing, two with climbing, one with catching and four with clumsiness, but none were reported to have problems with kicking, hopping or doing up buttons or shoe laces. After surgery, six patients were reported to have problems with writing, three with climbing, four with catching, four with kicking, seven with hopping on one leg, three with doing up buttons, three with doing up shoe laces and six with clumsiness. Only three out of the fifteen patients were not reported to have problems with any of these aspects of motor abilities. These parental reports indicate that motor difficulties are commonly seen in these patients with tumours in the posterior fossa region and that these difficulties are particularly prominent post-surgery. It is interesting to note that the motor difficulties before surgery in patients PFT2, PFT4, PFT5 and PFT12 tended to disappear after surgery. On the other hand, a number of patients who did not suffer from motor problems before surgery did report motor difficulties after surgery.

3. Family histories

None of the patients with PFT had evidence of psychiatric disorders, neurological problems, learning difficulties or any speech, language or motor difficulties in their immediate families.

Summary of the characteristics of the patients with PFT

Fifteen patients who had received treatment for posterior fossa tumours (astrocytomas) in the cerebellum participated in the study. The patients were subdivided on the basis of clinical scans and medical notes at surgery into three subgroups related to the location of their tumour: left hemisphere (n = 5), right hemisphere (n = 5) and midline (n = 5). The age range was from eight to twenty years, the age at surgery ranged from 1:9 to 15:2 years and the time since surgery ranged from 2:1 to 16:9 years. Parental reports suggested that these patients may have difficulties with motor functions and memory, and with affect, particularly with temper-control.

2.3.2 Controls for patients with PFT

Ten normally developing children were selected to act as controls for the patients with PFT. They were each sent an information sheet (see Appendix K) to give them details about what the study would involve. The controls were recruited through local schools and were screened with regard to IQ, age and sex so that they could be group-matched to the patients with PFT. Individuals were excluded if they did not have English as their first language, if they had any neurological or psychiatric diagnosis, or they had any history of dyslexia or dyspraxia (as determined by the parental questionnaire – see Appendix F).

Altogether, 15 possible age-matched controls were approached out of which 10 were identified as appropriate to participate in the study. It should be noted that although the lowest IQ within the group with PFT was 66, the lowest measure of IQ for a control participant that was deemed acceptable for the study was 80. This is because individuals with IQs lower than 80 are more likely to have some form of neurological impairment and they can therefore not necessarily be considered to be "normal" controls.

The mean IQs and the ages at assessment (as well as the standard deviations and ranges) of the controls and the patients with PFT are shown in table 2.5.

Table 2.5: Mean FSIQ, VIQ, PIQ and age at assessment of patients with PFT and their matched controls

	Patients with PFT	PFT controls
Mean FSIQ	**97.5** (sd=16.4, range 66-125)	**98.8** (sd=13.3, range 81-122)
Mean VIQ	**101.1** (sd=19.4, range 72-140)	**98.4** (sd=13.7, range 83-119)
Mean PIQ	**93.8** (sd=13.0, range 66-112)	**99.8** (sd=12.2, range 82-121)
Mean age at assessment	**13.5** (sd=3.8, range 8-20)	**14.6** (sd=4.0, range 9-20)

In order to confirm that the PFT controls had been successfully age-matched to the patient group with PFT, between-group statistical analysis (t-tests) was carried out on the age at assessment. The results showed that there was no significant difference in age at assessment between patients with PFT and their controls ($t = -0.6$; $df = 23$; $p = 0.5$).

The same developmental questionnaire that was administered to the patients with AS (see Appendix F) was also administered to the control participants (this questionnaire was also essentially the same as that administered to the patients with PFT with the exception of the section on medical history which was minimised for patients with AS and controls).

The results of the developmental questionnaire are divided into two sections for the control participants. The first section involves parental reports of motor and cognitive function from Sections 1 (School and Education), and 3 (motor abilities) of the developmental questionnaire. The second section summarizes the results of Section 6 (Family), detailing which patients had a family history of psychiatric disorders, neurological problems, learning difficulties or any speech, language or motor difficulties.

1. Parental reports of cognitive and motor function in PFT controls

a) Cognitive function: None of the PFT controls were reported by their parents to have problems with memory or language.

b) Motor function: None of the PFT controls were reported by their parents to have problems with motor function.

2. Family histories

There were no reports of psychiatric disorders, neurological problems, learning difficulties or speech, language or motor difficulties in the first degree relatives of PFT controls. These parental reports are thus consistent with the entry criteria detailed above.

2.3.3 Intellectual function in patients with PFT and their controls

The mean IQs for the patients with PFT and the controls were provided in Table 2.5 above. Statistical analysis showed that there was no significant difference between patients with PFT as a group and their controls on any of the measures of IQ: FIQ ($t = -0.2$; $df = 23$; $p = 0.833$), VIQ ($t = 0.4$; $df = 23$; $p = 0.703$), PIQ ($t = -1.2$; $df = 23$; $p = 0.259$), indicating that the groups had been satisfactorily matched on IQ. The mean IQs for the tumour location subgroups are shown in Table 2.6.

Table 2.6: Mean full-scale IQ (FIQ), verbal IQ (VIQ) and performance IQ (PIQ) for the tumour location sub-groups

Group	FIQ	VIQ	PIQ
Left hemisphere PFT (n = 5)	89.6 (14.9)	89.4 (13.2)	91.8 (15.7)
Right hemisphere PFT (n = 5)	106.4 (17.1)	114.0 (20.4)	97.6 (14.0)
Midline PFT (n = 5)	96.4 (15.9)	100.0 (18.4)	92.0 (11.1)

Mean (sd)

It is interesting to note that there is a discrepancy between the mean VIQ and PIQ for the patient group with PFT in favour of the former (see Table 2.5). In order to investigate whether this was due to one particular tumour location subgroup more than the others, paired sample t-tests were carried out between PIQ and VIQ scores for each of the tumour location subgroups separately. The results showed that there was no significant difference between these two measures of IQ for the left hemisphere subgroup ($t = -0.541$, $df = 4$, $p = 0.617$) or for the midline subgroup ($t = 1.382$, $df = 4$ $p = 0.239$), but there was a significant difference for the right hemisphere subgroup ($t = 2.883$, $df = 4$, $p = 0.045$). The discrepancy between PIQ and VIQ for the patients with PFT as a group is primarily a reflection of the large discrepancy between PIQ and VIQ (with VIQ being approximately 16 points higher than PIQ) in the subgroup of patients with right hemisphere pathology.

Further analysis of the patient sub-groups with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no

significant difference between the performance of the patients in each of the tumour location subgroups on any of the measures of IQ: FIQ ($F(2,14) = 1.399$, $p = 0.284$), PIQ ($F(2,14) = 2.451$, $p = 0.128$), VIQ ($F(2,14) = 0.287$, $p = 0.755$).

The standardized scores for the performance of the patients with PFT and their controls on each of the subtests of the WISC and WAIS were analysed separately in order to examine performance on each individual task. The subtests are divided into those used to calculate verbal IQ (see Table 2.7), those used to calculate performance IQ (see Table 2.8) and the remaining subtests which are not directly used to determine IQ measures but can provide useful indicators of domains indirectly related to intelligence (see Table 2.9).

Table 2.7: Mean standard score on verbal IQ subtests for patients with PFT and controls

Group	Information	Similarities	Arithmetic	Vocabulary	Comprehension
PFT	10.47 (4.37)	10.60 (3.48)	10.67 (3.56)	10.33 (3.52)	8.87 (2.92)
Control	10.00 (3.09)	10.70 (3.23)	9.00 (4.30)	9.90 (2.73)	9.10 (1.85)

Mean (sd)

Statistical analysis using independent sample t-tests showed that there was no significant difference between the performance of patients with PFT and controls on any of the verbal IQ subtests.

Table 2.8: Mean standard score on performance IQ subtests for patients with PFT and controls

Group	Picture completion	Coding	Picture arrangement	Block design	Object assembly
PFT	9.53 (2.39)	8.87 (2.42)	8.87 (3.00)	9.80 (3.30)	8.00 (2.56)
Control	10.20 (1.93)	11.70 (2.95)	9.60 (2.37)	9.30 (2.83)	8.30 (1.89)

Mean (sd)

Statistical analysis using independent sample t-tests showed that the only performance subtest for which there was a significant difference between patients with PFT compared to controls was the coding subtest (Mann Whitney U: $z = -2.467$, $p = 0.014$), on which patients with PFT performed more poorly than controls.

Table 2.9: Mean standard score on remaining IQ subtests for patients with PFT and controls

Group	Symbol search	Mazes	Digit Span	Matrices
PFT	9.73 (2.52)	8.20 (2.31)	10.67 (3.72)	10.25 (2.87)
Control	11.22 (1.64)	8.00 (3.20)	10.44 (2.67)	11.50 (0.58)

Mean (sd)

Statistical analysis using independent sample t-tests showed that there was no significant difference between the performance of patients with PFT and controls on any of the remaining IQ subtests.

Taken together, these results show that the only IQ subtest on which patients with PFT performed particularly poorly is the coding subtest. Further analysis of the patient sub-groups (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was a significant interaction between location of tumour and performance on the vocabulary subtest ($F(2,12) = 4.277$, $p = 0.040$) and weak evidence for a significant interaction between location of tumour and performance on the comprehension subtest ($F(2,12) = 3.604$, $p = 0.059$). The mean scores for each of the PFT tumour location sub-groups on these two subtests are shown in Table 2.10 below.

Table 2.10: Mean scores on the vocabulary and comprehension subtests for PFT sub-groups

Group	Vocabulary	Comprehension
LH damage	8.40 (1.82)	6.60 (2.61)
Midline damage	9.20 (2.28)	9.20 (2.95)
RH damage	13.40 (4.10)	10.80 (1.79)

Mean (sd)

Patients with left cerebellar hemisphere damage performed more poorly than the other two groups on both the vocabulary and comprehension subtests, whereas those with right hemisphere damage performed best on these tasks. Post hoc analysis (Tukey's test) showed that for the vocabulary subtest, there was a significant difference between those with left hemisphere and those with right hemisphere damage ($p = 0.045$) and weak evidence for a significant difference between those with right hemisphere and those with midline damage ($p = 0.096$). For the comprehension subtest, there was weak evidence for a significant difference between those with left hemisphere and those with right hemisphere damage ($p = 0.051$).

Summary of IQ results for patients with PFT and controls

Statistical analyses showed that control subjects were well matched on IQ and age to the patients with PFT. Analysis of performance on the IQ subtests showed that patients with PFT performed significantly more poorly than controls on the coding subtest. Within the patient group with PFT, the subgroup with pathology of the left cerebellar hemisphere performed poorly on the vocabulary and comprehension subtests of the WISC/WAIS.

Effects of age at surgery for patients with PFT

Correlation analyses aimed at examining the relation between age (in months) at surgery and each of the measures of IQ (FSIQ, VIQ and PIQ) showed no significant effects. Correlation analyses were then performed between age at surgery and the results of each of the sub-tests of the WISC/WAIS described above. The results showed that there was a significant negative correlation between age at surgery and performance on the mazes subtest of the WISC (Pearson correlation coefficient = -0.519, p = 0.047) and weak evidence for a significant negative correlation between age at surgery and performance on the arithmetic (Pearson correlation coefficient = -0.483, p = 0.068) and vocabulary (Pearson correlation coefficient = -0.451, p = 0.092) subtests of the WISC/WAIS.

Effects of time since surgery for patients with PFT

Correlation analyses were also performed between time in months since surgery and each of the measures of IQ and each of the sub-tests of the WISC/WAIS. The only significant finding was a negative correlation between time since surgery and performance on the coding subtest of the WISC/WAIS (Pearson correlation coefficient = -0.517, p = 0.049).

2.3.4 Patients with AS

Fourteen individuals with Asperger's Syndrome (AS) participated in the study (see table 2.11), all of whom had received a diagnosis of AS from independent clinicians (including clinical psychologists, psychiatrists and paediatricians).

Table 2.11: Details of the patients with AS

ID	Age at diagnosis	Gender	Handedness	Age at assessment	FSIQ	VIQ	PIQ
AS1	3	Male	Right	16y 3m	106	98	116
AS2	4	Male	Right	16y 0m	97	96	99
AS3	4	Male	Right	13y 2m	102	108	95
AS4	6	Male	Right	11y 6m	115	123	101
AS5	7	Male	Right	8y 2m	106	122	82
AS6	10	Male	Left	12y 7m	116	99	125
AS7	10	Male	Right	15y 5m	111	102	121
AS8	10	Male	Right	12y 10m	118	133	95
AS9	11	Male	Right	19y 0m	109	111	106
AS10	13	Male	Right	18y 4m	116	119	109
AS11	14	Male	Left	18y 3m	99	103	94
AS12	?	Male	Left	14y 6m	104	95	115
AS13	?	Male	Right	16y 7m	107	133	76
AS14	?	Female	Right	13y 2m	135	122	142

The participants with AS included 13 males and one female. Eleven of these patients had taken part in a previous study at the Institute of Child Health (as part of a PhD project carried out by Claire Salmond entitled, "Investigating the role of the medial temporal lobes in autism"), the remaining three (patients AS5, AS8 and AS9) were recruited through an advertisement placed on the Autinet website (http://www.iol.ie/~wise/autinet/). Each patient was sent an information sheet (see Appendix K) to give them details about what the study would involve.

Participation was voluntary and individuals were excluded if they had any additional neurological or psychiatric diagnosis (including epilepsy, dyspraxia, ADHD and fragile X syndrome) and if they did not have average verbal IQ (>85) and/or age appropriate academic performance. Altogether, four possible participants could not be included in the study: two had ADHD and two had dyspraxia in addition to AS.

Further to the requirement of a clinical diagnosis of AS, parental interviews were carried out by a clinical neuropsychologist (Professor Vargha-Khadem) and the Australian Scale for Asperger's Syndrome was completed in order to obtain a characterization of the type of autistic behaviours that were typical for each individual. The results of both the parental interviews and the Australian Scale for Asperger's Syndrome are outlined below.

1. Developmental questionnaire results from parental interview

The parental interview involved the completion of the developmental questionnaire that can be found in Appendix F. The results of the developmental questionnaire are divided into three parts. The first part provides case histories for each of the patients with AS, including any parental reports of memory or language problems. The information for this part comes from Sections 1 (School and Education) and 2 (Developmental milestones) of the developmental questionnaire. The second part looks at parental reports of motor function which come from Section 3 (motor abilities). The third and final part summarises the results of Section 6 (Family), detailing which patients had a family history of psychiatric disorders, neurological problems, learning difficulties or any speech, language or motor difficulties.

a) Case histories

Table 2.12 provides a summary of any history of medical, memory, language, affective or temperament problems in the patients with AS.

Table 2.12: Summary of case histories of patients with AS

ID	Medical history	Memory and language	Affective/ temperament
AS1	Cord tied around neck at birth and needed resuscitation, breathed within 1 minute of birth; slept very badly as a baby; blocked tear duct, ear infections, gromits fitted three times and on antibiotics during first 2 years.	Parental reports of language problems	Didn't like being held as a baby.
AS2	Slept very badly as a baby	Parents reports of language problems	
AS3	Bad chest infection, ear infections and colds during first two years; received antibiotics.	Parental reports of memory and language problems; lost hearing and speech from age 2.	Withdrawn; sometimes wild and aggressive
AS4	Normal delivery at 36 weeks. Slept very badly as a baby	Parental reports of language problems	
AS5	Would not take solid foods	Parental reports of memory problems	
AS6	Delivered by emergency c-section at 35 weeks because of pre-eclampsia. Slept very badly as a baby	Parental reports of language problems	
AS7	Constant ear infections in first two years. Diagnosed with 25% hearing loss aged 4; with asthma aged 2	Parental reports of memory and language problems; diagnosed with word accessing problems aged 6.	
AS8	Slept very badly as a baby. Diagnosed with Irlen Syndrome aged 8 – problems with peripheral vision corrected with coloured lense glasses	Parental reports of language problems	
AS9	Slept very badly as a baby; febrile convulsions until about age 8.	Parental reports of memory problems; diagnosed with mild dyslexia aged 18	
AS10		Parental reports of memory and language problems; late to start speaking, immature speech at age 3.	
AS11	Delivered by emergency c-section at 37 weeks due to foetal distress. Slept very badly as a baby; projectile vomiting until 15 months; didn't like taste of many foods	Parental reports of memory problems	
AS12	In distress before birth, but normal delivery. Bronchitis at 20 months	Parental reports of memory problems	
AS13	Delivered by emergency c-section at 36 weeks; special care baby unit; jaundice treated with bilirubin. Glue ear and grommets in first 2 years. Slept very badly from age 3 months-11 years	No parental reports of memory or language problems	High anxiety levels

AS14	Ventouse delivery at term. Renal problems and failure to thrive from 4 months – on antibiotics; problems with solid foods; pneumonia at 15 months	Parental reports of memory and language problems

The table shows that the patients with AS experienced a variety of medical problems which appeared to be particularly prominent during the first couple of years of life and many of these individuals slept very badly as babies. Out of the fourteen patients with AS, eight were reported by their parents to have difficulties with memory and nine were reported to have difficulties with language. This suggests that the patients with AS are likely to have difficulties with some of the neuropsychological measures of memory and language ability that will be administered in this study. It is interesting to note that not all of the patients with memory problems have language problems, and vice versa, indicating that the two do not necessarily occur together.

b) Motor function

Table 2.13 below shows which patients were reported by their parents to have problems with aspects of motor functions.

Table 2.13: Parental reports of types of motor problems in patients with AS

ID	writing	climbing	catching	kicking	hopping	buttons	shoe laces	clumsiness
AS1	X	X	X	X	X	X	X	X
AS2	X	√	X	X	√	√	√	√
AS3	√	X	X	X	√	√	√	√
AS4	X	X	√	√	X	√	√	√
AS5	√	X	√	√	√	√	√	√
AS6	√	√	X	X	√	√	√	√
AS7	√	X	X	√	√	X	X	X
AS8	√	X	√	√	√	X	X	√
AS9	√	X	X	√	X	√	√	X
AS10	√	X	√	X	X	X	√	√
AS11	√	X	√	√	√	√	√	√
AS12	X	X	X	X	X	X	X	X
AS13	X	√	√	√	X	√	√	√
AS14	√	√	√	√	√	√	√	√

The table shows that out of the fourteen patients with AS, nine were reported to have problems with writing, four with climbing, seven with catching, eight with kicking, eight with hopping on one leg, nine with doing up buttons, ten with doing up shoe laces and ten with clumsiness. These parental reports indicate that it is likely that patients with AS will have difficulties with some of the measures of motor function that will be administered in this study.

2. Family histories

Table 2.14 below summarises the incidence of psychiatric disorders, neurological problems, learning difficulties or any speech, language or motor difficulties in the immediate family (first degree relatives) of any of the patients with AS.

Table 2.14: Family history of first degree relatives of patients with AS

Patient	Family history of first degree relatives
AS1	Father, mother and younger brother all dyslexic
AS3	Two older brothers on autistic spectrum, older sister has autistic symptoms and possibly dyslexia. Mother has had nervous breakdown.
AS4	Brother brain-damaged after chicken pox, Broca's area damaged
AS5	Unstable mother
AS9	Older sister has AS; father has bipolar disorder and possibly schizophrenia
AS10	Older brother and mother are dyslexic, younger brother has dyscalculia
AS11	Mother has speech problems and used to see speech therapist
AS12	Mother and father have both had depression. Social worker believes father has AS
AS14	Father has AS; 3 younger brothers all on autistic spectrum (one also has semantic pragmatic disorder)

The remaining five patients with AS had no immediate family history of psychiatric disorders, neurological problems, learning difficulties or any speech, language or motor difficulties. Nevertheless, the fact that nine out of fourteen patients did report problems indicates that there is a high incidence of psychiatric disorders and learning difficulties in the families of the patients with AS.

The Australian Scale for Asperger's Syndrome

The Australian Scale for Asperger's Syndrome (ASAS, Garnet and Attwood, 1997) is a parental behaviour checklist that aims to identify which characteristics representative of Asperger's Syndrome are present in an individual child. The ASAS (which can be found in Appendix G) is divided into six sections (A-F). Parents are asked to give a rating from 0

(rarely) to 6 (frequently) to show how often their child carries out the behaviour described in each of sections A-E. For section F, parents are asked to answer yes or no to show whether or not their child has ever shown any of the characteristics described. The sections of the ASAS are described below:

A: Social and emotional abilities
This section assesses the understanding of how to play, the understanding of social conventions, awareness of other people's feelings and ideas, empathy and displays of emotion and interaction with peers. There are 10 questions in this section, and the maximum score is 60.

B: Communication skills
The second section asks for ratings of literal understanding, unusual eye-contact or tone of voice, lack of reciprocal conversation and pedantry. There are six questions in this section and the maximum score is 36.

C: Cognitive skills
The next section is about memory, reading and imaginative play. There are three questions in this section and the maximum score is nine.

D: Specific interests
Section D assesses preoccupations, dislike of change, routines and rituals. There are three questions in this section and the maximum score is nine.

E: Movement skills
The next section concerns odd gait and poor co-ordination. There are two questions in this section and the maximum score is six.

F: Other characteristics
The final section looks at fears and phobias, sensitivity to pain and motor mannerisms. There are ten measures for this section and the maximum score is six.

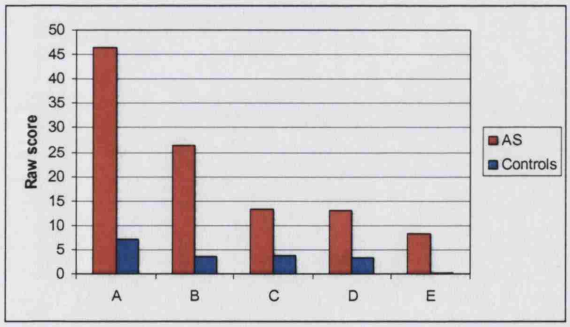
The individual ratings for the patients with AS on sections A-E of the ASAS are presented in Table 2.15 as well as the mean scores for the AS group and for the AS controls (details of the AS controls are provided in Section 2.3.5; however their scores on the ASAS are presented here in order to illustrate the relative level of the scores of the patients with AS compared to normal controls). For the ASAS, a higher score indicates a greater tendency to show behaviours known to be characteristic of Asperger's Syndrome.

Table 2.15: Parental ratings of patients with AS on sections A-E of the ASAS and mean ratings for patients with AS and AS controls

AS Patient	Social and emotional abilities (max. = 60)	Communication skills (max. = 36)	Cognitive skills (max. = 9)	Specific interests (max. = 9)	Movement skills (max. = 6)
AS1	42	21	15	13	1
AS2	45	27	17	13	4
AS3	57	36	16	12	8
AS4	44	31	14	13	10
AS5	49	36	18	18	12
AS6	47	27	15	17	10
AS7	43	29	7	10	6
AS8	47	31	14	12	12
AS9	53	25	15	13	8
AS10	40	24	9	9	9
AS11	57	31	16	16	11
AS12	33	11	9	6	1
AS13	46	22	10	15	12
AS14	46	17	11	17	12
AS MEAN	**46.36**	**26.29**	**13.29**	**13.14**	**8.29**
AS Control MEAN	**7.14**	**3.57**	**3.71**	**3.29**	**0.29**

The ratings for the patients with AS and their controls on sections A-E of the ASAS are presented in Figure 2.1 below.

Figure 2.1: Ratings for patients with AS and controls on sections A-E of the ASAS



These results show that, as expected, patients with AS obtained much higher ratings than controls on each of sections A-E of the ASAS. This indicates that the patients with AS have more characteristics thought to be representative of this developmental disorder than do the control participants.

Table 2.16 shows the ratings for patients with AS and their matched controls on section F of the ASAS.

Table 2.16: Ratings for patients with AS and controls on section F of the ASAS

Unusual fear or distress due to:	Number of patients with AS	Number of AS controls
Ordinary sound	8	1
Light touch on skin or scalp	10	0
Wearing particular items of clothing	10	0
Unexpected noises	9	1
Seeing certain objects	5	0
Noisy, crowded places	10	1
Tendency to flap or rock when excited	8	0
Lack of sensitivity to low levels of pain	8	0
Late in acquiring speech	5	0
Unusual facial grimaces or tics	5	0

These results show that a much larger proportion of patients with AS than control participants were reported by their parents to show abnormal fears, phobias, motor mannerisms and sensitivity to pain.

Summary of the characteristics of the patients with AS

Fourteen patients who had a clinical diagnosis of Asperger's Syndrome participated in this study. The age range was from eight to nineteen years. Parental reports suggested that these patients may have difficulties with memory, language and motor functions and also that they show a variety of unusual characteristics relating to the understanding of social conventions (empathy and displays of emotion), communication (unusual eye-contact or tone of voice, pedantry and lack of reciprocal conversation), unusual fears, phobias, motor mannerisms, sensitivity to pain, and a tendency to be obsessed with specific interests.

2.3.5 Controls for patients with AS

Ten normally developing control children were selected to act as controls for the patients with AS (none of these were the same individuals who acted as controls for the patients with PFT). They were each sent an information sheet (see Appendix K) to give them details about what the study would involve. The controls were recruited through local schools and were screened with regard to IQ so that they could be group-matched on chronological age, sex and full-scale IQ to the patients with AS. Individuals were excluded if they did not have English as their first language, if they had any neurological or

psychiatric diagnosis or they had any history of dyslexia or dyspraxia (as determined by the parental questionnaire – see Appendix F).

Altogether, 13 possible age-matched controls were approached out of whom 10 appropriate matches were identified. The mean IQs and the ages at assessment (as well as the standard deviations and ranges) of the controls and the patients with AS are shown in table 2.17.

Table 2.17: Mean FSIQ, VIQ, PIQ and age at assessment of patients with AS and their matched controls

	Patients with AS	AS controls
Mean FSIQ	**110.1** (sd=9.7, range 97-135)	**110.2** (sd=14.8, range 93-137)
Mean VIQ	**111.7** (sd=13.5, range 95-133)	**112.0** (sd=11.1, range 90-129)
Mean PIQ	**105.4** (sd=17.6, range 76-142)	**105.5** (sd=19.2, range 80-139)
Mean age at assessment	**14.4** (sd=3.1, range 8-19)	**14.8** (sd=2.1, range 12-18)

In order to confirm that the AS controls had been successfully age-matched to the patient group with AS, between-group statistical analysis (t-tests) was carried out on the age at assessment. The results showed that there was no significant difference in age at assessment between patients with AS and their controls ($t = -0.5$; $df = 22$; $p = 0.7$).

The same developmental questionnaire that was administered to the patients with AS (see Appendix F) and the PFT controls was also administered to the AS controls. As was the case for the PFT controls, the results of the developmental questionnaire are divided into two sections:

1. Parental reports of cognitive and motor function in AS controls

a) Cognitive function: None of the AS controls were reported by their parents to have problems with memory or language.

b) Motor function: Two of the AS controls were reported by their parents to have problems with aspects of motor function. One control was reported to have difficulties with hopping and clumsiness and the other was reported to have difficulties with tying shoe laces.

2. Family histories

There were no reports of psychiatric disorders, neurological problems, learning difficulties or speech, language or motor difficulties in the first degree relatives of AS controls.

These parental reports are thus consistent with the entry criteria detailed above.

2.3.6 Intellectual function in patients with AS and their controls

The mean IQs for the patients with AS and their controls were shown in Table 2.17. Patients with AS performed at a very similar level to their controls on measures of full-scale IQ, verbal IQ and performance IQ, and statistical analysis using independent sample t-tests showed that there was no significant difference between the patients with AS and their controls on any of these measures of IQ: FIQ ($t = -0.03$; $df = 22$; $p = 0.980$), VIQ ($t = -0.06$; $df = 22$; $p = 0.957$), PIQ ($t = -0.01$; $df = 22$; $p = 0.993$).

The standardized scores for the performance of the patients with AS and their controls on each of the subtests of the WISC and WAIS were analysed separately in order to look at performance on each subtest. The subtests are divided into those used to calculate verbal IQ (see Table 2.18), those used to calculate performance IQ (see Table 2.19) and the remaining subtests which are not directly used to determine IQ measures but can provide useful indicators of domains indirectly related to intelligence (see Table 2.20).

Table 2.18: Mean standard score on verbal IQ subtests for patients with AS and controls

Group	Information	Similarities	Arithmetic	Vocabulary	Comprehension
AS	13.43 (3.20)	12.93 (2.06)	11.93 (3.20)	11.57 (3.35)	10.14 (3.51)
Control	12.50 (2.64)	11.30 (2.36)	14.10 (2.92)	11.80 (2.35)	10.70 (2.58)

Mean (sd)

Statistical analysis using independent sample t-tests showed that there was no significant difference between patients with AS and controls on the verbal IQ subtests except for the similarities subtest where there was weak evidence for a difference (after log transformation: $t = 1.916$, $df = 22$, $p = 0.068$), with patients with AS performing slightly better than controls.

Table 2.19: Mean standard score on performance IQ subtests for patients with AS and controls

Group	Picture completion	Coding	Picture arrangement	Block design	Object assembly
AS	11.64 (2.76)	8.50 (3.84)	11.50 (3.90)	12.21 (2.36)	9.93 (3.39)
Control	10.50 (3.14)	9.90 (2.23)	10.70 (4.37)	12.20 (3.23)	10.30 (3.65)

Mean (sd)

Statistical analysis using independent sample t-tests showed that there was no significant difference between patients with AS and controls on any of the performance IQ subtests.

Table 2.20: Mean standard score on remaining IQ subtests for patients with AS and controls

Group	Symbol search	Mazes	Digit Span	Matrices
AS	10.14 (3.61)	9.21 (3.07)	10.36 (4.52)	12.00 (2.65)
Control	11.70 (3.23)	9.30 (2.45)	11.80 (2.97)	10.00 (1.73)

Mean (sd)

Statistical analysis using independent sample t-tests showed that there was no significant difference between patients with AS and controls on any of the remaining IQ subtests.

Summary of IQ results for patients with AS and their controls

Statistical analyses showed that AS control subjects were well matched on IQ and age at assessment to the patient group with AS.

2.4 Discussion

(i) Patients with PFT

a) Developmental questionnaire results

The results of the developmental questionnaires proved to be very informative. Out of fifteen patients with PFT, twelve were reported to have problems with a variety of motor abilities, and the problems were particularly prominent post-surgery. These findings indicate that motor difficulties are commonly associated with excised tumours in the posterior fossa region. This is consistent with the extensive evidence that the cerebellum is involved in motor functions (e.g. Marr, 1969; Allen and Tsukahara, 1974; Ivry et al. 1988; Akshoomoff and Courchesne, 1992; Blinkenberg et al. 1996; Jueptner et al., 1997; Inoue et al., 1998; Braitenberg et al., 1997; Miall et al., 2000; Debaere et al. 2004). However, there is still little understanding of the extent to which there may be localisation of function in the

cerebellum. This is one of the questions that will be investigated in this thesis. Given that the patients with PFT who participated in the study have pathology affecting a variety of different regions of the cerebellum, it should be possible to look for associations between the regions that are damaged and the motor functions that are impaired in those particular patients, thereby determining whether particular cerebellar regions are necessary for particular motor functions. These investigations will be described in Chapter 6.

In addition to the problems with motor functions, the results of the developmental questionnaire also revealed some problems with memory. Six out of fifteen patients with PFT were reported by their parents to have difficulties with memory, which suggests that memory problems are a common feature in this patient population. Previous research has implicated the cerebellum as playing an important role in working memory (Paulesu et al., 1993, 1995; Andreasen et al. 1995, Fiez et al., 1996; Desmond et al., 1997; Nyberg et al. 2001) and it would therefore expected that pathology of the cerebellum will result in problems with the aspects of memory in which the cerebellum is normally involved.

Furthermore, the finding that only one patient was reported to have problems with language is quite surprising. There is growing evidence to suggest that the cerebellum is involved in a number of aspects of language, including semantic discrimination (Xiang et al., 2003), lexical processing (Petersen and Fiez, 1993; Leiner et al., 1993; Fabbro et al. 2000) and speech (Ackermann et al. 1997; Gasparini et al. 1999; Belton et al. 2003). It would therefore be expected that language problems would be relatively common after pathology of the cerebellum. However, despite the fact that parental reports only identified one patient with language problems, the results from the WISC/WAIS showed that language problems may in fact present in a larger number of the patients, particularly in those with left cerebellar hemisphere pathology (see section b) below on Baseline neuropsychological assessment of intellectual function).

The final section of the developmental questionnaire, which examined family histories, revealed that none of the patients with PFT reported the presence of psychiatric disorders,

neurological problems, learning difficulties or speech, language or motor difficulties in any of their first degree relatives.

b) Baseline neuropsychological assessment of intellectual function

The results from the baseline neuropsychological assessments showed that there was no difference on measures of intelligence between the patients with PFT and their controls, confirming that the control group had been successfully matched to the patient group. Further analysis showed that the only IQ subtest for which there was a significant difference between patients with PFT compared to controls was the coding subtest on which patients with PFT performed particularly poorly. The coding subtest depends on visual perception, attention, writing and speed of processing abilities and it is possible that the problems encountered by patients with PFT on this test may be due to motor difficulties with the writing aspect of the test given the role that the cerebellum is known to play in motor functions; or with attention difficulties as functional imaging studies have implicated the cerebellum as playing a role in attention (Allen et al., 1997; Le et al., 1998; Rees et al., 1997); or with poor speed of processing due to a failure of reorganization of the brain after surgery. Motor and attention abilities in patients with PFT are considered in more detail in Chapters 3 and 4 respectively where their performance on tests of motor function and attention are reported.

Analysis within the group of patients with PFT showed an interesting association between language abilities and tumour location. Individuals with left cerebellar hemisphere pathology performed poorly on tests of vocabulary and comprehension, whereas individuals with right cerebellar hemisphere pathology performed well on these tests. These findings suggest firstly that speech and language problems are more common than the results of the developmental questionnaire (where only one patient with PFT was reported by their parents to have language problems) might imply. Secondly, these findings provide preliminary indications that there may be functional localisation within the cerebellum in relation to speech and language processing. However, it is important to note that the current findings are not actually consistent with previous research. Although patients with left cerebellar pathology were found to have particular problems with vocabulary and

reading comprehension, previous studies have found that it is patients with pathology of the right cerebellar hemisphere who have language problems (Riva & Giorgi, 2000). Furthermore, imaging studies have shown activation in the right cerebellar hemisphere during language tasks (Petersen et al. 1988, 1989; Raichle et al. 1994; Martin et al. 1995). Given the crossed connections between the cerebellum and the cerebral hemispheres, it would actually be predicted that the right cerebellum (which is connected to the left "language" cerebral hemisphere) is involved in language functions (Scott et al., 2001). For these reasons, the finding that patients with left cerebellar pathology have particular difficulties with language is unexpected. It is possible that the problems with language in individuals with left cerebellar hemisphere pathology are related to associated damage to other brain areas rather than to the cerebellar damage per se. This possibility will be investigated in Chapter 6 when the results of the neuroimaging investigations are presented. In addition, investigations reported in Chapter 6 should establish whether there are any language tasks on which patients with right cerebellar pathology have particular problems in line with previous work.

Effects of age at surgery and time since surgery for patients with PFT

The correlation analyses suggested that surgery carried out at an older age has a negative effect on the ability to carry out the mazes task (which depends on problem solving abilities). This is in line with the idea that pathology that occurs later during childhood after some degree of brain organization has taken place will result in selective impairments in behavioural function (see Section 1.14).

The results also showed that the longer time that has passed since surgery, the more poorly patients with PFT tended to perform on the coding subtest (which depends on visual perception, attention, writing and speed of processing abilities). This may be due to motor difficulties which impact on writing abilities. However, it is also possible that patients with PFT are not as efficient as controls on tasks such as coding which require a fast speed of processing due to a failure of reorganization of the brain after surgery.

These significant findings for effects of age at surgery and time since surgery for patients with PFT should be interpreted with some caution. It must be noted that correlation

analyses were carried out for all of the IQ subtests and there is therefore a high probability of obtaining false positive results. For this reason these results will be interpreted as providing indications for the functions that may be associated with age at surgery or time since surgery rather than as direct evidence, and these possible associations will be further investigated in Chapters 3 and 4.

(ii) Patients with AS

a) Australian Scale for Asperger's Syndrome (ASAS) results

The results of the ASAS showed that compared to controls, patients with AS showed far more unusual characteristics relating to the understanding of social conventions, communication, unusual fears, phobias, motor mannerisms, sensitivity to pain, and a tendency to be obsessed with specific interests. Each of the characteristics targeted by the ASAS is thought to be particularly representative of individuals with Asperger's Syndrome and the fact that the parental ratings were so high indicates that, as expected, they possess a large number of characteristics known to be common in AS. This finding provides additional evidence to support their diagnosis of AS.

b) Developmental questionnaire results

The results of the developmental questionnaire showed that twelve out of fourteen patients with AS were reported by their parents to have problems with a variety of motor abilities suggesting that such problems are common in individuals with AS. This is in line with previous investigations which have found a variety of movement abnormalities (including awkward or odd posture and poorly coordinated motor actions) in individuals with AS (e.g. Wing, 1981; Burgoyne and Wing, 1983; Ghadziuddin et al. 1992; Gillberg, 1989; Manjiviona and Prior, 1995).

Furthermore, the results from the developmental questionnaire showed that eight patients with AS were reported to have difficulties with memory and nine were reported to have difficulties with language. This indicates that both memory and language problems are common in individuals with AS. It is likely that the problems with memory are not general problems, however, as previous studies of memory function in autism and AS have

revealed that while some forms of memory are impaired (e.g. delayed recall, episodic memory) other forms of memory appear to be intact (e.g. working memory, semantic memory and recognition) (Bennetto et al., 1996; Minshew and Goldstein, 2001; Ozonoff and Strayer, 2001). Language abilities, on the other hand, are known to be abnormal in autism and AS. An impairment in verbal communication is one of the defining characteristics of autism as language is often used for instrumental purposes rather than for social interaction and the language used has a tendency to be egocentric and repetitive (Tager-Flusberg, 1996). It is therefore not surprising that such a large proportion of the individuals with AS participating in the current study have been reported to have language problems.

The final section of the developmental questionnaire, which examined family histories, revealed that the parents of nine out of the fourteen patients with AS reported the presence of psychiatric disorders, neurological problems, learning difficulties or speech, language or motor difficulties in at least one of the patients' first degree relatives.

c) Baseline neuropsychological assessment of intellectual function

The results from the baseline neuropsychological assessments showed that there was no difference on measures of intelligence between the patients with AS and their controls, confirming that the control participants had been satisfactorily matched to the patient group.

Summary

Altogether 49 subjects participated in this study. There were 15 individuals who had undergone surgery for posterior fossa tumours, 14 individuals with Asperger's Syndrome and 20 normally developing control children, ten matched on age, sex and IQ to the patients with PFT, and ten to the patients with AS. A number of abnormalities in motor, memory and language function were reported in each of the two patient groups, and these will be further investigated in the experimental chapters of this thesis (chapters 3 and 4).

CHAPTER 3: MOTOR FUNCTION

The aims of the studies presented in this chapter were to characterize the motor abilities of the patient groups with posterior fossa tumours and Asperger's Syndrome and to gain an understanding of the pattern of intact and impaired motor functions that may be associated with different types of cerebellar abnormality.

Ever since the earliest investigations of cerebellar function, this structure has been understood to be involved in the co-ordination of movement. The first person to show that the removal of the cerebellum results in problems with movement was Rolando (1809), who carried out ablation experiments on rats. He argued that his finding indicated that the cerebellum is important for the initiation of movement. However, Flourens (1824) carried out investigations which involved the removal of the cerebellum from pigeons and found that this resulted in degraded movement rather than an absence of movement, indicating that an intact cerebellum is not essential for movement initiation. This critical finding is thought to be the origin of the current understanding that the cerebellum is involved in movement co-ordination rather than in movement generation (Schmahmann, 2000).

Some of the most intricate observational studies of cerebellar function were carried out by Gordon Holmes in the early 20th Century. Gordon Holmes studied World War I patients who had suffered gun-shot wounds in the cerebellum (Holmes, 1917) and found that damage to the cerebellum results in four principal types of movement abnormalities: (1) hypotonia or atonia (loss of muscle tone); (2) asthenia (muscle weakness) and faster tiring of ipsilateral limbs; (3) abnormalities of voluntary movement (delayed initiation of movement, slowness in achieving the full power of a movement and delayed and slowed relaxation); and (4) failure to execute certain movements.

Since these early investigations, studies have implicated the cerebellum in the planning (Allen and Tsukahara, 1974; Eccles, 1977), execution (Allen and Tsukahara, 1974; Rivkin et al., 2003; Thickbroom et al., 2003), timing (Ivry et al. 1988; Akshoomoff and Courchesne, 1992; Penhune et al., 1998; Rivkin et al., 2003; Bengtsson et al. 2004), control

(Ellerman, et al., 1994; Braitenberg et al., 1997), learning (Marr, 1969; Jenkins and Frackowiak, 1993; Schweighofer et al. 1998) co-ordination (Miall et al., 2000; Miall et al. 2001; Debaere et al. 2004) and fine-tuning (Thach et al. 1992; Jueptner and Weiller, 1998) of motor actions. Thus there is strong evidence to show that the cerebellum is involved in motor actions, particularly in the co-ordination and control of movement.

Many of these previous studies have tended to consider the cerebellum as a whole. However, there is growing evidence in support of the possibility of localization of function in the cerebellum. Functional imaging studies, for example, have indicated that the anterior lobe (lobules I-V) of the cerebellum is particularly involved in motor actions (Kuhtz-Buschbeck et al. 2003; Rivkin et al. 2003). Movement of the fingers has been shown to involve hemispheric lobules IV (Jueptner et al. 1997) and V (Fox et al. 1985; Blinkenberg et al. 1996; Sadato et al. 1996; Jueptner et al. 1997) and movement of the feet has been associated with vermal lobules II and III (Nitschke et al. 1996). However, although it does seem likely that the anterior cerebellum is particularly involved in movement, the precise nature and extent of localisation of function in the cerebellum remains to be discovered. It is hoped that the current investigations will help to increase the current understanding in this area. By investigating motor function in patients with neurodevelopmental versus acquired cerebellar pathology, it is anticipated that it will be possible to increase understanding of the way in which motor function is organized and compensated in the cerebellum:

(i) **Patients with PFT:** Studies of patients with PFT will enable further investigation of the idea of localization of function. Patients with PFT have had particular regions of the cerebellum removed during surgery and it will therefore be possible to investigate whether there are associations between impaired aspects of motor function and particular cerebellar regions that are damaged in different patients.

(ii) **Patients with AS:** Studies of patients with AS are less likely to provide information on functional localization in the cerebellum because the cerebellar abnormalities in these patients are not so clearly localized to particular regions

of the cerebellum. By investigating motor function in this population with developmental cerebellar abnormalities it is anticipated that it will be possible to investigate the effects on movement of subtle, more diffuse abnormalities in the cerebellum.

Before detailing the particular tests of motor function that were used in the current study, previous work on motor abilities in patients with PFT and in patients with AS will first be considered.

Chapter outline

The chapter starts with an overview of previous studies of motor function in each of the two patient groups. On the basis of this previous work, as well as the functional imaging studies of the cerebellum considered in Chapter 1, hypotheses as to the predicted outcomes of the motor tests administered in this study will then be outlined. The methods and results of the different tests are split into three sections: uni-manual motor action, bi-manual motor action and motor learning. The chapter ends with a discussion and summary of the pattern of intact and impaired motor abilities in each of the two patient groups.

3.1 Motor function in patients with PFT

The motor abilities of individuals with PFT are still relatively unknown. This is because the few studies that have been carried out on this patient population have tended to focus on cognitive rather than motor function, in line with the recent suggestions that the cerebellum is not a purely motor structure, but may also be involved in cognition. Nevertheless, preliminary evidence suggests that tumours in the cerebellum may affect the ability to carry out fine motor skills, as a study by Levisohn et al. (2000) found that 14 out of 19 patients with PFT showed impairment in fine motor co-ordination.

In addition, it is clear that motor abnormalities are often present in patients with PFT as these are in fact one of the major symptoms that led to the diagnosis of the tumour in the first place. The diagnostic motor symptoms include general weakness, loss of balance, lack of co-ordination and inability to walk. After excision of the tumour, these severe problems

seem to dissipate rapidly. However, while the obvious problems may thus be resolved, it is likely that some form of motoric difficulties remain, given the role that the cerebellum is known to play in motor function. For this reason it is important to investigate the nature of any motor difficulties, however subtle, that are present after surgery and to see whether these are associated with the region of the cerebellum that has been excised in these patients.

In the absence of further evidence from the particular patient population involved in the current study, it may be useful to look at motor function after acquired lesions of the cerebellum caused by factors other than tumours in order to gain an understanding of the types of difficulties that may be found in the current investigations.

Studies have shown that midline cerebellar lesions are associated with a selective deficit in motion perception (Nawrot and Rizzo, 1995; 1998), whereas more lateralized damage caused by infarctions of the posterior inferior or superior cerebellar artery has been shown to result in significantly slower movements of both the ipsilateral and contralateral arms (Immisch et al. 2003). In addition, Fellows et al. (2001) studied a group of patients with damage to the posterior inferior cerebellar artery or the superior cerebellar artery or with cortical cerebellar degeneration. They found that these patients had difficulty in co-ordinating the timing of movement sequences when required to lift an object in a precision grip. Further evidence for problems with timing of motor actions after cerebellar damage comes from a study by Timmann et al. (2000). They found that in a ball-throwing task, three cerebellar patients (with right sided damage after cerebellar artery infarction or cerebellar haemorrhage) threw the ball less accurately and more slowly than controls and also showed more variation in the timing of ball release and in the direction of the hand path. Timmann et al. (2000) explained these problems by proposing that cerebellar patients have a disorder in central commands to the joints that are involved in the hand path, and to those involved in the timing of finger opening for ball release.

In summary, studies of patients with cerebellar damage have revealed difficulties with fine motor action, abnormalities in motion perception, a reduction in the speed of movements

and a disruption of temporal co-ordination of joint movements. It is likely that some of these motor difficulties will be present in the patients with PFT who are taking part in this study and it is anticipated that the chosen motor tests will reveal the motor problems that may be present.

3.2 Motor function in patients with autism and AS

Autism is characterized by a triad of impairments in social interaction and communication and restricted and repetitive behaviours and interests (see Section 1.4.3.2.1). However, there is one more characteristic which, despite not being defined as one of the core features of autism, is also very common in this disorder. This is clumsiness. Clumsiness is due to difficulties in the co-ordination of motor actions and the fact that individuals with autism are generally diagnosed with clumsiness indicates that there are problems with motor function in this patient population.

It is interesting to note that in order to receive a clinical diagnosis of autism or AS, an individual is not required to show any motor abnormalities. Nevertheless, in Asperger's (1944) original paper, he describes a number of movement difficulties in his patients, including both gross (lack of fluency in locomotion) and fine (poor fine motor co-ordination) movement problems. In addition, since this early work, numerous studies have identified movement abnormalities (in the form of awkward or odd posture and poorly co-ordinated motor actions) as being common features of autism and AS (Wing, 1981; Burgoyne and Wing, 1983; Ghadziuddin et al. 1992; Gillberg, 1989; Manjiviona and Prior, 1995; Tantam, 1988, 1991; Szatmari et al. 1989b; Hardan et al. 2003). Thus, despite not being a diagnostic requirement in DSM IV or ICD-10 criteria, clumsiness is a common characteristic of the autistic syndrome.

In order to gain a greater understanding of the nature of motor abnormalities in individuals with AS in particular, a number of studies that have assessed motor function in this patient population are now considered.

A study by Ghaziuddin et al. (1994) found that all eleven children with AS who participated in their study performed abnormally poorly on at least one measure of motor performance (gross motor, fine motor or upper limb co-ordination) as measured by the Bruininks-Oseretsky test (Bruininks, 1978), and that eight of these children performed abnormally poorly on all three measures of this test. In addition, a study by Klin et al. (1995) found that patients with AS had deficits in both fine and gross motor actions. However these investigators included clumsiness and a delay in attaining motor milestones as selection criteria, thereby biasing their study group towards having motor problems (Green et al. 2002).

A study with a less biased group of patients with AS was carried out by Manjiviona and Pryor (1995) who found that patients with AS performed poorly on the Test of Motor Impairment (Stott et al. 1984). In addition, patients with AS have been found to be impaired on the Movement ABC (Henderson and Sugden, 1992), a test of motor abilities and motor development difficulties (Miyahara et al., 1997; Miller and Ozonoff, 2000; Green et al., 2002).

Despite all this evidence for the presence of motor abnormalities in AS, Weimer et al. (2001) have shown that individuals with AS are not impaired on all tests of motor function. Weimer et al. (2001) found that although their patients with AS were impaired on tests of apraxia, finger-thumb opposition, tandem gait, and balancing on one leg with eyes closed, they did not perform significantly more poorly than controls on the Grooved Pegboard or on tests of finger tapping. This indicates that patients with AS may have selective motor difficulties, and emphasizes the need for further studies to investigate the precise nature of the movement abnormalities in this disorder.

To summarize, movement abnormalities including clumsiness, poor fine motor co-ordination and lack of fluency in gross motor actions are common features of AS. However, these are not necessarily present in all individuals with a diagnosis of AS as movement abnormalities are not included as diagnostic criteria in either ICD-10 or DSM IV.

3.3 Methods

3.3.1 Motor tests administered

The particular motor tests included in this study were selected to tap a whole range of motor functions including simple and complex fine motor action, bi-manual co-ordination, and motor learning, in order to gain an understanding of the pattern of intact and impaired motor functions that are associated with different types of cerebellar damage. The ordering of the tests was such that it was possible to determine whether participants were able to perform simple uni-manual motor actions and then bi-manual motor actions, and finally at tasks that depend not only on intact motoric ability, but also the ability to learn new motor actions. Thus tests of basic motor actions were first administered and then the tests were built up on the basis of the level of complexity in order to investigate the precise nature of any motor problems in either of the patient populations. The methods and results for each test are presented in this same hierarchical order.

(i) Uni-manual motor function:

The first test administered was the Annett Pegboard which is a simple test of uni-manual motor action. This test examines the ability to place pegs in circular holes as quickly as possible with both the dominant and then the non-dominant hand and is a good measure of basic fine motor skill. The Annett Pegboard was chosen because it is a simple motor task which is suitable for the entire age range of the participants taking part in the study and because it would provide a good baseline of motor skill ability in each of the patient groups from which to build on more complex motor skills. Furthermore, this test was initially designed by Annett to quantify motor deficits in hemiplegic children, and this test should therefore also reveal any differences in fine motor ability between the patients with PFT with tumours in the right versus the left cerebellar hemisphere.

The second test administered was the Grooved Pegboard. This test builds upon the skills required in the Annett Pegboard as the pegs and holes are shaped so that the pegs must be placed in the correct orientation in order to fit them into the holes. Thus, compared to the Annett Pegboard, this task requires a higher level of uni-manual fine motor dexterity. The Grooved Pegboard was chosen because there is evidence that the cerebellum is involved in

fine motor actions. Furthermore, if subjects succeeded on the simple Annett Pegboard task, but had problems with the Grooved Pegboard, it would demonstrate that certain individuals had particular problems with intricate fine motor actions, not simply with all aspects of fine motor actions. Both the Annett Pegboard and the Grooved Pegboard also have a timing element to them as they depend on the accurate timing of motor actions in order to successfully slot the pegs into the pegboards.

The third test of manual motor function administered here was the posting task. This is a test of motor control which depends on more gross movements of the hand and arm and particularly on the ability to correctly orient the hand and wrist in order to post cards through a slot positioned at various different angles. This task was included in order to assess whether motor control of the hand, wrist and arm is impaired in either of the patient populations and also to investigate whether the patients had difficulties with the gross movements required here.

(ii) Bi-manual motor function:

Two tests were administered to examine bi-manual motor function: the bead threading task and the tapping task. The bead threading task was used to assess bi-manual fine motor action and co-ordination, as subjects had to thread different shaped and sized beads onto a piece of thread which they held with their other hand. Thus, similar fine motor actions of the hand and fingers as required in the pegboard tasks are needed here; however attention must also be paid to the other hand holding and directing the thread. This task was used in order to assess bi-manual co-ordination abilities for fine motor actions.

The second bi-manual task was the tapping task. In this task, participants are required to use a stylus to tap sequentially in four quadrants of a circle, first using each hand separately and then using both hands simultaneously. This task assesses more gross movements of the hand and arm rather than fine motor actions of the fingers. It was hoped that by comparing performance on this task with performance on the posting task, it would be possible to determine whether individuals had general difficulties with movements of the hand and arm, or whether difficulties were related to whether uni- or bi-manual skills were required.

Furthermore, by comparing performance on the tapping task with performance on the bead threading task, it was hoped that it would be possible to determine whether individuals had more difficulties with fine-motor co-ordination abilities or with gross-motor co-ordination. Finally, by partialling out performance on uni-manual tapping, it would be possible to determine whether any difficulties on the bi-manual task could be explained by general difficulties with the task itself rather than with bi-manual co-ordination per se.

(iii) Motor learning:

The final two tests of motor function were the mirror tracing and rotary pursuit tasks, which are used to assess motor learning abilities. The cerebellum has long been known to be involved in motor learning (Marr, 1969; Jenkins and Frackowiak, 1993; Schweighofer et al. 1998) and these tests were administered in order to investigate the extent to which individuals with different types of cerebellar damage would have difficulties with motor learning. The rotary pursuit task is more simple than the mirror tracing. In the rotary pursuit, participants are simply required to learn new gross motor actions of the hand and arm (large circular movements as they follow a light stimulus around a turntable). For the mirror tracing, participants have to learn to mirror transpose their movements – they can only see their hand in a mirror and thus the directions of motion are all reversed. The movements required in the mirror tracing are smaller and more precise than those in the rotary pursuit – for the mirror tracing, a pen-shaped stylus is held in the hand and participants are required to trace a star. By partialling out performance on the simple fine and gross-motor tasks detailed above, it should be possible to determine whether any difficulties on these tasks are due to problems with manual motor function or with motor learning in particular. It is likely that the neocerebellum (lateral regions of the cerebellar hemispheres) is particularly involved in these two tests of motor learning. This is based on a functional imaging study carried out by Jueptner and Weiller (1998), who found that the neocerebellum was particularly involved in the monitoring of movement outcomes and the associated correction or optimization of movements on the basis of sensory feedback information. In order to perform well on both the mirror tracing and rotary pursuit tasks, it is necessary to be able to adapt movements on the basis of sensory (particularly visual) feedback and thereby improve accuracy, thus demonstrating motor learning.

3.3.2 Aims and predictions

On the basis of previous studies of patients with PFT, of patients with AS and of cerebellar function, the hypotheses for the motor abilities of each of the two patient groups are as follows:

(i) Patients with PFT

Given the extent to which the cerebellum is known to be involved in motor actions, it is predicted that patients with PFT who have had sections of the cerebellum removed will have difficulties with a wide variety of motor functions. Furthermore, the results of the developmental questionnaire (see Chapter 2) showed that patients with PFT had difficulties with writing, climbing, catching, kicking, hopping on one leg, doing up buttons, tying shoe laces and clumsiness, indicating that there are a variety of motor difficulties in this patient population. The particular predictions for the motor tests included in this study are as follows:

- **Annett Pegboard and Grooved Pegboard (tests of fine motor action):** Patients with PFT have been shown to have difficulties with fine motor actions (Levisohn et al., 2000) and the cerebellum has been implicated in the timing of motor actions (Ivry et al., 1988; Akshoomoff and Couchesne, 1992; Bengtsson et al., 2004). It is therefore predicted that the patients with PFT will be found to be impaired on the Annett Pegboard and the Grooved Pegboard.
- **Posting task (test of motor control and of gross motor action of the hand and arm):** This test particularly assesses motor control (the ability to accurately post cards through a slot) and depends on gross movements of the hand and arm and fine movements of the wrist. The cerebellum has been implicated in motor control (Ellerman, et al., 1994; Braitenberg et al., 1997) and in accurate orientation of the wrist (Glickstein et al., 1998) and it is therefore predicted that patients with PFT will perform more poorly than controls on the posting task.
- **Bead threading and the Tapping task (tests of bi-manual motor action):** There is evidence to show that the cerebellum is involved in the co-ordination of movement (Miall et al., 2000; Miall et al. 2001; Debaere et al. 2004) and it is

therefore predicted that patients with PFT will be impaired on the bead threading and tapping tasks as these require co-ordinated movements of the two hands.

- **Mirror tracing and rotary pursuit (tests of motor learning):** The cerebellum has been particularly implicated in motor learning (Marr, 1969; Jenkins and Frackowiak, 1993; Schweighofer et al. 1998) and previous studies have shown that the mirror tracing task is cerebellar dependent (Sanes et al., 1990; Laforce and Doyon, 2002). It is therefore predicted that patients with PFT will perform significantly more poorly than controls on the two tests of motor learning (mirror tracing and rotary pursuit).

• Previous research has shown that damage to lateral regions of the cerebellum is associated with a reduction in the speed of arm movements (Immisch et al. 2003). It is therefore predicted that patients with pathology of the cerebellar hemispheres will perform more poorly than patients with midline pathology on the timed tests of uni-manual and bi-manual motor action which depend on fast movement of the hand and arm (the Annett Pegboard, the Grooved Pegboard, the posting task, the bead threading task and the tapping task). Damage to midline cerebellum, on the other hand, has been found to be associated with a deficit in motion perception (Nawrot and Rizzo, 1995; 1998). It is therefore predicted that patients with midline pathology will perform more poorly than patients with pathology of the cerebellar hemispheres on the rotary pursuit task as this depends on motion perception of the light stimulus. Furthermore, previous research has shown that the anterior lobe (lobules I-V) is particularly involved in motor function. It would therefore be predicted that individuals with pathology affecting these lobules would have particular difficulties with motor actions. This possibility will be further investigated in Chapter 5 where the particular location of the pathology in each individual patient with PFT is detailed.

• There will be greater recovery of motor function after early (age five and younger) compared to late (age six and above) lesions of the posterior fossa, reflecting the higher level of plasticity of the brain at younger ages.

• There will be very few significant correlations between time since surgery and performance on any of the motor tests. This is because all of the patients with PFT who are

taking part in this study are seen at least two years post-surgery and it is predicted that after this time there will be no more major compensatory changes in the brain.

(ii) Patients with AS

The abnormalities in the cerebellum in individuals with AS are more subtle and less localized than those in individuals with PFT. There is evidence to suggest that individuals with AS have a variety of motor problems and these may be associated with their cerebellar abnormalities (Allen and Courchesne, 2003). Furthermore, the results of the developmental questionnaire showed that patients with AS had difficulties with a wide variety of motor actions including writing, climbing, catching, kicking, hopping on one leg, doing up buttons, tying shoe laces, and clumsiness. It is important to note, however, that previous studies have shown that individuals with AS do not have difficulties with all types of movement (Weimer et al., 2001) and it is therefore predicted that there will not be significant group differences between patients with AS and controls for every test of motor function administered here. The particular predictions for the motor tests included in this study are as follows:

- **Annett Pegboard and Grooved Pegboard (tests of fine motor action):** Previous research has shown that patients with AS have problems with fine motor actions (Ghaziuddin et al. 1994; Klin et al. 1995) and it is therefore predicted that patients with AS will be found to have difficulties with the Annett Pegboard which tests simple fine motor skills. For the Grooved Pegboard, however, although individuals with autism have been found to be impaired on this test (Hardan et al. 2003), a study of individuals with AS found that they did not perform significantly more poorly than controls on the Grooved Pegboard (Weimer et al. 2001). This indicates that the particular fine motor abilities required for the Grooved Pegboard may be intact in individuals with AS and it is therefore predicted that in the current study, patients with AS will not be found to be impaired on the Grooved Pegboard.
- **Posting task (test of motor control and of gross motor action of the hand and arm):** Clumsiness is very common in autism and AS, suggesting problems with gross motor actions of the limbs and body. Furthermore, a number of studies have investigated gross motor actions and found that patients with AS are impaired on

these actions compared to controls (Ghaziuddin et al. 1994; Klin et al. 1995). For these reasons, it is predicted that patients with AS will be found to perform more poorly than controls on the posting task.

- **Bead threading and the Tapping task (tests of bi-manual motor action):** Because of the problems with motor co-ordination manifested in the form of clumsiness in individuals with AS, it is predicted that patients with AS will perform more poorly than controls on both the bead threading and the tapping task which require the co-ordination of motor actions between the right and left hands.
- **Mirror tracing and rotary pursuit (tests of motor learning):** Previous research has found no difference between the performance of individuals with autism and control participants on the rotary pursuit task (Wek and Husak, 1989), indicating that individuals with autism are not impaired on motor learning. It is therefore predicted that patients with AS will not be found to perform significantly worse than controls on either of the tests of motor learning administered here (the mirror tracing and the rotary pursuit tasks).

3.3.3 Statistical analyses

The main statistical methods employed in this study were detailed in Section 2.2.3. However, it was decided that in order to increase the effects of this study, because of the small number of participants, the control groups would be combined for the motor tasks after determining that there were no significant correlations between FIQ, VIQ or PIQ and any of the measures of manual motor skill or motor learning for either of the control groups. Statistical analysis was carried out separately for each of the two patient groups and the combined control group using independent sample t-tests. In addition, ANCOVA analyses were carried out with age as a covariate in order to determine whether the age of the participants had any effect on the results.

ANOVAs were carried out in order to investigate whether there were any within-group differences in the patients with PFT related to the location of the tumour (left hemisphere, right hemisphere or midline tumour) and in order to determine whether there were any effects of age at pathology or time since pathology, correlation analyses (Pearson's) were

carried out separately between each of these measures and each of the measures of motor function.

For the tests which were carried out for both the dominant and non-dominant hand (the Annett pegboard, the Grooved Pegboard, simple and sequential tapping and the posting task), mixed-model analyses (repeated measure ANOVAs) were carried out in addition to the independent sample t-tests, in order to investigate whether there was a similar level of performance between the two hands for patients and controls. In this way, it was possible to determine whether each of the patient groups showed a similar degree of enhanced performance with their dominant hand compared to their non-dominant hand as that which is characteristic of normal controls. In these analyses, the presence or absence of injury (i.e. patient or control) and location of tumour (left hemisphere, right hemisphere or midline pathology) were entered as the between-subject factors, and hand (dominant and non-dominant) was entered as the within-subjects factor.

The two tests of motor learning (mirror tracing and rotary pursuit) involved time-series data over repeated trials and it was therefore necessary to analyse these tests using different methods from those described in Chapter 2. For both of these tests, the learning trajectory for each individual was first plotted separately from the raw scores. In order to minimize any effects of measurement error and noise, linear, logarithmic and quadratic curves were then fitted to each individual learning trajectory. After visual inspection, the function that best captured the learning of each individual was used to obtain summary statistics (predicted scores). The predicted scores and the raw scores were then used separately in order to derive a number of measures of learning (see Section 3.4.3) and these measures were used to compare the motor learning performance of the patient groups with their controls using independent sample t-tests. This method of using summary measures is a standard approach to analyzing time-series data (Matthews et al. 1990).

As explained in Section 2.2.3, multiple comparison adjustment was not performed in this thesis. Instead a cut-off of $p<0.05$ was chosen as a mechanism for flagging potential problematic motor functions in the patient groups which will require further investigation in future studies. Any significant findings at this level (p-values <0.05) will be interpreted

with caution and where there were strong expectations of effects, p values in the range 0.05 - 0.1 will also be commented upon (these will be referred to as weak evidence for an effect).

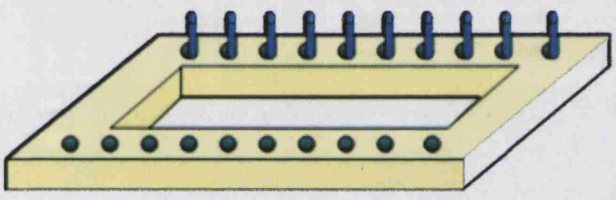
3.4 Results

3.4.1 Tests of uni-manual motor action

3.4.1.1 Annett Pegboard

This is a test of fine motor action of the hands and fingers, but it also depends on smooth execution of arm movements. The pegboard was devised by Annett (1970) and consists of two parallel rows of ten circular holes at a distance of 20cm from one another (see Figure 3.1). In one of the rows, each hole is filled with a cylindrical peg and subjects are required to move each of these ten pegs one by one, using only their dominant hand, from the top row to the bottom row as fast as possible. This is then repeated with the non-dominant hand and then four more times with each hand so that the task is repeated a total of five times with each hand. The mean of these five times is then calculated for each hand.

Figure 3.1: Annett pegboard and pegs



(i) Patients with PFT: Annett Pegboard

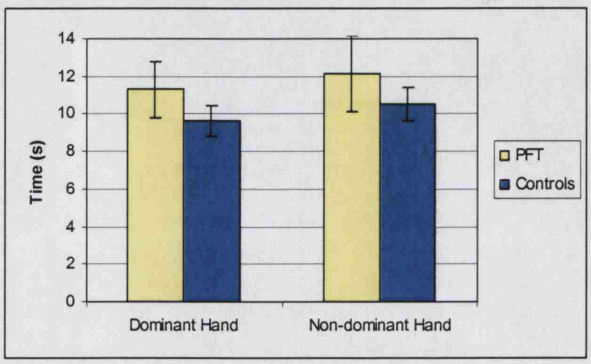
Table 3.1 and Figure 3.2 show the mean time (in seconds) taken to move ten pegs from the top row to the bottom row on the Annett Pegboard by patients with PFT and controls.

Table 3.1: Mean time taken for the Annett Pegboard by patients with PFT and controls

Group	Dominant Hand	Non-dominant hand
PFT	11.31 (1.51)	12.15 (2.02)
Controls	9.62 (0.78)	10.52 (0.88)

Mean (sd)

Figure 3.2: Mean time taken for the Annett Pegboard by patients with PFT and controls



Patients with PFT performed significantly more poorly than controls on the Annett Pegboard. They took longer to complete the task with both the dominant and the non-dominant hand: dominant hand (Mann Whitney-U test: $z = -3.584$, $p < 0.001$; ANCOVA with age $F(1,35) = 17.714$, $p < 0.001$), non-dominant hand (Mann Whitney-U test: $z = -3.000$, $p = 0.003$; ANCOVA with age $F(1,35) = 11.057$, $p = 0.002$).

There was no significant difference between patients with PFT and controls in the relative level of performance between the dominant and the non-dominant hand on the Annett pegboard (repeated measure ANOVA $F(1,33) = 0.013$, $p = 0.909$).

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed a significant interaction between performance on the Annett Pegboard dominant hand and location of tumour ($F(2,14) = 6.364$, $p = 0.013$). The mean scores for each of the groups with PFT on the Annett Pegboard dominant hand are shown in Table 3.2 below.

Table 3.2: Mean scores on the Annett Pegboard dominant hand for the groups with PFT

Group	Dominant Hand
LH damage	10.00 (0.51)
Midline damage	12.56 (1.54)
RH damage	11.38 (1.12)

Mean (sd)

Individuals with midline damage performed most poorly and those with left hemisphere damage performed best on this task. Post hoc analysis showed that there was a significant difference between those with left hemisphere damage and those with midline damage ($p = 0.010$).

There was no significant difference between the different tumour location subgroups in the relative level of performance between the dominant and the non-dominant hand on the Annett pegboard (repeated measure ANOVA $F(1,12) = 0.008$, $p = 0.992$).

(ii) Patients with AS: Annett Pegboard

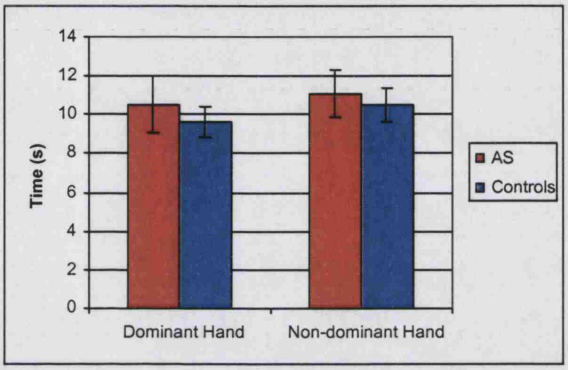
Table 3.3 and Figure 3.3 show the mean time (in seconds) taken to move ten pegs from the top row to the bottom row on the Annett Pegboard by patients with AS and controls.

Table 3.3: Mean time taken for the Annett Pegboard by patients with AS and controls

Group	Dominant Hand	Non-dominant Hand
AS	10.53 (1.45)	11.08 (1.25)
Controls	9.62 (0.78)	10.52 (0.88)

Mean (sd)

Figure 3.3: Mean time taken for the Annett Pegboard by patients with AS and controls



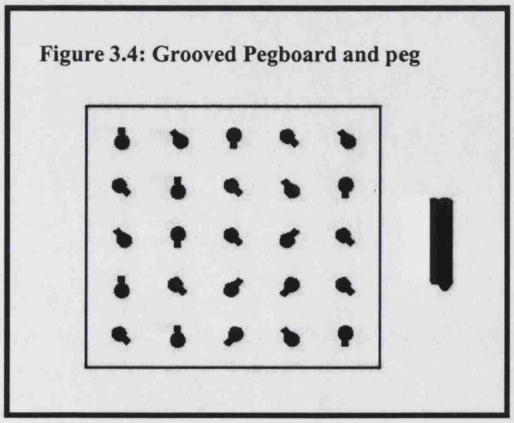
Statistical analysis showed that patients with AS were significantly slower than controls to complete the Annett pegboard with the dominant hand ($t = 2.363$, $df = 32$, $p = 0.024$; ANCOVA with age $F(1,34) = 5.299$, $p = 0.028$). However, there was no significant difference between patients with AS and controls for the non-dominant hand ($t = 1.518$, $df = 32$, $p = 0.139$; ANCOVA with age $F(1,34) = 2.086$, $p = 0.159$).

There was no significant difference between patients with AS and controls in the relative level of performance between the dominant and the non-dominant hand on the Annett pegboard (repeated measure ANOVA $F(1,32) = 1.662$, $p = 0.207$).

3.4.1.2 Grooved Pegboard

The Grooved Pegboard is a test of manipulative dexterity. The pegboard (produced by Lafayette Instruments) consists of five rows of five "grooved" holes with the slots positioned at random angles (see Figure 3.4). The pegs are the same shape as the holes, with a round side and a square side so that it is necessary to rotate each peg to the appropriate orientation before it can be inserted into the hole. Subjects are

Figure 3.4: Grooved Pegboard and peg



required to start at the top row and place a peg in each of the holes in the correct sequence as fast as possible using only the dominant hand (and then only the non-dominant hand on the next trial), until all 25 holes are full. The test thus requires more accurate fine movements of the fingers and more complex visuo-motor co-ordination than the Annett Pegboard. The test is repeated twice with each hand and the mean is calculated for each hand separately.

(i) Patients with PFT: Grooved Pegboard

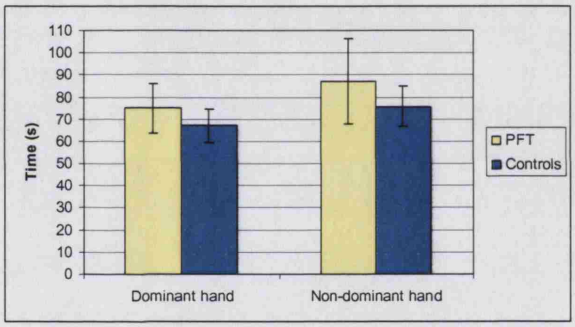
Table 3.4 and Figure 3.5 show the mean time (in seconds) taken to complete the Grooved Pegboard by patients with PFT and controls.

Table 3.4: Mean time taken for the Grooved Pegboard by patients with PFT and controls

Group	Dominant Hand	Non-dominant Hand
PFT	74.87 (11.17)	87.09 (19.21)
Controls	67.05 (7.48)	75.66 (9.17)

Mean (sd)

Figure 3.5: Mean time taken for the Grooved Pegboard by patients with PFT and controls



Statistical analysis showed that patients with PFT were significantly slower than controls to complete the Grooved Pegboard with the dominant hand ($t = 2.481$, $df = 33$, $p = 0.018$; ANCOVA with age $F(1, 35) = 5.462$, $p = 0.026$). However there was no significant difference between patients with PFT and controls for the non-dominant hand (Mann Whitney-U test: $z = -1.617$ $p = 0.106$; although this did reach significance after age was co-varied: ANCOVA with age $F(1,35) = 5.178$, $p = 0.030$).

In order to investigate whether the difficulties encountered by patients with PFT were due to difficulties with simple fine motor tasks or whether they were particularly associated with the intricacy of the movements needed to complete the Grooved Pegboard, performance on the Annett Pegboard (a simple test of fine motor action) was partialled out in an ANCOVA. The results showed no significant difference between the performance of patients with PFT and their controls on the Grooved Pegboard: dominant hand (ANCOVA

with Annett Pegboard dominant hand $F(1,35) = 0.153$, $p = 0.698$); non-dominant hand (ANCOVA with Annett Pegboard non-dominant hand $F(1,35) = 0.000$, $p = 0.989$). This suggests that the difficulties on the Grooved Pegboard are likely to reflect difficulties with fine motor actions in general.

There was no significant difference between patients with PFT and controls in the relative level of performance between the dominant and the non-dominant hand on the Grooved Pegboard (repeated measure ANOVA $F(1,33) = 0.569$, $p = 0.456$).

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the Grooved Pegboard task. In addition, there was no significant difference between the different tumour location subgroups in the relative level of performance between the dominant and the non-dominant hand on the Grooved Pegboard (repeated measure ANOVA $F(1,12) = 0.073$, $p = 0.930$).

(ii) Patients with AS: Grooved Pegboard

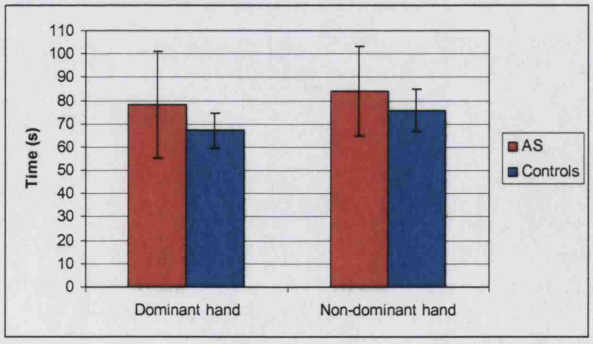
Table 3.5 and Figure 3.6 show the mean time (in seconds) taken to complete the Grooved Pegboard by patients with AS and controls.

Table 3.5: Mean time taken for the Grooved Pegboard by patients with AS and controls

Group	Dominant Hand	Non-dominant Hand
AS	78.07 (22.94)	83.81 (19.39)
Controls	67.05 (7.48)	75.66 (9.17)

Mean (sd)

Figure 3.6: Mean time taken for the Grooved Pegboard by patients with AS and controls



Statistical analysis showed that there was no significant difference between the performance of patients with AS and controls on the Grooved Pegboard with the dominant

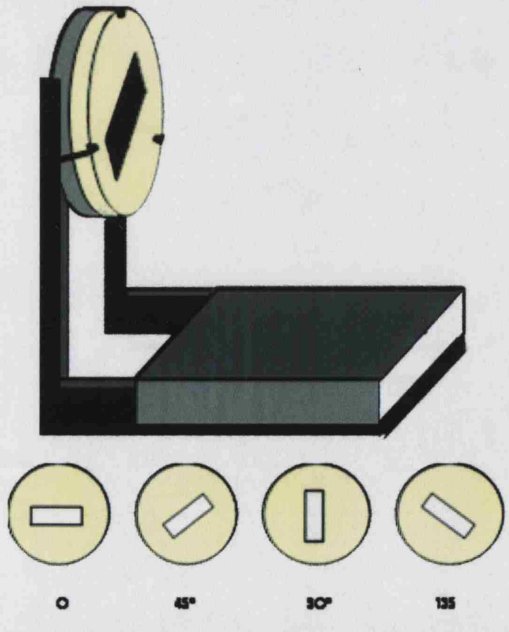
hand (Mann Whitney U-test z = -1.190, p = 0.234, although there was weak evidence for a significant difference when age was co-varied: ANCOVA with age F(1,34) = 3.828, p = 0.059), and no significant difference for the non-dominant hand (Mann Whitney U-test z = -1.347, p = 0.178, ANCOVA with age F(1,34) = 2.621, p = 0.116).

There was no significant difference between patients with AS and controls in the relative level of performance between the dominant and the non-dominant hand on the Grooved Pegboard (repeated measure ANOVA F(1,32) = 1.119, p = 0.298).

3.4.1.3 Posting task

This test examines visuo-spatial judgement as well as visuo-motor function (in terms of the ability to position the hand at specific orientations). The task is based on the posting task designed by Milner et al. (1991) and used on the famous amnesic patient HM. The apparatus (shown in Figure 3.7) consists of a circular piece of wood, 250mm in diameter, with a rectangular slot cut in the centre measuring 125mm by 40mm. This is mounted on two pieces of wood to a height of 300mm. The circular section can be turned freely. Subjects are required to post 10 cards measuring 80mm by 80mm one at a time as fast as possible using only one hand through the slot in the vertical circle. This slot can be positioned at an orientation of 0, 45, 90 and 135 degrees (see Figure 3.7), and for each of these variables, timings are obtained for posting the ten cards using only the dominant hand and for using only the non-dominant hand. The slot is then reduced in size by covering up the top three-quarters to make a slot measuring 125mm by 10mm and the posting task is repeated as outlined above. The task with the smaller slot tests more high-level visuo-spatial judgment and visuo-motor skills.

Figure 3.7: Posting task apparatus



(iii) Patients with PFT: Posting task

Tables 3.6 and 3.7 and Figure 3.8 show the results of the posting task for patients with PFT and their matched controls.

Table 3.6: Dominant hand full and quarter gaps:

	Group	0°	45°	90°	135°
FULL GAP	PFT	12.95 (1.60)	13.03 (2.49)	13.31 (2.35)	11.89 (1.74)
	Controls	10.81 (1.57)	10.58 (1.64)	11.73 (2.26)	10.42 (1.70)
QUARTER GAP	PFT	14.85 (1.99)	14.75 (2.22)	17.92 (4.50)	15.98 (2.56)
	Controls	12.68 (1.75)	12.32 (1.89)	14.29 (2.27)	13.48 (2.05)

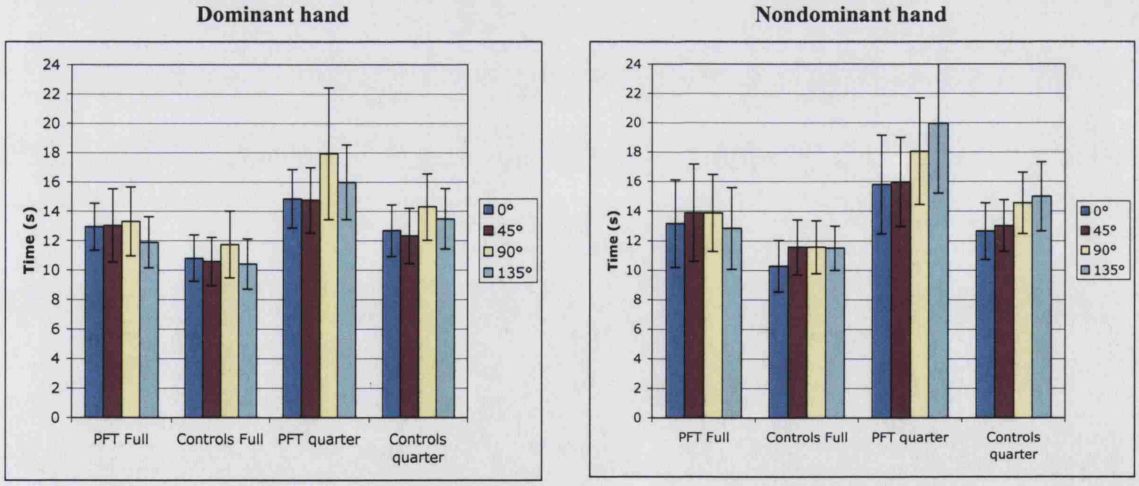
Mean (sd)

Table 3.7: Non-dominant hand full and quarter gaps:

	Group	0°	45°	90°	135°
FULL GAP	PFT	13.15 (2.97)	13.88 (3.30)	13.87 (2.61)	12.83 (2.77)
	Controls	10.27 (1.75)	11.55 (1.87)	11.56 (1.79)	11.49 (1.49)
QUARTER GAP	PFT	15.80 (3.36)	15.97 (3.05)	18.06 (3.61)	19.95 (4.74)
	Controls	12.63 (1.92)	13.01 (1.75)	14.55 (2.07)	14.99 (2.35)

Mean (sd)

Figure 3.8: Mean scores on the posting task for patients with PFT and their controls for the dominant and non-dominant hands



Statistical analysis showed that patients with PFT were significantly slower than their matched controls on all of the posting task trials except for dominant hand 90 degrees full

gap and non-dominant hand 135 degrees full gap, for which there was weak evidence for a significant difference (see Table 3.8).

Table 3.8: P-values for independent sample t-tests between patients with PFT and controls on the posting task

	Dominant hand				Non-dominant hand			
	0°	45°	90°	135°	0°	45°	90°	135°
FULL GAP	0.000	0.001	0.056	0.020	0.001	0.013	0.004	0.078
QUARTER GAP	0.002	0.002	0.004	0.003	0.001	0.001	0.001	0.000

ANCOVA analyses showed that there was no effect of age at testing for any of the trials (see Table 3.9).

Table 3.9: P-values for ANCOVA with age for patients with PFT and controls on the posting task

	Dominant hand				Non-dominant hand			
	0°	45°	90°	135°	0°	45°	90°	135°
FULL GAP	0.001	0.003	0.088	0.028	0.002	0.018	0.007	0.059
QUARTER GAP	0.004	0.003	0.003	0.006	0.001	0.002	0.001	0.001

Analyses with repeated measure ANOVA showed that there was no significant difference between patients with PFT and controls in the relative level of performance between the dominant and the non-dominant hand on any of the posting task trials.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed a significant interaction between performance on the posting task and location of tumour ($F(2,11) = 7.695$, $p = 0.008$). Patients with left hemisphere damage performed best on all of the posting task trials. Patients with midline and those with right hemisphere damage performed at similar levels. Post hoc analysis showed significant differences between the mean scores of patients with left hemisphere and those with midline damage ($p = 0.010$) and between those with left hemisphere and those with right hemisphere damage ($p = 0.028$). It should be noted that the assumptions for equality of variance were violated for two conditions (full gap non-dominant 135 degrees and quarter gap non-dominant 45 degrees), even after log transformation, and these results should therefore be interpreted with caution.

Analyses with repeated measure ANOVA showed that there was no significant difference between the tumour location subgroups in the relative level of performance between the dominant and the non-dominant hand on any of the posting task trials.

In order to determine whether the patients with PFT had significantly more problems with the quarter gap than the controls relative to performance on the full gap task, t-tests were carried out on the percentage increase in time taken to post the cards in the quarter gap task compared to the full gap task. The results showed that the only trial where patients with PFT were significantly slower was for the non-dominant hand at 135 degrees ($t = 2.881$, $df = 32$, $p = 0.007$). They were not significantly faster on any of the trials. The non-dominant hand 135 degrees is a particularly difficult angle at which to orient the hand and arm and it is therefore not surprising that patients with PFT had particular problems with this trial when the posting gap was small.

(iv) Patients with AS: Posting task

Tables 3.10 and 3.11 and Figure 3.9 show the results of the posting task for patients with AS and their matched controls.

Table 3.10: Dominant hand full and quarter gaps:

	Group	0°	45°	90°	135°
FULL GAP	AS	14.82 (4.24)	12.84 (2.94)	14.59 (4.45)	12.67 (2.71)
	Controls	10.81 (1.57)	10.58 (1.64)	11.73 (2.26)	10.42 (1.70)
QUARTER GAP	AS	15.09 (3.49)	14.89 (4.53)	18.99 (4.93)	15.79 (4.49)
	Controls	12.68 (1.75)	12.32 (1.89)	14.29 (2.27)	13.48 (2.05)

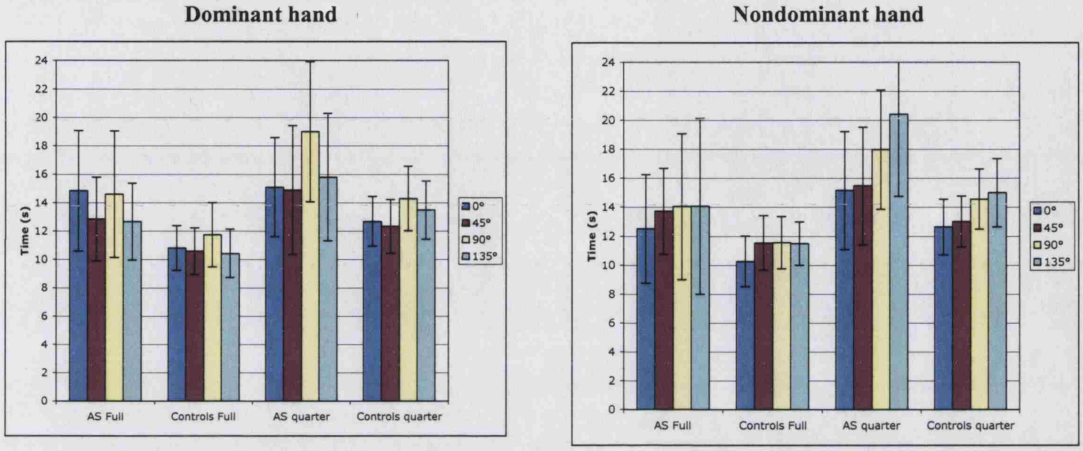
Mean (sd)

Table 3.11: Non-dominant hand full and quarter gaps:

	Group	0°	45°	90°	135°
FULL GAP	AS	12.51 (3.74)	13.72 (2.95)	14.04 (5.03)	14.06 (6.07)
	Controls	10.27 (1.75)	11.55 (1.87)	11.56 (1.79)	11.49 (1.49)
QUARTER GAP	AS	15.15 (4.07)	15.47 (4.05)	17.97 (4.12)	20.41 (5.66)
	Controls	12.63 (1.92)	13.01 (1.75)	14.55 (2.07)	14.99 (2.35)

Mean (sd)

Figure 3.9: Mean scores on the posting task for patients with AS and their controls for the dominant and non-dominant hands



Statistical analysis showed that patients with AS were significantly slower than their matched controls on all of the posting task trials except for the non-dominant hand 135 degrees full gap and the dominant hand 135 degrees quarter gap for which there was weak evidence for a significant difference (see Table 3.12).

Table 3.12: P-values for independent sample t-tests between patients with AS and controls on the posting task

	Dominant hand				Non-dominant hand			
	0°	45°	90°	135°	0°	45°	90°	135°
FULL GAP	0.000	0.007	0.019	0.006	0.025	0.013	0.049	0.078
QUARTER GAP	0.012	0.029	0.001	0.051	0.021	0.021	0.003	0.001

ANCOVA analyses indicated that there was an effect of age for non-dominant hand 90 degrees full gap and dominant hand 135 degrees quarter gap as the difference between patients with AS and controls was not significant for these two trials after age was co-varied (see Table 3.13).

Table 3.13: P-values for ANCOVA with age for patients with AS and controls on the posting task

	Dominant hand				Non-dominant hand			
	0°	45°	90°	135°	0°	45°	90°	135°
FULL GAP	0.001	0.009	0.023	0.007	0.028	0.012	0.057	0.089
QUARTER GAP	0.015	0.035	0.001	0.059	0.023	0.025	0.004	0.001

Analyses with repeated measure ANOVA showed that there was no significant difference between patients with AS and controls in the relative level of performance between the dominant and the non-dominant hand on any of the posting task trials.

In order to determine whether the patients with AS had significantly more problems with the quarter gap than the controls relative to performance on the full gap task, t-tests were carried out on the percentage increase in time taken to post the cards in the quarter gap task compared to the full gap task. The results showed that the only trials where patients with AS showed a significant difference was for the dominant hand at 0 degrees ($t = -2.176$, $df = 32$, $p = 0.037$) and for the non-dominant hand at 135 degrees ($t = 2.588$, $df = 32$, $p = 0.014$). It is important to note that given the large number of statistical tests carried out here, there is a high probability that these findings may be false positives.

3.4.2 Tests of bi-manual motor action

3.4.2.1 Bead Threading

The bead threading task is a bi-manual task used to look at fine motor abilities of the hands and fingers. Participants are given a thread (a length of thin leather) to hold in their dominant hand and are told that they will be required to thread a number of beads onto this thread as fast as possible using their non-dominant hand. The different shapes of the beads used in this task are shown in Figure 3.10. There are five different conditions, each of which requires 15 beads to be threaded and the score for each condition is the time (in seconds) taken to thread 15 beads.

Figure 3.10: Beads used in the bead-threading task

a) Round b) Tube-shaped c) Disc-shaped

(i) In the first condition, a small plastic container is placed in front of the participant. This bowl contains 15 identical round blue beads with a radius of approximately 7mm which must be threaded as fast as possible.

(ii) In the second condition, the plastic container contains eight round blue beads and seven round green beads and subjects are asked to thread these alternately, starting with a blue bead.

(iii) In the third condition, there are five flat blue circular disc beads, five blue tube-shaped beads and five blue ball-shaped beads which subjects must thread in the following order: disc then tube then ball.

(iv) The fourth condition is designed to be more cognitively taxing. Here four identical plastic bowls are placed in a row in front of the subject. The first bowl contains blue discs, the second contains blue tubes, the third contains blue circles and the fourth contains green circles. Subjects are told to thread one from the first bowl (blue discs), two from the second (blue tubes), three from the third (blue circles) and then one from the fourth (green circles), two from the first one (blue discs), three from the next one (blue tubes), one from the next one (blue circles) and so on until they are asked to stop (when a total of 15 beads have been threaded).

(v) In the fifth and final condition, subjects are presented with 15 tiny blue beads (with a radius of approximately 2mm) to thread as quickly as they can.

For all these five conditions, a sample thread is placed in front of the subjects that they can refer to at any time – this is to ensure that the task is not tapping short-term memory.

(i) Patients with PFT: Bead threading

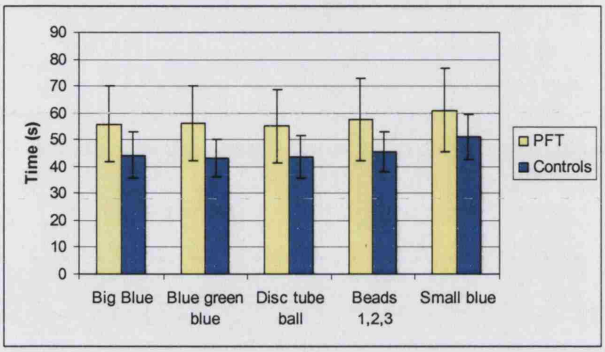
Table 3.14 and Figure 3.11 show the mean time (in seconds) taken for each of the conditions of the bead threading task for patients with PFT and controls.

Table 3.14: Mean time (in seconds) taken for each of the conditions of the bead threading task for patients with PFT and controls

Group	Big Blue beads	Blue green blue beads	Disc tube ball beads	Beads 1,2,3	Small blue beads
PFT	55.88 (14.11)	56.07 (13.91)	55.05 (13.82)	57.43 (15.31)	60.96 (15.42)
Controls	44.29 (8.44)	43.04 (7.03)	43.63 (7.94)	45.51 (7.57)	50.88 (8.35)

Mean (sd)

Figure 3.11: Mean scores on the bead threading task for patients with PFT and controls



Statistical analysis showed that patients with PFT performed significantly more poorly than their controls on all of the bead threading tasks: big blue beads (Mann Whitney-U test: $z = -2.900$, $p = 0.004$; ANCOVA with age $F(1,35) = 7.903$, $p = 0.008$), blue green blue beads (Mann Whitney-U test: $z = -3.601$, $p < 0.001$; ANCOVA with age $F(1,35) = 12.228$, $p = 0.001$), disc tube ball beads (Mann Whitney-U test: $z = -3.167$, $p = 0.002$; ANCOVA with age $F(1,35) = 8.237$, $p = 0.007$), beads 1,2,3 (after log transformation, $t = 3.080$, $df = 33$, $p = 0.004$; ANCOVA with age $F(1,35) = 7.970$, $p = 0.008$), small blue beads (after log transformation, $t = 2.432$, $df = 33$, $p = 0.021$; ANCOVA with age $F(1,35) = 5.245$, $p = 0.029$).

In order to investigate whether the difficulties encountered by patients with PFT on the bead threading task were due to difficulties with simple fine motor tasks or whether they were particularly associated with the bi-manual co-ordination needed to complete the task, performance on the Annett Pegboard (dominant hand) was partialled out in an ANCOVA. The results showed that when performance on the Annett Pegboard was partialled out, there was still a significant difference for blue green blue beads (ANCOVA with Annett Pegboard $F(1,35) = 4.708$, $p = 0.038$). However, there was only weak evidence for a significant difference for big blue beads (ANCOVA with Annett Pegboard $F(1,35) = 3.217$, $p = 0.082$); disc tube ball (ANCOVA with Annett Pegboard $F(1,35) = 4.098$, $p = 0.051$); and beads 1,2,3 (ANCOVA with Annett Pegboard $F(1,35) = 3.933$, $p = 0.056$); and there was no significant difference on small blue beads (ANCOVA with Annett Pegboard $F(1,35) = 1.144$, $p = 0.293$). These results indicate that although some of the difficulties on the bead threading task may be due to underlying difficulties with fine motor function, patients with PFT do appear to have some problems with the bi-manual co-ordination aspect as well.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed a significant interaction between performance on all measures of the bead threading task and location of

tumour: big blue ($F(2,12) = 5.651$, $p = 0.019$); blue green blue ($F(2,12) = 10.717$, $p = 0.002$); disc tube ball ($F(2.12) = 6.392$, $p = 0.013$); beads 1,2,3 ($F(2.12) = 7.772$, $p = 0.007$); and small blue ($F(2,12) = 5.938$, $p = 0.016$). The mean time (in seconds) taken for each of the conditions of the bead threading task for each of the groups with PFT are shown in Table 3.15 below.

Table 3.15: Mean time (in seconds) taken for each of the conditions of the bead threading task for groups with PFT

Group	Big blue	Blue green blue	Disc tube ball	Beads 1,2,3	Small blue
LH damage	46.95 (5.20)	46.21 (4.05)	48.57 (5.11)	49.42 (9.41)	49.80 (9.53)
Midline damage	51.67 (10.92)	50.97 (4.53)	47.97 (10.10)	49.72 (6.01)	58.06 (7.44)
RH damage	69.02 (14.57)	71.04 (14.35)	68.61 (13.99)	73.15 (15.26)	75.04 (16.49)

Mean (sd)

Patients with right hemisphere damage performed more poorly than the other two groups on all of the bead threading tasks, whereas patients with left hemisphere damage performed best on all but one (disc, tube, ball) of these tasks. Post hoc analysis showed significant differences between those with right hemisphere damage and those with left hemisphere damage for big blue beads ($p = 0.020$), blue green blue ($p = 0.002$), disc tube ball ($p = 0.025$), beads 1,2,3 ($p = 0.013$) and small blue beads ($p = 0.014$). Furthermore, there was a significant difference between those with right hemisphere damage and those with midline damage for blue green blue beads ($p = 0.011$), disc tube ball ($p = 0.022$) and beads 1,2,3 ($p = 0.014$) and weak evidence for a significant difference on big blue beads ($p = 0.066$) and small blue beads ($p = 0.099$). There was no significant difference between the performance of patients with left hemisphere damage and those with midline damage on any of the measures of bead threading.

(ii) Patients with AS: Bead threading

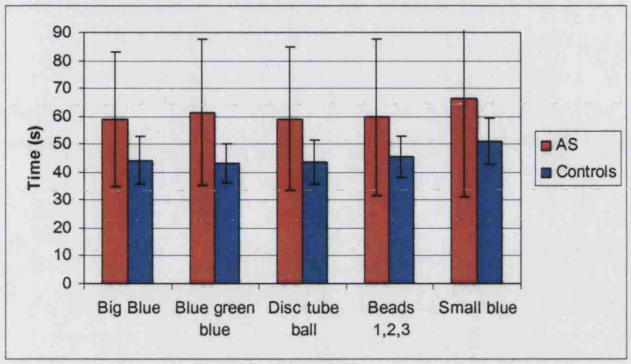
Table 3.16 and Figure 3.12 show the mean time (in seconds) taken for each of the conditions of the bead threading task for patients with AS and controls.

Table 3.16: Mean scores on the bead threading task for patients with AS and controls

Group	Big Blue beads	Blue green blue beads	Disc tube ball beads	Beads 1,2,3	Small blue beads
AS	58.94 (24.25)	61.36 (26.10)	59.00 (25.73)	59.75 (28.02)	66.33 (35.33)
Controls	44.29 (8.44)	43.04 (7.03)	43.63 (7.94)	45.51 (7.57)	50.88 (8.35)

Mean (sd)

Figure 3.12: Mean scores on the bead threading task for patients with AS and controls



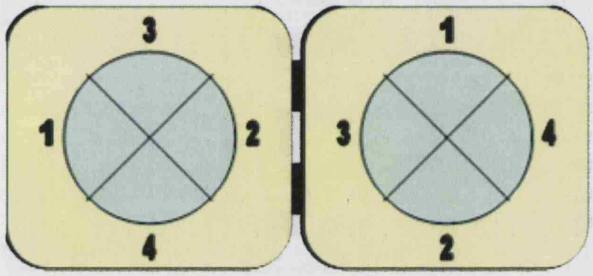
Statistical analysis showed that patients with AS performed significantly more poorly than their controls on all of the bead threading tasks: big blue beads (Mann Whitney U-test: $z = -2.695$, $p = 0.007$; ANCOVA with age $F(1,34) = 6.579$, $p = 0.015$), blue green blue beads (Mann Whitney U-test: $z = -3.080$, $p = 0.002$; ANCOVA with age $F(1,34) = 9.169$, $p = 0.005$), disc tube ball beads (Mann Whitney U-test: $z = -3.132$, $p = 0.002$; ANCOVA with age $F(1,34) = 6.607$, $p = 0.015$), beads 1,2,3 (Mann Whitney U-test: $z = -2.502$, $p = 0.012$; ANCOVA with age $F(1,34) = 4.814$, $p = 0.036$) and small blue beads (Mann Whitney U-test: $z = -2.205$, $p = 0.027$, when age is co-varied, there is only weak evidence for a significant difference: ANCOVA with age $F(1,34) = 3.494$, $p = 0.071$).

In order to investigate whether the difficulties encountered by patients with AS on the bead threading task were due to difficulties with simple fine motor tasks or whether they were particularly associated with the bi-manual co-ordination needed to complete the task, performance on a test of simple fine motor action (the Annett Pegboard dominant hand) was partialled out in an ANCOVA. The results showed that when performance on the Annett Pegboard was partialled out, there was no significant difference between the performance of the patients with AS and the controls: big blue beads (ANCOVA with Annett Pegboard $F(1,34) = 1.860$, $p = 0.182$); blue green blue beads (ANCOVA with Annett Pegboard $F(1,35) = 3.885$, $p = 0.058$); disc tube ball (ANCOVA with Annett Pegboard $F(1,35) = 2.330$, $p = 0.137$); beads 1,2,3 (ANCOVA with Annett Pegboard $F(1,35) = 1.630$, $p = 0.211$); small blue (ANCOVA with Annett Pegboard $F(1,35) = 1.139$, $p = 0.294$). These results indicate that the difficulties encountered by patients with AS on the bead threading task are mainly due to the fact that they have difficulties with fast and accurate fine motor actions, rather than that they have difficulties with the bi-manual co-ordination of these motor actions per se.

3.4.2.2 Uni-manual and bi-manual tapping

This is a tapping task used to look at uni- and bi-manual co-ordination abilities. The apparatus, which consists of two circular brass plates mounted on black plastic bases, is shown in Figure 3.13. Each brass plate has a diameter of 130mm and is divided into four quarters, each of which is numbered 1, 2, 3 or 4. Subjects are required to use a stylus to tap sequentially on these quarters, using first their dominant hand and then their non-dominant hand, as many times as possible in 30 seconds. Subjects are then asked to use both hands simultaneously, a task which requires a high level of bi-manual co-ordination skill as the numbers for the two sets of quadrants are in different positions. Subjects are then required to carry out the uni-manual tapping again once with the dominant and once with the non-dominant hand, and the mean for sequential tapping for each hand is calculated. The final part of this test is for subjects to tap on one quadrant as many times as they can with the stylus in 15 seconds with their dominant hand and then for 15 seconds with their non-dominant hand.

Figure 3.13: Apparatus for the Uni-manual and Bi-manual Tapping tasks



(i) Patients with PFT: Tapping task

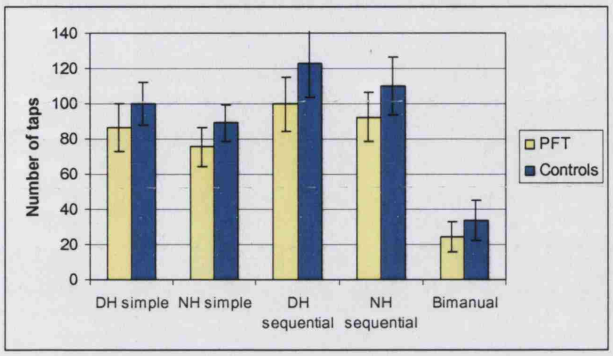
Table 3.17 and Figure 3.14 show the mean numbers of taps for each trial of the uni- and bi-manual tapping task for patients with PFT and controls.

Table 3.17: Mean number of taps for each trial of the tapping task for patients with PFT and controls

Group	Dominant Simple	Non-dominant Simple	Dominant Sequential	Non-dominant Sequential	Bi-manual
PFT	86.40 (13.79)	75.53 (11.05)	99.93 (15.41)	92.50 (14.21)	24.27 (8.87)
Controls	100.00 (12.34)	89.00 (10.18)	122.70 (19.35)	109.73 (16.40)	33.45 (11.47)

Mean (sd)

Figure 3.14: Mean number of taps for each trial of the tapping task for patients with PFT and controls



Statistical analysis showed that patients with PFT performed significantly more poorly than controls on all of the tapping tasks: dominant sequential tapping ($t = -3.748$, $df = 33$, $p = 0.001$; ANCOVA with age $F(1,35) = 13.707$, $p = 0.001$), non-dominant sequential tapping ($t = -3.252$, $df = 33$, $p = 0.003$; ANCOVA with age $F(1,35) = 9.857$, $p = 0.004$), bi-manual sequential tapping ($t = -2.573$, $df = 33$, $p = 0.015$; ANCOVA with age $F(1,35) = 5.744$, $p = 0.023$).

In order to further investigate the difficulties encountered by patients with PFT on the tapping task, a number of different measures were co-varied in an ANCOVA to see whether the differences remained once these variables had been accounted for: motor control of hand and arm movements (dominant hand 0 degrees from the posting task); tapping ability (dominant hand simple tapping); simple sequential movements (dominant hand sequential tapping); non-sequential bi-manual motor function (bead threading big blue beads).

(i) Motor control of hand and arm movements

ANCOVA with dominant hand 0 degrees from the posting task showed that although the significance levels on the tapping task all decreased, there was still evidence for a significant difference between patients with PFT and controls on non-dominant simple tapping (ANCOVA with Annett Pegboard $F(1,35) = 5.420$, $p = 0.027$); and on dominant sequential tapping (ANCOVA with posting task $F(1,35) = 7.382$, $p = 0.011$) and weak evidence for a significant difference on dominant simple tapping (ANCOVA with posting task $F(1,35) = 3.506$, $p = 0.071$); non-dominant sequential tapping (ANCOVA with Annett Pegboard $F(1,35) = 3.351$, $p = 0.077$); and bi-manual sequential tapping (ANCOVA with Annett Pegboard $F(1,35) = 3.577$, $p = 0.069$). This indicates that the differences in

performance between patients with PFT and controls on the tapping task are not simply due to differences in the motor control abilities for hand and arm movements.

(ii) Simple tapping

ANCOVA with dominant hand simple tapping showed that although the significance levels on the bi-manual tapping task decreased, there was still evidence for a significant difference between patients with PFT and controls on this measure (ANCOVA with dominant hand simple tapping: $F(1,35) = 4.942$, $p = 0.033$). This indicates that the difference in performance between patients with PFT and controls on the bi-manual tapping task is not simply due to differences in simple tapping abilities.

(iii) Simple sequential movements

ANCOVA with dominant hand sequential tapping showed that there was no significant difference between patients with PFT and controls on bi-manual tapping when differences in simple sequential tapping were accounted for (ANCOVA with dominant sequential tapping $F(1,35) = 0.015$, $p = 0.902$). These results show that the difficulties on the bi-manual tapping task may not simply be due to difficulties with the co-ordination of motor actions for the bi-manual nature of the task, but they may be associated with more general difficulties with simple sequential tapping movements.

(iv) Non-sequential bi-manual motor function

When performance on another bi-manual task (big blue beads from the bead threading task) was partialled out, the differences between patients with PFT and controls disappeared (ANCOVA with big blue beads: $F(1,35) = 2.437$, $p = 0.128$), indicating that difficulties with the bimanual tapping task are associated with bi-manual co-ordination.

Taken together, these findings indicate that patients with PFT have difficulties on the tapping task because they have problems with both sequential movements and with the co-ordination required in order to carry out bi-manual tasks. Their problems on this task are not related to difficulties with motor control of hand and arm movements, nor with problems with simple tapping abilities.

It is interesting to note that there was no significant difference between patients with PFT and controls in the relative level of performance between the dominant and the non-dominant hand on the simple tapping tasks (repeated measure ANOVA $F(1,33) = 0.001$, $p = 0.980$), but there was weak evidence for a significant difference on the sequential tapping tasks (repeated measure ANOVA $F(1,33) = 2.914$, $p = 0.097$). As can be seen in Table 3.17 above, both patients with PFT and controls performed better with their dominant hand than their non-dominant hand, but the relative difference between the two hands was slightly greater for the controls than for the patients with PFT. This suggests that for the sequential tapping task, patients with PFT may not show the expected level of enhanced performance with the dominant hand compared to the non-dominant hand.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the uni- or bi-manual tapping tasks. In addition, there was no significant difference between the tumour location subgroups in the relative level of performance between the dominant and the non-dominant hand on the simple tapping tasks (repeated measure ANOVA $F(1,12) = 0.215$, $p = 0.810$), or on the sequential tapping tasks (repeated measure ANOVA $F(1,12) = 0.219$, $p = 0.806$).

(v) Patients with AS: Tapping task

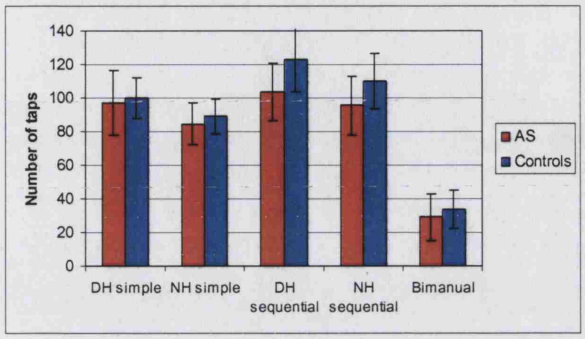
Table 3.18 and Figure 3.15 show the mean numbers of taps for each trial of the uni- and bi-manual tapping task for patients with AS and controls.

Table 3.18: Mean number of taps for each trial of the tapping task for patients with AS and controls

Group	Dominant Simple	Non-dominant Simple	Dominant Sequential	Non-dominant Sequential	Bi-manual
AS	97.14 (19.43)	84.57 (12.65)	103.54 (17.37)	95.36 (17.30)	28.93 (13.76)
Controls	100.00 (12.34)	89.00 (10.18)	122.70 (19.35)	109.73 (16.40)	33.45 (11.47)

Mean (sd)

Figure 3.15: Mean number of taps for each trial of the tapping task for patients with AS and controls



Statistical analysis showed that patients with AS performed significantly more poorly than controls on dominant sequential tapping ($t = -2.962$, $df = 32$, $p = 0.006$; ANCOVA with age $F(1,34) = 9.796$, $p = 0.004$) and non-dominant sequential tapping ($t = -2.458$, $df = 32$, $p = 0.020$; ANCOVA with age $F(1,34) = 6.927$, $p = 0.013$). There was however no evidence for a significant difference between patients with AS and their controls on bi-manual sequential tapping ($t = -1.042$, $df = 32$, $p = 0.305$; ANCOVA with age $F(1,34) = 0.914$, $p = 0.346$); on dominant tapping ($t = -0.525$, $df = 32$, $p = 0.603$; ANCOVA with age $F(1,34) = 0.186$, $p = 0.669$); nor on non-dominant tapping ($t = -1.130$, $df = 32$, $p = 0.267$; ANCOVA with age $F(1,34) = 1.104$, $p = 0.301$).

In order to further investigate the difficulties encountered by patients with AS with uni-manual sequential tapping, a number of different measures that were viewed as related to tapping performance were co-varied in an ANCOVA to see whether the differences remained once these variables had been accounted for: motor control of hand and arm movements (dominant hand 0 degrees from the posting task); tapping ability (dominant hand simple tapping); and complex sequential movements (bi-manual sequential tapping).

(i) Motor control of hand and arm movements

When performance on the posting task (dominant hand 0 degrees) was partialled out, there was no significant difference for dominant sequential tapping (ANCOVA with posting task $F(1,34) = 2.912$, $p = 0.098$) nor for non-dominant sequential tapping (ANCOVA with Annett Pegboard $F(1,34) = 1.300$, $p = 0.263$). This suggests that differences in the performance on the tapping task are associated with differences in the level of motor control of hand and arm movements between patients with AS and controls. As detailed in Section 3.2, there is a strong tendency for patients with AS to have clumsiness (or a lack of control and co-ordination of movements) and it is therefore not surprising that problems

with such motor control may underlie the difficulties encountered by patients with AS on the unimanual sequential tapping.

(ii) Simple tapping

When simple tapping ability (dominant hand simple tapping) was partialled out, there was still a significant difference for dominant hand sequential tapping (ANCOVA with dominant hand simple tapping: $F(1,34) = 8.708$, $p = 0.006$) and non-dominant hand sequential tapping (ANCOVA with dominant hand simple tapping: $F(1,34) = 5.826$, $p = 0.022$). These results indicate that difficulties on uni-manual sequential tapping cannot be explained by differences in simple tapping ability, and that it is the addition of sequences that brings out the differences.

(iii) Complex sequential movements

When complex sequential tapping ability (bi-manual sequential tapping) was partialled out, there was still a significant difference between patients with AS and controls on dominant sequential tapping (ANCOVA with dominant sequential tapping $F(1,34) = 8.279$, $p = 0.007$) and on non-dominant sequential tapping (ANCOVA with dominant sequential tapping $F(1,34) = 5.195$, $p = 0.030$). These results indicate that difficulties on uni-manual sequential tapping cannot be explained by differences in complex sequential tapping ability.

Taken together, these findings indicate that the difficulties encountered by patients with AS on the uni-manual sequential tapping tasks are associated with difficulties with motor control of the hand and arm but not with simple tapping or complex sequential tapping ability.

It is interesting to note that there was no significant difference between the performance of patients with AS and controls in the relative rate of tapping between the dominant and the non-dominant hand on the simple tapping tasks (repeated measure ANOVA $F(1,32) = 0.144$, $p = 0.707$), but there was weak evidence for a significant difference on the sequential tapping tasks (repeated measure ANOVA $F(1,32) = 4.066$, $p = 0.052$). As can be seen in Table 3.18 above, both patients with AS and controls performed better with their dominant

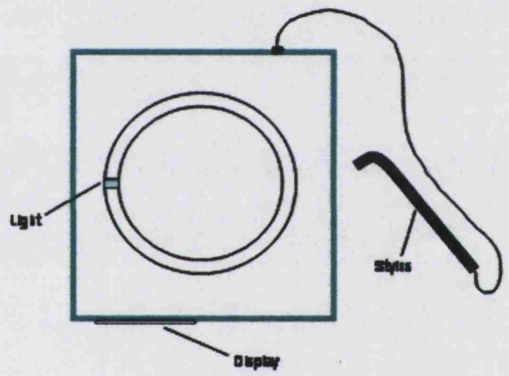
hand than their non-dominant hand on the sequential tapping task. However, the relative difference between the two hands was greater for the controls than for the patients with AS. This suggests that for the sequential tapping task, as was the case for the patients with PFT, patients with AS may not show the expected level of enhanced performance with the dominant hand compared to the non-dominant hand.

3.4.3 Tests of motor learning

3.4.3.1 Rotary pursuit

This task assesses the ability to learn a new motor action. Subjects are given a stylus to hold in their dominant hand and are required to follow a target light as it rotates in circles around a turntable (see Figure 3.16).

Figure 3.16: Apparatus for rotary pursuit



A total of six blocks of four trials of twenty seconds each is completed. The blocks are administered in pairs, with a 60 second break between the pairs, and a 30 minute break between each set of pairs. An outline of this task is as follows:

Block 1		Block 2		Block 3		Block 4		Block 5		Block 6
1	60 second break	1	**30 minute break**	1	60 second break	1	**30 minute break**	1	60 second break	1
2		2		2		2		2		2
3		3		3		3		3		3
4		4		4		4		4		4

The speed of rotation of the light is decided for each participant individually during 15 practice trials. The speed (either 15, 30, 45 or 60 rpm) at which the participant is able to maintain contact with the target for 25% of the trial or less, is selected.

Three measures of motor learning were calculated for this task:

a) **Initial ability:** this was the score at block 1 of the trials and was compared in order to determine whether all subjects started at a similar level of ability. It should be noted that subjects were given 15 practice trials prior to measurement of block 1 and it is therefore possible that a high score on block 1 could demonstrate rapid learning.
b) **Fast learning:** time on target for block 2 – time on target for block 1
c) **Slow learning:** time on target for block 6 – time on target for block 1

As detailed in Section 3.3.3, this test involves time-series data over repeated trials and in order to minimize any effects of measurement error and noise, the learning trajectory for each individual was first plotted from the raw scores and then linear, logarithmic and quadratic curves were fitted to each individual learning trajectory. After visual inspection, the function that best captured the learning of each individual was used to obtain summary statistics (model scores). The raw scores and the model scores were analysed separately using independent sample t-tests in order to compare patients and controls on the measures of initial ability, fast learning and slow learning described above.

(i) Patients with PFT: Rotary pursuit

The raw scores for rotary pursuit of patients with PFT and controls are shown in Figures 3.17 and 3.18 and table 3.19. The results from the model scores are shown in Figures 3.19 and 3.20 and table 3.20.

Figure 3.17: Raw scores on the rotary pursuit for patients with PFT

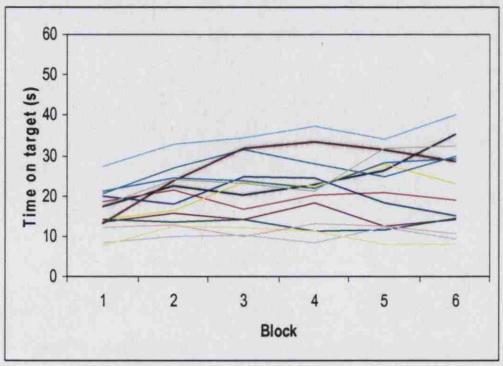


Figure 3.18: Raw scores on the rotary pursuit for controls

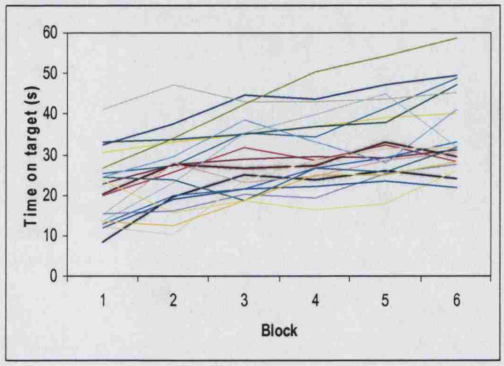


Table 3.19: Raw scores (in seconds) on the rotary pursuit for patients with PFT and controls:

Group	Initial ability	Fast learning	Slow learning
PFT	16.14 (5.25)	3.50 (3.21)	5.96 (7.44)
Controls	21.38 (8.63)	4.16 (4.97)	13.93 (7.00)

Mean (sd)

Statistical analysis showed that there was no significant difference between patients with PFT and their controls on initial ability ($t = -2.021$, $df = 32$, $p = 0.052$, ANCOVA with age $F(1,34) = 3.026$, $p = 0.092$) or on fast learning ($t = -0.437$, $df = 32$, $p = 0.665$, ANCOVA with age $F(1,34) = 0.076$, $p = 0.785$), but there was a significant difference on slow learning ($t = -3.185$, $df = 32$, $p = 0.003$, ANCOVA with age $F(1,34) = 8.842$, $p = 0.006$), indicating that controls show significantly more slow learning than patients with PFT.

Figure 3.19: Model scores on the rotary pursuit for patients with PFT

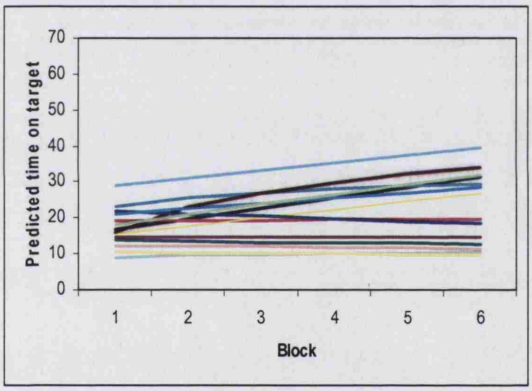


Figure 3.20: Model scores on the rotary pursuit for controls

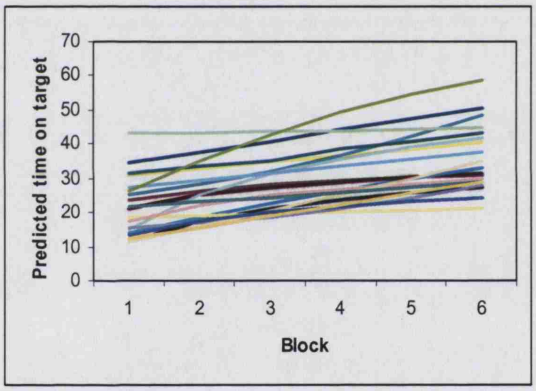


Table 3.20: Model scores (in seconds) on the rotary pursuit for patients with PFT and controls

Group	Initial ability	Fast learning	Slow learning
PFT	17.21 (5.39)	1.44 (2.04)	5.55 (7.01)
Controls	21.72 (8.65)	3.70 (2.53)	14.01 (7.89)

Mean (sd)

For the model values, there was no significant difference between patients with PFT and their controls on initial ability ($t = -1.725$, $df = 32$, $p = 0.094$; ANCOVA with age $F(1,34) = 2.000$, $p = 0.167$), but there was a significant difference on fast learning (Mann Whitney U-test $z = -2.904$, $p = 0.004$, ANCOVA with age $F(1,34) = 6.802$, $p = 0.014$) and on slow learning ($t = -3.220$, $df = 32$, $p = 0.003$, ANCOVA with age $F(1,34) = 9.276$, $p = 0.005$), with controls performing better than patients with PFT on both of these measures.

In order to investigate whether any difficulties on the rotary pursuit were due to problems with arm movements rather than with motor learning, measures of arm movement ability (posting task dominant hand 0 degrees) were partialled out. The results showed that there was no significant difference on any of the trials when measures of arm movement ability were partialled out: initial ability raw scores (ANCOVA with posting task dominant hand 0 degrees: $F(1,34) = 2.502$, $p = 0.124$), Initial ability model scores (ANCOVA with posting task DH 0 degrees: $F(1,34) = 1.975$, $p = 0.170$), fast learning raw scores (ANCOVA with posting task dominant hand 0 degrees: $F(1,34) = 0.139$, $p = 0.711$), fast learning model scores (ANCOVA with posting task DH 0 degrees: $F(1,34) = 2.907$, $p = 0.098$), slow learning raw scores (ANCOVA with posting task dominant hand 0 degrees: $F(1,34) = 2.678$, $p = 0.112$), slow learning model scores (ANCOVA with posting task DH 0 degrees: $F(1,34) = 3.313$, $p = 0.078$). This indicates that the difficulties encountered by patients with PFT on the rotary pursuit are likely to be associated with difficulties with motor control of arm movements.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed no evidence for a significant interaction between performance on the rotary pursuit task and location of tumour. However, because there was a specific prediction that individuals with midline pathology would perform more poorly than patients with pathology of the hemispheres due to problems with motion perception that have been associated with damage to the midline cerebellum, the scores for each of the groups on the rotary pursuit are presented in table 3.21 below.

Table 3.21: Actual and model scores on the rotary pursuit for the tumour location subgroups

	Actual scores			Model scores		
Group	**Initial ability**	**Fast learning**	**Slow learning**	**Initial ability**	**Fast learning**	**Slow learning**
Left hemisphere	17.44 (7.09)	4.20 (2.08)	8.30 (7.59)	18.45 (7.78)	1.65 (1.25)	6.67 (6.03)
Midline	16.02 (3.68)	1.66 (1.67)	3.26 (5.10)	16.44 (3.68)	0.63 (1.19)	3.38 (5.68)
Right Hemisphere	14.65 (5.33)	4.93 (5.10)	6.41 (10.33)	16.61 (4.83)	2.18 (3.48)	6.86 (10.45)

Mean (sd)

This table shows that, as predicted, patients with midline cerebellar damage performed more poorly than patients with pathology of the hemispheres on fast and slow learning (for both actual and model scores) and for initial ability (model scores). The only measure on which patients with midline pathology did not perform more poorly than the other tumour groups was initial ability (actual scores). These results suggest that, although the differences were not found to be significant, patients with midline pathology may have some difficulties with the rotary pursuit task that are not encountered by individuals with pathology of the hemispheres. It is possible that these differences may be associated with problems with motion perception after vermal damage in line with the work of Nawrot and Rizzo (1995, 1998).

(ii) Patients with AS: Rotary pursuit

The raw scores from the rotary pursuit task for patients with AS and controls are shown in Figures 3.21 and 3.22 and table 3.22. The results of the predicted scores are shown in Figures 3.23 and 3.24 and table 3.23.

Figure 3.21: Raw scores on the rotary pursuit for patients with AS

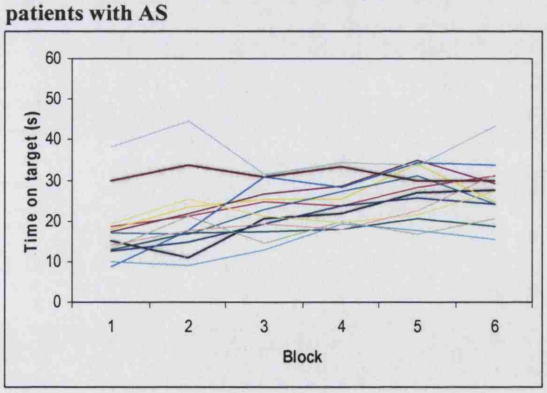


Figure 3.22: Raw scores on the rotary pursuit for controls

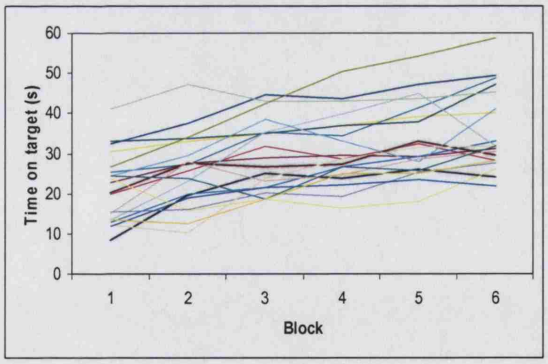


Table 3.22: Raw scores on the rotary pursuit for patients with AS and controls:

Group	Initial ability	Fast learning	Slow learning
AS	17.44 (7.88)	3.63 (3.60)	9.77 (6.23)
Controls	21.38 (8.63)	4.16 (4.97)	13.93 (7.00)

Mean (sd)

Statistical analysis of the results for the rotary pursuit task showed that there was no significant difference between patients with AS and their controls on initial ability (after log transformation t = -1.359, df = 32, p = 0.184, ANCOVA with age F (1,34) = 1.689 p = 0.203) or on fast learning (t = -0.346, df = 32, p = 0.732, ANCOVA with age F (1,34) = 0.049 p = 0.826), but there was weak evidence for a significant difference on slow learning (t = -1.784, df = 32, p = 0.084, ANCOVA with age F (1,34) = 2.972, p = 0.095).

Figure 3.23: Model scores on the rotary pursuit for patients with AS

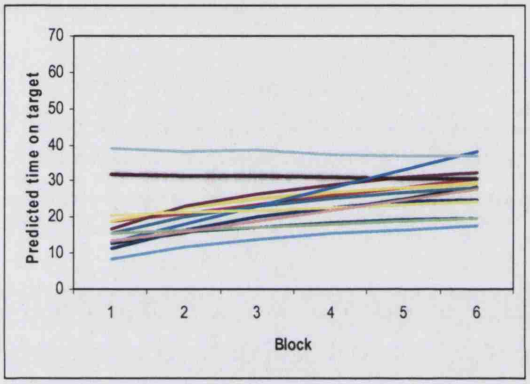


Figure 3.24: Model scores on the rotary pursuit for controls

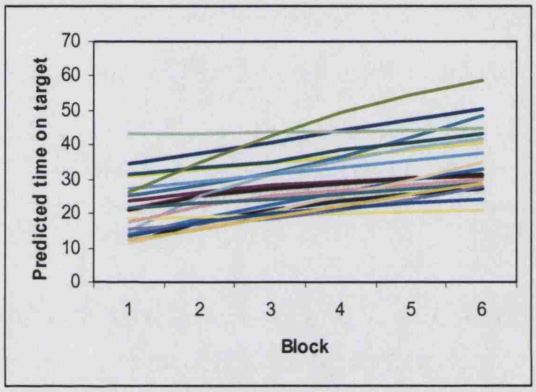


Table 3.23: Model scores on the rotary pursuit for patients with AS and controls:

Group	Initial ability	Fast learning	Slow learning
AS	17.78 (8.21)	2.82 (2.07)	9.90 (7.29)
Controls	21.72 (8.65)	3.70 (2.53)	14.01 (7.89)

Mean (sd)

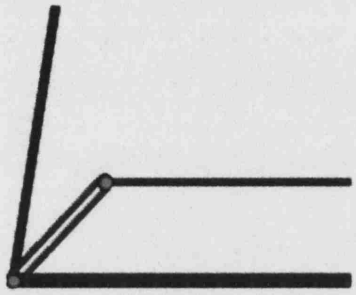
For the model values, there was no significant difference between patients with AS and their controls on initial ability (t = -1.332, df = 32, p = 0.192, ANCOVA with age F (1,34) = 1.639, p = 0.210). In addition, there was no significant difference on fast learning (Mann Whitney U-test, z = -0.560, p = 0.576, ANCOVA with age F (1,34) = 1.054, p = 0.312) or on slow learning (t = -1.544, df = 32, p = 0.132, ANCOVA with age F (1,34) = 2.352, p = 0.135).

3.4.3.2 Mirror tracing

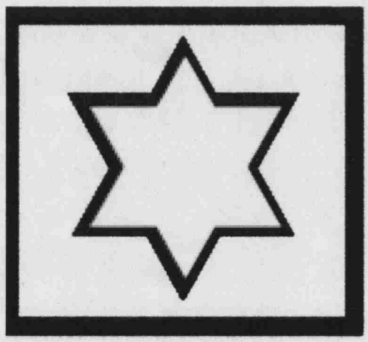
This test examines the learning of a new visuo-motor task. Subjects are presented with a reflection of a star in a mirror (see Figure 3.25) and are required to trace this star as quickly and accurately as possible despite only being able to see a reflection of their hand (both the time taken (in seconds) to trace the star and the number of errors (number of deviations outside the star) are recorded). The movements required in this task will tend to be in reverse of those normally executed when a stimulus is not mirror-reversed. In order to assess motor learning, subjects are given five trials with their dominant hand and then another five trials with the same hand three hours later. In addition, before the first set of trials and after the final set of trials, subjects are required to trace the star using their non-dominant hand. The performance with the non-dominant hand is used as a control here because it is not trained on this task, instead it is used to check for the learning effect.

Figure 3.25: Apparatus for mirror tracing

a) Side view of apparatus



b) Top-down view of star to be traced



A time plan for this task is as follows:

NDH trial	DH trials					3 hour break	DH trials					NDH trial
1	1	2	3	4	5		6	7	8	9	10	2

Six measures of motor learning were calculated for this task:

a) **Initial ability:** this was the score at block 1 of the trials and was compared in order to determine whether all subjects started at a similar level of ability.

b) **Fast learning:** time on target for block 2 – time on target for block 1

c) **Slow learning:** time on target for block 10 – time on target for block 1

d) **Retention of learning:** time on target for block 6 – time on target for block 5

e) **Changes in performance with the untrained hand:** time on target for block 2 with the non-dominant hand – time on target for block 1 with the non-dominant hand.

f) **Errors:** total number of errors (hits outside of the star being traced).

As detailed in Section 3.3.3, this test involves time-series data over repeated trials. In order to minimize any effects of measurement error and noise, the learning trajectory for each individual was first plotted from the raw scores and then linear, logarithmic and quadratic curves were fitted to each individual learning trajectory. After visual inspection, the function that best captured the learning of each individual was used to obtain summary statistics (predicted scores). The raw scores and the predicted scores were analysed separately using independent sample t-tests in order to compare patients and controls on the measures of learning (a to f) described above.

(i) Patients with PFT: Mirror tracing

The raw scores of patients with PFT and controls on the mirror tracing are shown in Figures 3.26 and 3.27 and table 3.24. The results from the predicted scores are shown in Figures 3.28 and 3.29 and table 3.25.

Figure 3.26: Raw scores (in seconds) on the mirror tracing task for patients with PFT

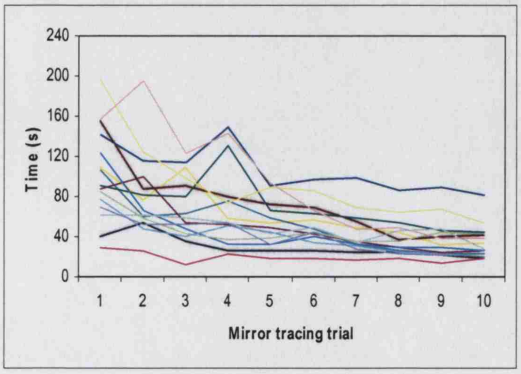


Figure 3.27: Raw scores (in seconds) on the mirror tracing task for controls

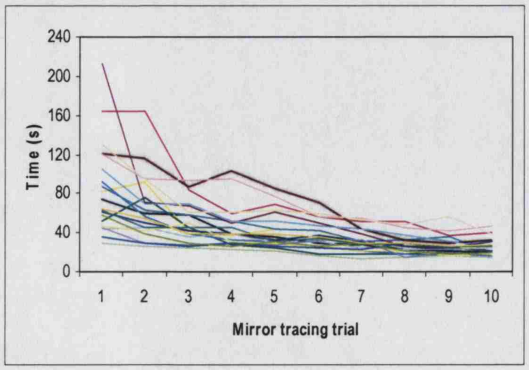


Table 3.24: Raw data for patients with PFT and controls on the mirror tracing task

Group	Initial ability	Fast learning	Slow learning	Retention of learning	Untrained hand	Errors
PFT	101.92(46.43)	-21.44 (31.37)	-67.63 (37.74)	-1.53 (10.03)	-46.18 (38.34)	55.87 (44.30)
Controls	84.35 (46.75)	-18.79 (32.65)	-59.43 (42.76)	-4.62 (6.45)	-33.50 (18.82)	73.95 (64.75)

Mean (sd)

Statistical analysis of the raw scores showed that there was no evidence for a significant difference between the scores of patients with PFT and their controls on initial ability ($t = 1.104$, $df = 33$, $p = 0.278$, ANCOVA with age $F(1,35) = 0.717$, $p = 0.404$). In addition, there was no significant difference on fast learning ($t = -0.242$, $df = 33$, $p = 0.811$, ANCOVA with age $F(1,35) = 0.003$, $p = 0.959$), on slow learning ($t = -0.590$, $df = 33$, $p = 0.559$, ANCOVA with age $F(1,35) = 0.114$, $p = 0.738$), on retention of learning ($t = 1.106$, $df = 33$, $p = 0.277$, ANCOVA with age $F(1,35) = 1.216$, $p = 0.278$), on changes in performance with the untrained hand (Mann Whitney U-test $z = -0.600$, $p = 0.549$, ANCOVA with age $F(1,35) = 1.027$, $p = 0.318$) or on number of errors ($t = -0.929$, $df = 33$, $p = 0.360$, ANCOVA with age $F(1.35) = 2.118$, $p = 0.155$).

Figure 3.28: Predicted scores (in seconds) on the mirror tracing task for patients with PFT

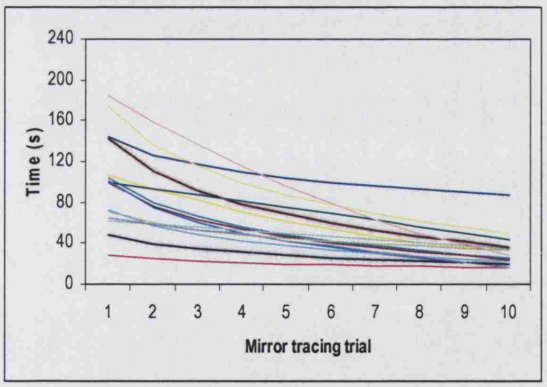


Figure 3.29: Predicted scores (in seconds) on the mirror tracing task for controls

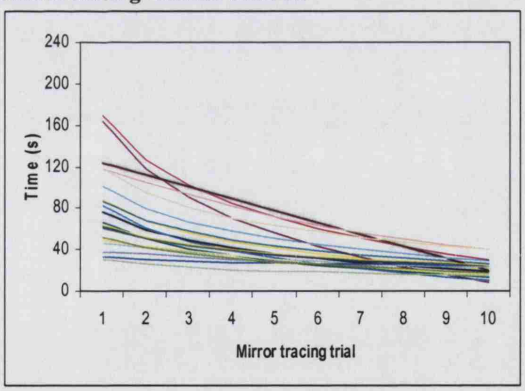


Figure 3.25: Predicted scores on the mirror tracing for patients with PFT and controls:

Group	Initial ability	Fast learning	Slow learning	Retention of learning
PFT	99.92 (45.11)	-16.58 (10.64)	-67.49 (38.61)	-6.11 (3.93)
Controls	81.15 (40.38)	-15.75 (11.79)	-59.10 (38.92)	-5.09 (3.35)

Mean (sd)

For the predicted values, statistical analysis showed that there was no evidence for a significant difference between the scores of patients with PFT and their controls on initial

ability (t = 1.295, df = 33, p = 0.204, ANCOVA with age F (1,35) = 1.124, p = 0.297). In addition, there was no significant difference between scores on fast learning (t = -0.215, df = 33, p = 0.831, ANCOVA with age F (1,35) = 0.003, p = 0.957), on slow learning (t = -0.633, df = 33, p = 0.531, ANCOVA with age F (1,35) = 0.177, p = 0.677) or on retention of learning (t = -0.827, df = 33, p = 0.414, ANCOVA with age F (1,35) = 0.465, p = 0.500).

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed a significant interaction between initial ability and location of tumour for both raw (F(2,12) = 6.287, p = 0.014) and predicted (F(2,12) = 5.823, p = 0.017) values. The mean scores for initial ability for each of the PFT groups are shown in Table 3.26 below.

Table 3.26: The mean scores for initial ability for each of the groups with PFT

Group	Initial ability: raw scores	Initial ability: predicted scores
LH damage	74.62 (25.60)	76.83 (23.74)
Midline damage	84.19 (36.80)	79.80 (32.91)
RH damage	146.96 (40.92)	143.14 (44.35)

Mean (sd)

Patients with right hemisphere damage performed most poorly and those with left hemisphere damage performed best. Post hoc analysis (Tukey's test) showed significant differences between those with left hemisphere and those with right hemisphere damage for both the raw (p = 0.017) and predicted (p = 0.027) values and a significant difference between those with right hemisphere and those with midline damage for both the raw (p = 0.037) and predicted (0.034) values.

(ii) Patients with AS: Mirror tracing

The raw scores of the patients with AS and controls on the mirror tracing task are shown in Figures 3.30 and 3.31 and table 3.27. The results from the predicted scores are shown in Figures 3.32 and 3.33 and table 3.28.

Figure 3.30: Raw scores (in seconds) on the mirror tracing task for patients with AS

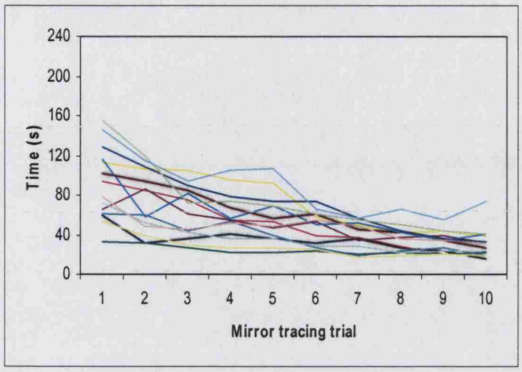


Figure 3.31: Raw scores (in seconds) on the mirror tracing task for controls

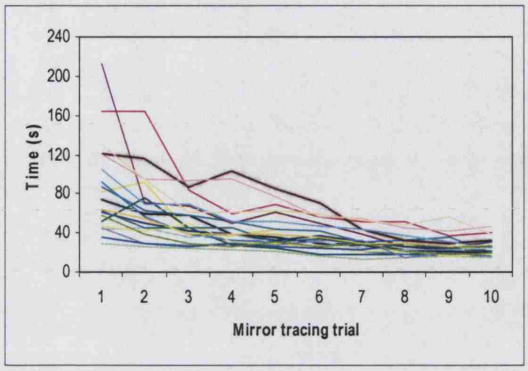


Table 3.27: Raw scores on the mirror tracing for patients with AS

Group	Initial ability	Fast learning	Slow learning	Retention of learning	Untrained hand	Errors
AS	91.21 (36.95)	-17.24 (19.45)	-60.35 (27.94)	-8.81 (14.51)	-50.82 (27.01)	58.86 (73.07)
Controls	84.35 (46.75)	-18.79 (32.65)	-59.43 (42.76)	-4.62 (6.45)	-33.50 (18.82)	73.95 (64.75)

Mean (sd)

Statistical analysis of the raw scores for the mirror tracing task showed that there was no evidence for a significant difference between patients with AS and their controls on initial ability ($t = 0.458$, $df = 32$, $p = 0.650$, ANCOVA with age $F(1,34) = 0.144$, $p = 0.707$). There was no significant difference on fast learning ($t = 0.158$, $df = 32$, $p = 0.875$, ANCOVA with age $F(1,34) = 0.055$, $p = 0.817$), on slow learning ($t = -0.071$, $df = 32$, $p = 0.944$, ANCOVA with age $F(1,34) = 0.000$, $p = 0.987$), on retention of learning (Mann Whitney U-test, $z = -0.525$, $p = 0.600$, ANCOVA with age $F(1,34) = 1.132$, $p = 0.296$) or on total number of errors ($t = -0.635$, $df = 32$, $p = 0.530$, ANCOVA with age $F(1,34) = 0.950$, $p = 0.337$). There was however a significant difference on changes in performance with the untrained hand (-2.208, $df = 32$, $p = 0.035$, ANCOVA with age $F(1,34) = 0.950$, $p = 0.337$), with patients with AS showing a greater improvement in the untrained (non-dominant) hand than controls.

Figure 3.32: Predicted scores (in seconds) on the mirror tracing for patients with AS

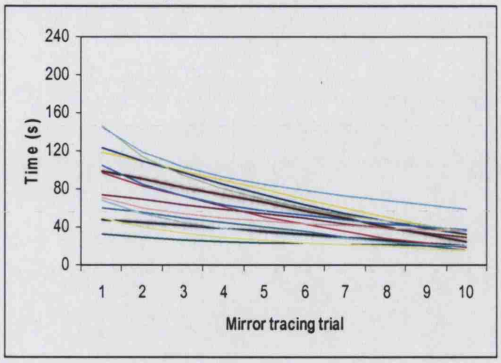


Figure 3.33: Predicted scores (in seconds) on the mirror tracing for controls

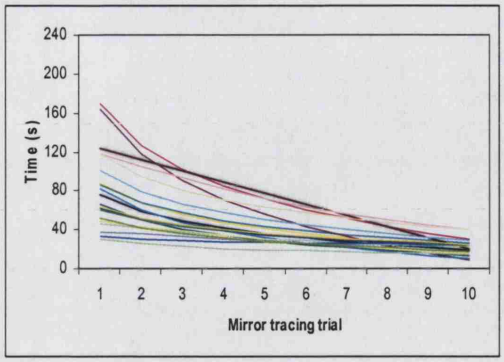


Table 3.28: Predicted scores on the mirror tracing for patients with AS and controls:

Group	Initial ability	Fast learning	Slow learning	Retention of learning
AS	88.09 (36.20)	-12.56 (8.71)	-60.06 (28.64)	-5.78 (2.94)
Controls	81.15 (40.38)	-15.75 (11.79)	-59.10 (38.92)	-5.09 (3.35)

Mean (sd)

For the predicted values, statistical analysis showed that there was no evidence for a significant difference between the scores of patients with AS and their controls on initial ability ($t = 0.514$, $df = 32$, $p = 0.611$, ANCOVA with age $F(1,34) = 0.196$, $p = 0.661$). In addition, there was no significant difference on fast learning ($t = 0.860$, $df = 32$, $p = 0.396$, ANCOVA with age $F(1,34) = 0.860$, $p = 0.361$), on slow learning ($t = -0.078$, $df = 32$, $p = 0.938$, ANCOVA with age $F(1,34) = 0.001$, $p = 0.977$) or on retention of learning ($t = -0.618$, $df = 32$, $p = 0.541$, ANCOVA with age $F(1,34) = 0.339$, $p = 0.565$).

Effects of age at surgery for patients with PFT

Correlation analyses were performed between age at surgery (in months) and the results of each of the motor tests described above for the patients with PFT. The results showed that there was a significant positive correlation between age at surgery and fast learning on the mirror tracing task (Pearson correlation coefficient = 0.610, $p = 0.016$), indicating that patients who were younger at occurrence of pathology tended to show greater fast learning than patients who were older at occurrence of pathology.

Correlation analyses also showed that there was weak evidence for a significant negative correlation between age at surgery and performance on the beads 1,2,3 task (Pearson correlation coefficient = -0.446, p = 0.096). There were no other significant correlations.

There was a specific hypothesis that patients with early pathology of the cerebellum (age five and younger) would perform better on tests of motor function than patients with later pathology (age six and above) due to the greater plasticity of the younger brain. In order to investigate this possibility, independent sample t-tests were carried out between the performance of patients with PFT who had pathology at age five and younger and patients with PFT who had pathology at age six and older on each of the motor tests considered above.

The results showed that the only measures on which the two groups differed were fast learning on mirror tracing (for actual values) and initial ability on the rotary pursuit (for both actual and predicted values).

The mean scores of the two groups on these three measures are shown in table 3.29 below.

Table 3.29: Scores on the mirror tracing fast learning and rotary pursuit initial ability (actual and predicted) for the early and late groups with PFT

Group	Mirror tracing fast learning	Rotary pursuit initial ability (actual)	Rotary pursuit initial ability (predicted)
Early	-38.43 (18.49)	18.84 (5.07)	20.23 (5.35)
Late	-6.57 (33.67)	13.44 (4.12)	14.19 (3.62)

Mean (sd)

Statistical analysis showed that the late group demonstrated significantly less fast learning on the mirror tracing task than the early group ($t = -2.221$, $df = 13$, $p = 0.045$). In addition, the late group performed significantly more poorly than the early group on initial ability on the rotary pursuit for both raw ($t = 2.186$, $df = 12$, $p = 0.049$) and predicted ($t = 2.474$, $df = 12$, $p = 0.029$) values.

Given the large number of statistical tests carried out here, it is important to note that there is a high probability of obtaining false positive results and these findings should therefore be interpreted with caution.

Effects of time since surgery for patients with PFT

Correlation analyses were also performed between time in months since surgery and the results of each of the motor tests described above. The results showed that there was a significant positive correlation between time since surgery and posting task quarter gap dominant hand 90 degrees (Pearson correlation coefficient = 0.543, p = 0.045). There was weak evidence for a significant negative correlation between time since surgery and fast learning on the mirror tracing task (Pearson correlation coefficient = -0.468, p = 0.079) and for a significant positive correlation between time since surgery and initial ability on the rotary pursuit task, both for the raw (Pearson correlation coefficient = 0.528, p = 0.052) and predicted (Pearson correlation coefficient = 0.516, p = 0.059) scores. There were no other significant correlations. As was the case for the correlations with age at injury, these results should be interpreted with caution due to the high probability of a Type I error associated with the large number of statistical tests carried out here.

3.5 Discussion

As stated in the methods section, adjustment for multiple comparisons was not performed in this thesis. Instead, a cut-off was chosen in order to flag problematic motor functions in each of the two patient groups which will require further investigation in future studies. It is important therefore to re-iterate that the results should be interpreted with some caution.

3.5.1 Patients with PFT

The performance of patients with PFT on the motor tests is summarized in table 3.30 below.

Table 3.30: Performance of patients with PFT on the motor tests

Motor Domain	Test	Performance by patients with PFT
1. Uni-manual motor function	Annett Pegboard	Impaired on dominant and non-dominant hand
	Grooved Pegboard	Impaired on dominant hand, and non-dominant hand (when age co-varied)
	Posting task	Impaired
2. Bi-manual motor function	Bead threading	Impaired
	Tapping task	Impaired
3. Motor learning	Rotary pursuit	Impaired on fast and slow learning
	Mirror tracing	Not impaired

1. Uni-manual motor function

The predictions that patients with PFT would perform more poorly on all of the tests of uni-manual motor function (the Annett Pegboard and Grooved Pegboard which assess fine motor action and the posting task which assesses motor control of the arm and hand) were supported.

The Annett Pegboard was the most basic test of fine motor action and patients with PFT performed significantly more poorly than controls on this task with both the dominant and non-dominant hand, demonstrating that these patients have problems with even the most simple uni-manual fine motor actions.

The Grooved Pegboard required more fine motor dexterity than the Annett Pegboard and the results showed that patients with PFT performed significantly more poorly on this test with the dominant hand, and with the non-dominant hand when differences in age were co-varied. It is interesting to note that the difficulties experienced by patients with PFT on the Grooved Pegboard could be accounted for by their difficulties on the Annett Pegboard, indicating that they did not have additional problems with the high level of dexterity needed to complete the task, but that their problems were related to more general difficulties with fine motor actions.

These findings that patients with PFT have difficulties with fine motor action are in line with a previous study of patients with PFT carried out by Levisohn et al. (2000), and also with functional imaging studies that have found cerebellar activation during movement of the fingers (Fox et al. 1985; Blinkenberg et al. 1996; Sadato et al. 1996; Jueptner et al. 1997; Nitschke et al. 2003).

The results of the posting task showed that patients with PFT had significantly more difficulties with the control of arm and hand movement than did controls. This is in line with research that has shown that the cerebellum is involved in the control of motor actions (Ellerman, et al., 1994; Braitenberg et al., 1997). However, it is important to note that

comparison between posting ability through a small slot and a large slot showed that patients with PFT may not have particular problems with the accuracy of movements.

2. Bi-manual motor function

In line with predictions, patients with PFT were found to be impaired on the two tests of bi-manual motor action (bead threading and the tapping task).

For the bead threading task, patients with PFT performed significantly more poorly than controls on all of the variables. These difficulties were not merely due to difficulties with fine motor actions because there was still evidence for a difference between the performance of patients with PFT and controls on the bead threading task when differences in performance on a simple fine motor task (the Annett Pegboard) were partialled out. These findings indicate that the problems encountered by the patients with PFT are likely to be associated with difficulties with bi-manual co-ordination abilities.

For the tapping task, patients with PFT performed more poorly than controls on all of the variables, including both the uni-manual and bi-manual trials. None of the difficulties on this task were due to difficulties with motor control of the hand and arm, and the difficulties on the sequential tapping tasks were not due to difficulties with the motoric action of tapping. However, difficulties on the bi-manual sequential tapping were found to be associated with difficulties in carrying out uni-manual sequential movements and with the bi-manual nature of the task (the differences between patients with PFT and controls disappeared when differences in bi-manual function on the bead threading task were partialled out).

Taken together, the results from the two tests of bi-manual motor function demonstrated that patients with PFT have particular difficulties with the co-ordination of movements. This is in line with research that has shown that the cerebellum is involved in motor co-ordination (Miall et al., 2000; 2001; Debaere et al. 2004).

3. Motor learning

The prediction that patients with PFT would perform significantly more poorly than controls on the two measures of motor learning (the rotary pursuit and the mirror tracing) was not fully supported by the results. Analysis of both raw and model data showed that patients with PFT did not perform significantly differently from controls on any of the measures of motor learning assessed through the mirror tracing task. For the rotary pursuit task, however, patients with PFT performed significantly more poorly than controls on fast learning (predicted values) and on slow learning (raw and predicted values). This indicates that patients with PFT have significant difficulties with aspects of the rotary pursuit task that are not involved in the mirror tracing task. The rotary pursuit task has a greater timing component than the mirror tracing task as it involves the timed pursuit of a moving target and it is therefore possible that patients with PFT have particular difficulties with the timing aspects of this task. Visual observation of patients carrying out the rotary pursuit revealed consistent abnormalities in the way that the movements were carried out. Patients with PFT seemed unable to execute smooth sustained movements of the arm and hand, instead producing shorter, jerky movements as they tried to follow the rotating light with the stylus. The rotary pursuit and mirror tracing tasks do actually differ in the type of movement involved – the mirror tracing involves more distal movements of the hand and fingers, whereas the rotary pursuit involves more proximal movements of the arm. However, when measures of motor control of hand and arm movements (posting task dominant hand 0 degrees) were partialled out, the results were not affected, indicating that difficulties with arm movements could not account for all the problems encountered by the patients with PFT on the rotary pursuit task. These findings suggest that patients with PFT may have problems with the timing and motor learning aspects of the rotary pursuit task, not simply with the execution of the motor actions involved.

A) Associations between tumour location and functional impairment:

Comparisons between the performance of patients with PFT on the basis of the location of their tumour (left hemisphere, right hemisphere or midline) revealed that the groups demonstrated significantly different levels of performance on four tests: the Annett pegboard, the posting task, the bead threading and initial ability on the mirror tracing. For

all of the tests except the Annett pegboard, patients with left hemisphere performed best and patients with right hemisphere damage performed most poorly. For the Annett pegboard, patients with left hemisphere also performed best, but patients with midline damage performed more poorly than patients with right hemisphere damage.

It had been predicted that patients with pathology of the cerebellar hemispheres would perform more poorly than patients with midline pathology on timed tests of uni-manual and bi-manual motor action because damage to the cerebellar hemispheres had been associated with a reduction in the speed of arm movements (Immisch et al. 2003). This prediction was not supported, however, as patients with midline pathology performed more poorly than patients with right or left hemisphere pathology on the Annett pegboard which is a test that depends on fast movements of the hand and arm. These findings suggest either that the vermis is also important for arm movement speed, or that patients with midline damage had difficulties because the Annett pegboard tests another ability which depends on an intact cerebellar vermis (one possibility might be the grasping motion required to pick up the pegs between finger and thumb).

The fact that patients with right hemisphere damage performed particularly poorly on a number of measures of motor function, whereas patients with left hemisphere pathology performed relatively well on these measures would be consistent with localisation of function in the cerebellum. These findings suggest that regions of the right cerebellar hemisphere may play an integral role in motor control of the hand and arm (the posting task and initial ability on the mirror tracing) and in bi-manual coordination for fine motor abilities (the bead threading task); whereas an intact left cerebellum may not be essential for successful completion of these tests of motor function. However, this possibility requires further investigation in future studies.

The differences between the performance of the patients with damage to different cerebellar hemispheres is unlikely to be related to the extent of damage, as there was a similar overall level of damage in patients with right and left hemisphere pathology. The particular

lobules that are damaged (and thus the extent of pathology) in each of the groups with right or left hemisphere damage are reported in Chapter 5.

It had also been predicted that patients with midline pathology would perform particularly poorly on the rotary pursuit task as this depends on motion perception abilities which have been found to be affected by pathology of midline cerebellum (Nawrot and Rizzo, 1995; 1998). Although there was no significant difference between the performance of the tumour location subgroups on the rotary pursuit, examination of the scores showed that patients with midline pathology did perform more poorly on all but one (initial ability actual score) measures of the rotary pursuit, providing very preliminary support for the possibility that the midline cerebellum may play a role motion perception abilities.

B) Effects of age at pathology:

The possible effects of age at pathology on motor outcome were investigated with correlation analyses between the age at surgery and the results of each of the motor tests reported above and with direct comparisons between the performance of patients who had early pathology (age five and younger) and patients who had late pathology (age six and older) on these motor tests. It was predicted that patients with late pathology would perform more poorly than patients with early pathology due to the limited plasticity of the brain in older individuals. The results indicate that surgery performed at a late age (age six and above) may have a detrimental effect on the ability to learn new skills. It appears that it is the ability to rapidly learn these new skills that may be most affected as fast learning was impaired on the mirror tracing task, and initial ability (which is likely to reflect fast learning as this measure is taken after a number of practice trials) was impaired on the rotary pursuit. The two groups did not differ on measures of slow learning.

It is important to emphasize that due to the large number of statistical tests carried out in this study, the probability of obtaining false positive results is high and these findings should therefore be interpreted with caution. Nevertheless, this study has started to identify the aspects of motor function that may be of particular interest for future investigations into the effects of pathology at different ages.

C) Effects of time since surgery:

The possible effects of time elapsed since surgery on motor outcome was investigated with correlation analyses between the time since surgery and the results of each of the motor tests reported above. In line with the prediction, there were very few correlations between time since surgery and performance on the motor tests. The only significant finding was that the shorter time that has passed since surgery, the more poorly patients with PFT tend to perform on one of the posting task trials and there is a high probability that this single significant finding is a false positive result, given the large number of statistical tests carried out here.

The results of mixed-model analyses (repeated measure ANOVAs) which were carried out for all of the tests involving the same trial with both the dominant and the non-dominant hand showed that there was no evidence for a significant difference between the level of performance between the two hands for patients with PFT and controls.

3.5.2 Patients with AS

The performance of patients with AS on the motor tests is summarized in table 3.31 below.

Table 3.31: Performance of patients with AS on the motor tests

Motor Domain	Test	Performance by patients with AS
1. Uni-manual motor function	Annett Pegboard	Impaired on dominant hand but not on non-dominant hand
	Grooved Pegboard	Not impaired
	Posting task	Impaired on most trials
2. Bi-manual motor function	Bead threading	Impaired
	Tapping task	Impaired on uni-manual sequential tapping but not on uni-manual simple tapping or on bi-manual tapping
3. Motor learning	Rotary pursuit	Not impaired
	Mirror tracing	Not impaired

1. Uni-manual motor function

It was predicted that patients with AS would perform significantly more poorly than controls on the Annett Pegboard and the posting task, but not on the Grooved Pegboard. These predictions were partially supported by the results.

Patients with AS performed significantly more poorly than controls on the dominant hand for the Annett Pegboard but not on the non-dominant hand. This indicates that patients with AS have some difficulties with simple fine motor actions in line with previous research (Ghaziuddin et al. 1994; Klin et al. 1995). The finding that patients with AS were impaired with their dominant hand but not with their non-dominant hand suggests that there may be some asymmetry in the level of performance with the two hands in patients with AS.

For the Grooved Pegboard, patients with AS did not perform significantly more poorly than controls with either the dominant or the non-dominant hand, indicating that they did not have particular difficulties with the fine motor actions required in this task. This is in line with a study by Weimer et al. (2001) who found that patients with AS were not impaired on the Grooved Pegboard compared to controls.

For the posting task, patients with AS performed more poorly than controls on almost all of the trials, indicating that they did have problems with the control of more gross movements of the hand and arm. This result was expected because, as suggested in Section 3.3.2, difficulties with control of gross motor action are likely to be associated with the clumsiness that is often reported in individuals with autism. It is interesting to note that patients with AS did not seem to have problems with the accuracy of movements as they did not perform more poorly than controls on posting cards through a small slot compared to a large slot.

Taken together, the results from the tests of uni-manual motor function showed that patients with AS have limited difficulties with fine motor action, but have particular difficulties with motor control of hand and arm movements as assessed by the posting task.

2. Bi-manual motor function

It was predicted that because of the problems with motor co-ordination which are manifested in the form of clumsiness in individuals with AS, patients with AS would perform more poorly than controls on both the bead threading and the tapping task as these require the co-ordination of motor actions between the right and left hands. The results showed that patients with AS performed significantly more poorly than controls on all measures of the bead threading task and on uni-manual sequential tapping (dominant and non-dominant hand) but not on bi-manual tapping or on uni-manual simple tapping (dominant and non-dominant hand). Further investigation revealed that the difficulties on the bead threading could be explained by difficulties with fine motor action because the group differences disappeared when fine motor ability (performance on the Annett Pegboard dominant hand) was partialled out. This fact, together with the finding that patients with AS did not perform significantly more poorly than controls on the bi-manual tapping task, indicates that patients with AS do not have particular difficulties with bi-manual co-ordination.

Further investigation of the performance of patients with AS and controls on the tapping task showed that differences in performance on the uni-manual sequential tapping tasks could be explained by differences in motor control of the hand and arm. This is again in line with the fact that patients with AS have particular problems with clumsiness and gross motor control, and provides evidence that these problems with clumsiness manifest themselves in a variety of different motor actions.

3. Motor learning

The prediction that patients with AS would not perform significantly more poorly than controls on either of the tests of motor learning was supported. For the mirror tracing task, the only measure on which there was a significant difference between patients with AS and controls was for changes in performance with the untrained hand, with patients with AS actually showing a greater increase in performance with the untrained hand than controls. However, this is likely to be associated with the fact that the initial performance with the non-dominant hand was much poorer for patients with AS than for controls ($t = 2.103$, $df =$

32, p = 0.043). There was no significant difference between patients with AS and controls on any of the other measures of motor learning on the mirror tracing task, and in fact patients with AS actually performed better that controls on almost all the measures of this task.

For the rotary pursuit, there was no significant difference between the performance of patients with AS and their controls on any of the measures of motor learning. These findings thus support the prediction that patients with AS would not have significant problems with motor learning. It is worth noting that visual observation revealed that patients with AS did show odd movements when carrying out the rotary pursuit task. They had a tendency to grip the stylus tightly and rush the circular movements so that they repeatedly found themselves waiting for the light to catch up to the stylus before continuing to follow it round again.

The results of mixed-model analyses (repeated measure ANOVAs) which were carried out for all of the tests involving the same trial with both the dominant and the non-dominant hand showed that there was no evidence for a significant difference between the level of performance between the two hands for patients with AS and controls.

3.5 Summary

The investigations into motor function in patients with PFT and patients with AS have revealed that patients with PFT have difficulties with a variety of uni-manual and bi-manual motor functions but are not impaired on all measures of motor learning. Within the patient group with PFT, individuals with right hemisphere pathology had difficulties with all measures of motor function, individuals with left hemisphere pathology had relatively few difficulties and individuals with midline pathology had difficulty on a test of fine motor ability and some subtle problems with a task involving motion perception.

The results for the patients with AS showed that they have difficulties with motor control of the hand and arm and have some difficulties with fine motor action. It was argued that the problems with motor control of the hand and arm are related to the clumsiness frequently

reported in individuals with autism and AS. Despite these motor control difficulties, patients with AS did not have difficulties with bi-manual motor function or with motor learning, indicating that a number of motor functions may not be problematic for these patients.

CHAPTER 4: COGNITIVE FUNCTION

The aims of the studies presented in this chapter were to characterize the cognitive abilities of the patient groups with posterior fossa tumours, and those with Asperger's Syndrome and to gain an understanding of the pattern of intact and impaired cognitive functions that may be associated with different types of cerebellar abnormality.

As discussed in Section 1.1, depending on the timing and extent of brain pathology, there will be different effects on the development of behavioural and cognitive function. In AS, the brain abnormality is thought to be present right from the beginning of in utero development and is therefore presumed to affect the earliest connections and networks of the developing brain. This means that from the very start, the brains of individuals with AS are compromised in terms of their potential. Individuals with PFT, on the other hand, have had normal brains and normal development prior to the onset of the tumour. For these patients, further development of cognitive and behavioural function subsequent to the tumour will be dependent on a number of factors. These include the precise location of the tumour, the extent of the damage caused by the tumour as well as the timing of the damage (which will determine the extent to which lower-level as opposed to higher-level functions are affected).

Furthermore, different aspects of cognition do not develop in isolated modules, but rather in interaction and association with a wide variety of networks and neurobiological systems. For this reason, and because of the extensive number of connections between different functional brain systems, it is possible that pathology in one region (and the direct resultant effects on functions subserved by that region) will also indirectly compromise functions in other regions, systems or networks as well. Therefore, the focus of the investigations in this chapter will be not solely on the primary core deficits in each of the patient groups, but also on other associated problems or difficulties.

Before detailing the particular tests of cognitive function that were used in this study, previous work on cognition in patients with PFT and in patients with AS will first be considered.

Chapter outline

The chapter starts with an overview of previous studies of cognition in each of the two patient groups. On the basis of this previous work, as well as the functional imaging studies of the cerebellum considered in Chapter 1, hypotheses as to the predicted outcomes of the cognitive tests administered in this study will then be outlined. The methods and results of the different tests are divided into sections according to the cognitive domain they assess (e.g. literacy, numeracy, visual matching, copying and drawing, and executive function comprising the domains of attention, working memory, and category sorting). The chapter ends with a discussion and summary of the pattern of intact and impaired cognitive abilities in each of the two patient groups.

4.1 Cognitive function in patients with PFT

Relatively few investigations have been carried out on the cognitive functions of individuals who have undergone surgery for posterior fossa tumours. A number of these studies were described in Section 1.4.3.1.5 and will therefore only be briefly outlined here. Steinlin et al. (2003) found that patients with PFT had problems with memory, speed of processing and interference, and a number also had problems with attention. In addition, Steinlin et al. (2003) noted the presence of various psychiatric symptoms, including anorexia, phobia, temper tantrums and addiction problems. Riva & Giorgi (2000) found some evidence for localisation of function in the cerebellum. They found that damage to the right cerebellum was associated with deficits in auditory sequential memory and language processing, and damage to the left cerebellum was associated with deficits in spatial and visual sequential memory. Both of these studies found that damage to the vermis was specifically associated with behavioural disturbances or psychiatric complications. A study by Levisohn et al. (2000) found impairments in executive function, visuo-spatial function, expressive language, modulation of affect (particularly associated with vermal damage) and verbal memory in patients with PFT. In addition, they found that

the neurobehavioural outcome is related to age at surgery, with younger children being less likely to show cognitive or affective deficits. A study by George et al. (2003), which showed that patients with PFT were impaired on IQ and memory, also found associations between age at diagnosis and behavioural outcome. However, in their study, the children who had surgery at a younger age were more impaired, having significantly lower IQs than the older children.

It is interesting to consider these findings in the light of the mechanisms of normal and abnormal brain development. As was detailed in Section 1.1, early pathology tends to have more widespread adverse effects on cognitive function than late pathology, particularly if the brain damage is sustained before cognitive functions have developed. Such early pathology will consequently affect both basic functions and the more specialized abilities that develop through modularization and depend on these basic functions being intact. Furthermore, after early brain pathology, compensation mechanisms are thought to come into play that sacrifice high-level functions in order that basic functions can be rescued. It would therefore be predicted that posterior fossa tumours that develop early in life will result in restrictions in overall cognitive ability, and ultimately with restrictions in the development of higher-order cognitive functions. These latter functions may be sacrificed in order to ensure that basic functions such as speech and communication, and visuospatial processing can be rescued. In contrast, individuals who develop tumours later in life would be predicted to show little restriction in overall cognitive and intellectual function but more selective deficits depending on the site and extent of pathology.

Unfortunately, few studies of patients with PFT have directly examined the effects of age at surgery. The two studies detailed above that investigated effects of age at pathology found contradictory results: Levisohn et al. (2000) found that individuals who had surgery when they were older had more cognitive problems, whereas George et al. (2003) found that, in line with the predictions of the current study, individuals who had surgery when they were younger had more severe cognitive problems. However, it is important to consider the particular functions on which the different patient groups were found to have difficulties. Levisohn et al. (2000) found that their patients with PFT had difficulties with a

combination of low and high-level functions ranging from memory to executive functions and visuo-spatial abilities. They found that individuals who were older at age at surgery had more problems than younger children.

There is evidence from other patient populations in support of the idea that some aspects of cognitive abilities can be spared by compensatory mechanisms after early pathology. For example, Vargha-Khadem et al. (2003) carried out a study where they compared episodic, semantic, and immediate memory in a group of children who had hypoxic-ischemic events before the age of one (early group) with a group of children who had hypoxic-ischemic events between the ages of 6-14 (late group). They found that the early group performed significantly better than the late group on immediate memory, but that the groups performed at a similar level on episodic and semantic memory. This led Vargha-Khadem et al. (2003) to conclude that only some aspects of memory and learning may be effectively rescued by early brain injury, with others remaining deficient irrespective of early or late onset of pathology.

The idea that individuals who have pathology at a younger age are particularly impaired on high-level cognitive functions, whereas older individuals show more selective deficits related to the functions subserved by the particular region of the brain that is damaged will be further investigated in this thesis.

Additional work that has been carried out on children with cerebellar lesions includes a study by Scott et al. (2001). They carried out magnetic resonance imaging scans as well as neuropsychological tests on seven children with cerebellar lesions. The results showed that lateralized damage to the cerebellum might selectively impair the cognitive functions in which the contralateral hemisphere of the cerebrum is involved. Furthermore, Hetherington et al. (2000) found that lesions of the cerebellum that occur in childhood result in enduring problems in short-duration perception, despite intact functional estimation of long durations.

In summary, previous studies of cognitive function in patients with PFT suggest that they may have difficulties with a variety of cognitive functions including executive function,

language (expressive and receptive), memory, visuo-spatial abilities, attention and speed of processing. Furthermore, evidence suggests that there may be an association between age at surgery and the severity of cognitive deficits: pathology at an early age may result in problems with high-level cognitive functions despite intact basic functions; in contrast, pathology at a later age is more likely to result in selective deficits depending on the precise area of the brain that is damaged.

4.2 Cognitive function in patients with autism and AS

As detailed in Section 1.4.3.2.1, autism is characterized by a triad of impairments in social interaction and communication, and restricted and repetitive behaviours and interests. There has been much interest in autism and Asperger's Syndrome and numerous studies have been carried out to investigate cognitive function in these patients. The cognitive domains in which individuals with autism have most consistently been found to show impairments are language and communication, face recognition, executive function and memory, and research into each of these domains is considered in some detail below.

a) Language and communication

As detailed in Section 1.4.3.2.1, one of the defining characteristics of autism is an impairment in both verbal and non-verbal communication. Even when language is present, it is often used for instrumental purposes rather than for social interaction. Furthermore, the language used has a tendency to be egocentric and repetitive (Tager-Flusberg, 1996).

Studies have found that the comprehension of language is impaired in autism (Bowler, 1992; Kerbeshian and Burd, 1986), and comprehension problems are actually more severe than problems with expression in individuals with autism (Boucher, 2003). This is associated with the fact that the expressive language used by individuals with autism is particularly formulaic, in that phrases may be memorized and re-produced (Loveland et al., 1997), and specific grammatical orders may be repeated (Dobbinson et al. 1998).

Individuals with AS appear to have particular problems with semantics. They have problems in understanding non-literal language such as play on words, metaphors and irony,

despite the fact that they have normal levels of vocabulary and grammatical skills (Happé, 1994).

b) Visual perception (including face processing)

One of the most consistent findings in investigations of visual perceptual abilities in autism is an impairment in the recognition of faces which appears to be independent of basic visuospatial processing abilities (Kracke, 1994; Szatmari et al. 1990). Deruelle et al. (2004), for example, carried out a study on face processing in individuals with autism where they required subjects to recognize faces on the basis of a number of variables including identity, emotion, gender, direction of gaze and lip reading. The results showed that, in contrast to controls, individuals with autism were better at matching on high frequency than on low frequency facial information (i.e. on local rather than global facial features). Furthermore, compared to controls, individuals with autism had problems matching faces on all of the variables except for identity matching. The inability to recognize facial expressions is likely to be associated with difficulties in social interaction highlighted in the theory of mind explanation of autism. As explained in Section 1.4.3.2.1, theory of mind refers to the ability to infer mental states including beliefs, desires, intentions, imagination and emotions (e.g. Baron-Cohen et al. 1994). This ability to infer other people's thoughts or feelings relies heavily on the ability to interpret facial expressions, and given that individuals with autism have difficulty with this, it is not surprising that they are not able to identify other people's thoughts or feelings.

It is important to note that this inability to recognize faces and facial expressions does not appear to be due to a more global problem with visual perceptual abilities, but seems to be a very specific difficulty. Studies have shown that individuals with autism perform at a similar or possibly even better level than controls on tests of visual perception and matching that do not involve faces. These tests include a visual-spatial Stroop task (Rinehart et al. 2002), block design (Bowler, 1992; Kerbeshian and Burd, 1986) a task requiring the shifting of attention from local to global features (Rinehart et al. 2001) and the Embedded Figure Test that was designed to assess visual perception abilities (Shah and Frith, 1983; Joliffe and Baron-Cohen, 1997).

In summary, individuals with autism have particular difficulties with the identification of faces and facial expressions and it is likely that these problems are associated with their difficulties with social interaction. Despite this severe impairment in face recognition, evidence suggests that many other visual perceptual abilities are intact.

c) Executive function

Executive function refers to the ability to guide and influence behaviour by referring either to previous mental models or to anticipated future goals. There is much evidence to suggest that effective executive functioning depends on the integrity of the frontal lobes, and, as described in Section 1.4.3.2.1, there is evidence to suggest that the frontal lobes may be abnormal in autism (Carper and Courchesne, 2000; Minshew et al., 1993; Bailey et al., 1998; Hughes et al., 1994). Patients with AS have been shown to exhibit severe deficits on tests of executive function (Upton and Corcoran, 1995; Bechara et al. 1994; Bishop, 1993). Furthermore, one of the theories of autism, the theory of executive dysfunction, is based on the fact that individuals with autism have difficulties with executive functioning, which is associated with abnormalities in the regions of the frontal lobes that subserve those functions. A number of studies that have investigated executive function in individuals with autism are considered below in order to demonstrate the nature and extent of difficulties that these individuals encounter with executive functioning.

The first study to be considered was carried out by Ozonoff et al. (2004). They carried out an investigation of executive functions in individuals with autism using a planning task and a measure of set shifting ability from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The results showed that individuals with autism performed significantly more poorly than controls on both of these tasks, indicating that individuals with autism have difficulties with at least two forms of executive function: planning and set shifting. This study supported the group's previous findings that individuals with Asperger's Syndrome were impaired on two tests of executive function: the Tower of Hanoi (which assesses planning abilities) and the Wisconsin Card Sorting Task (WCST which assesses mental flexibility or set-shifting abilities) (Ozonoff et al. 1991).

Another study of executive function in autism was carried out by Geurts et al. (2004). They found that individuals with autism were significantly impaired on tests of a number of different executive functions, including inhibition, planning, cognitive flexibility and verbal fluency. Furthermore, they found that individuals with autism show more generalized and more profound problems with these tasks than do individuals with attention deficit hyperactivity disorder (ADHD), supporting the possibility that executive dysfunction is particularly prominent in autism compared to other developmental disorders.

In summary, evidence suggests that individuals with autism have difficulties with a number of aspects of executive function, including planning, set-shifting, inhibition and verbal fluency. Given that these functions are known to depend on the integrity of the frontal lobes, it is likely that these difficulties are associated with abnormalities in the frontal lobes in individuals with autism.

d) Memory

Studies of memory in individuals with autism have found that working memory and recognition skills tend to be intact, despite problems with long-term recall. Minshew and Goldstein (2001), for example, administered a battery of auditory and visual memory tests to a group of 52 individuals with autism and 40 matched control participants. The results showed that the individuals with autism performed particularly poorly on the immediate and delayed recall of a story and of a complex geometric figure, on a list-learning task, on word span and on repetition of complex sentences. However, they performed at a similar level to controls on working memory, paired-associated learning tasks and on letter span. Minshew and Goldstein (2001) concluded that the memory problems encountered by these individuals are not modality specific and that individuals with autism have greater difficulties with more complex materials. This is in line with a study by Ozonoff and Strayer (2001) who found that individuals with autism were not impaired on five dependent measures of working memory, and therefore argued that working memory is not one of the executive functions on which individuals with autism have particular difficulties.

Individuals with autism have been found to perform relatively well on tests of recall if this is cued or if the stimuli have previously been repeatedly presented. For example, a study by Boucher and Warrington (1976) demonstrated intact cued recall in individuals with autism. They showed that individuals with autism are able to recall pictures if they are provided with a semantic or a phonetic cue. Boucher and Warrington (1976) also demonstrated that individuals with autism were not significantly impaired on a recall task that involved the repeated presentation of stimuli over a number of trials. Thus it may be free recall in particular with which individuals with autism have difficulties. Support for this possibility comes from a study by Bowler et al. (1997) who showed that individuals with autism were impaired on a task involving the recall of a list of words after a single presentation of this list. In addition, Boucher and Warrington (1976) found that individuals with autism were impaired on a task involving free recall of pictures presented once.

Further support for problems with free recall in individuals with autism comes from a study by Bennetto et al. (1996). They found that individuals with autism performed significantly more poorly than controls on tests of source memory, temporal order memory, supraspan free recall and working memory, but not on short- and long-term recognition, cued recall or new learning ability. Bennetto et al. (1996) had hypothesized that given the difficulties with executive functions that have been reported in individuals with autism, these patients should perform at a similar level to other patient groups with executive function deficits. Their results supported this hypothesis and Bennetto et al. (1996) therefore argued that the memory difficulties encountered by individuals with autism were associated with a limit in the capacity of their central cognition.

This suggestion of a capacity limitation is in line with a study Russell et al. (1996). They administered tests of working memory to individuals with autism and found that, although they used similar articulatory rehearsal methods to the control participants, individuals with autism performed more poorly than matched controls on tests designed to look at the capacity of the central executive of working memory.

There is evidence to suggest that there may be a difference in the level of memory function between individuals at the top end of the autistic spectrum (individuals with high functioning autism and Asperger's Syndrome) and individuals lower down this spectrum. It has been argued that individuals at the top end of the autistic spectrum have intact semantic (factual) memory, but a selective impairment in episodic (contextual) memory. Individuals lower down the spectrum, on the other hand, are thought to have more widespread problems with both aspects of memory (Boucher, 1981; Boucher and Lewis, 1989; Farrant et al. 1998).

In summary, evidence suggests that individuals with autism have selective problems with memory. It seems that working memory, cued recall and recognition abilities are relatively intact, but that free recall tends to be impaired.

4.3 Methods

4.3.1 Cognitive tests administered

As discussed at the beginning of this chapter, cognition does not develop in isolation. For this reason, and because of the large number of connections between different functional brain systems, it was deemed to be important to focus not only on the primary core deficits in each of the patient groups, but also on other associated problems or difficulties that might be present. Therefore, the cognitive tests included in this study were selected to tap a variety of cognitive domains ranging from basic functions through to complex higher-order abilities in order to gain an understanding of the pattern of intact and impaired cognitive functions that may be associated with different types of cerebellar abnormality. The particular cognitive tests chosen for this study were those on which previous studies had found patients with cerebellar damage to be impaired (for example digit span and corsi block span). For those functions that had not previously been tested on cerebellar patients, common standardized tests were chosen wherever possible (for example the Benton test of facial recognition). The only test that does not fit into either of these categories is the face-sorting test. However, as described in Section 4.4.4.3 below, this test is a modified version of the Wisconsin Card Sorting test (WCST) on which patients with cerebellar damage have previously been found to show impairment. It was decided to use this test rather than the

WCST because this test still assesses executive function in the same way as the WCST, however it has the added benefit of testing face recognition abilities which are thought to be abnormal in individuals with autism (Kracke, 1994; Szatmari et al. 1990).

The first tests to be described are baseline tests of literacy (WORD) and numeracy (WOND) that were administered in order to gain an understanding of the general level of academic function of the different patient and control participants. The literacy test was particularly interesting for the patients with AS, because an abnormality in verbal communication is one of the defining characteristics of autism, and because the results of the developmental questionnaire showed that out of 14 patients, eight were reported by their parents to have language problems. Furthermore, by directly assessing literacy skills, it was hoped that it would be possible to determine whether language problems in AS were more severe than problems with other cognitive functions.

The next tests to be described are tests of visual matching abilities, which were used to investigate basic visual processing abilities in order to determine whether any impairments on more complex tasks (such as face-sorting which is described below) may be due to difficulties with visual matching abilities. The first of these tests is the Benton test of Line Judgment that looks at the ability to match lines presented at different orientations. This is a purely visual perceptual task that does not require any motor abilities and was included to test the prediction that individuals with autism have selective problems with visual perception that are confined to facial recognition, and that they should therefore perform at a level similar to controls on this test of visual perception abilities. The second test of visual perception abilities is the Benton test of facial recognition which examines abilities to match human faces under normal and unusual lighting conditions and when the faces are presented at different angles. There is much evidence to suggest that individuals with autism have difficulties with matching faces and recognizing facial expressions. This test is particularly useful because facial expressions are kept constant, but the cues by which the faces can be matched vary. This means that it should be possible to determine whether the patients with AS have difficulties with all aspects of face-matching, or whether there are particular parts on which they struggle. For patients with PFT, there is little evidence to

indicate that cerebellar pathology results in problems with visual perception. However, as explained at the beginning of this section, it is important to investigate not only the core deficits of patients but also to investigate other cognitive functions as it is very possible that cerebellar pathology also impacts on other functional brain systems.

The next test to be reported is a test of copying and drawing, which depends on attention, working memory and visual perceptual abilities. This is the test of visuo-motor integration (VMI). The VMI builds on the Benton lines test described above as it depends on similar visuo-perceptual abilities but also requires motor actions as subjects are required to copy a number of increasingly complex shapes, rather than simply identifying matching lines. This test was included because it was deemed interesting to investigate the degree to which visual perceptual abilities are intact in each of the patient groups and to see whether, if they performed well on the Benton lines test, they would also perform well on this test which required additional motor abilities.

Attention is an aspect of executive function subserved by the frontal lobes and as detailed in Section 1.4.3.2.1, there is evidence to suggest that individuals with autism have abnormalities in the frontal lobes. Furthermore, pathology of the cerebellum is likely to affect its connections to the frontal lobes and it is therefore likely that patients with PFT will experience difficulties with attention control. The tests selected to assess attention abilities are the letter and number cancellation tasks. These are simple tests that look at visual scanning and attention to detail and are suitable for the entire age range of individuals who participated in this study (age 8-20).

For working memory, tests of verbal (digit span and word and non-word repetition) and spatial (Corsi block-span) working memory were administered in order to investigate the extent of working memory function in the different patient populations. Individuals with autism have been argued to have intact working memory and we were interested in determining whether this was also true for individuals with Asperger's Syndrome. Furthermore, there is mounting evidence that the cerebellum is involved in memory (Fiez et al., 1996; Paulesu et al., 1993, 1995; Desmond et al., 1997; Mathiak et al. 2004) and that

individuals with PFT have difficulties with memory (Steinlin et al., 2003; Riva and Giorgi, 2000; Levisohn et al., 2000) and it was therefore also of particular interest to look at working memory function in individuals with PFT. Finally, the results of the developmental questionnaire showed that 6 out of 15 patients with PFT and 8 out of 14 patients with AS were reported by their parents to have problems with memory and it was therefore important to investigate these memory problems.

The final test to be reported is a complex test of executive function designed by Vargha-Khadem and Isaacs (unpublished) that requires the integration of a number of different abilities. This is the face-sorting task (an analogue of the Wisconsin Card Sorting Task) that requires attention, working memory, visual perception and matching abilities as well as the higher-level abilities of set maintenance and perseverance avoidance. This task builds on the simple matching required in the Benton test of facial recognition, as the faces in this task differ on emotion, age and race. This means that it should be possible to further investigate the nature of the difficulties with the identification of facial expressions in individuals with autism and also to investigate whether these patients are able to match faces on the basis of age and race. The executive functions tested by the face-sorting task are known to rely on the frontal lobes. Given the fact that there is evidence that the frontal lobes are abnormal in autism, and that the strong connections between the cerebellum and the frontal lobes mean that cerebellar pathology is likely to impact on frontal lobe function in patients with PFT, the results of this face-sorting test should be informative.

4.3.2 Aims and Predictions

The aims of the neuropsychological studies of cognitive function reported in this chapter were (1) to characterize the nature of cognitive difficulties that result after neurodevelopmental compared to acquired pathology of the cerebellum; (2) to determine whether, within the patient group with PFT, there is any association between location of tumour (left hemisphere, midline or right hemisphere) and functional impairment; (3) to determine whether, within the patient group with PFT, there is a relationship between age at pathology and functional impairment; (4) to determine whether, within the patient group with PFT, there is a relationship between time since surgery and functional impairment; (5)

to investigate whether individuals with AS have difficulties with executive functions, in line with the theory of executive dysfunction in autism; and (6) to investigate whether individuals with AS have global difficulties in face processing and whether these difficulties are associated with the socio-emotional impairments that are characteristic of autism.

Between-group comparisons of neuropsychological data from each of the patient groups and their matched control group were carried out. On the basis of previous studies of patients with PFT, of patients with AS and of cerebellar function, the predictions for the cognitive abilities of each of the two patient groups are as follows:

(i) Patients with PFT

Patients with PFT will have difficulties compared to control participants in:

- **Attention.** This is because previous studies of patients with PFT have revealed problems with attention (Steinlin et al. 2003); because functional imaging studies have found activation in the cerebellum during attention tasks (Allen et al., 1997; Le et al., 1998; Rees et al., 1997) and because attention relies on intact frontal lobe function and damage to the cerebellum is likely to impact on the frontal lobes because of the strong connections between these brain areas.
- **Working memory.** There is evidence from functional imaging studies to suggest that the cerebellum plays an important role in working memory (Andreasen et al. 1995; Desmond et al., 1997). Furthermore, the results from the developmental questionnaire presented in Chapter 2 showed that out of 15 patients, 6 were reported by their parents to have problems with memory. Tests of both verbal and spatial working memory are administered in order to investigate the working memory difficulties encountered by these patients.
- **Executive functions.** These functions are subserved by the frontal lobes and include the ability to maintain set and the ability to avoid perseverance in the face-sorting task. Patients with PFT are predicted to be impaired on executive functions because it is predicted that cerebellar pathology will result in damage to the

connections of the cerebellum and thus difficulties with functions in which the frontal lobes are involved.

- There will be an association between tumour location and functional impairment. Individuals with pathology of the right cerebellum will be impaired on tasks involving language (because the left cerebral hemisphere which controls language has contralateral connections to the right cerebellum) and individuals with pathology of the left cerebellum will be impaired on tasks involving spatial abilities (in line with Riva and Giorgi, 2000).
- Given that compensatory mechanisms are thought to come into play after early pathology of the brain which ensure that basic functions are intact, it is predicted that patients who had early pathology of the cerebellum (age five and younger, before children have received structured academic instruction) will perform better than patients who had later pathology (age six and above) on tests of basic functions (these include the WORD, the WOND which test academic attainment, the letter and number cancellation task which tests attention and the word and non-word repetition, digit span and Corsi block span which test working memory). However, given that compensatory mechanisms which come into play at an early age may have an adverse effect on the development of higher-level functions (see Section 1.1), it is predicted that patients who had early pathology of the cerebellum (age five and younger) will be impaired on high-level cognitive functions (executive function as assessed by the face-sorting task and visuo-spatial functions as assessed by the VMI, Benton test of facial recognition and Benton test of line judgment) compared to patients who had later pathology of the cerebellum (age six and above).
- There will be very few significant correlations between time since surgery and performance on any of the cognitive tests. This is because all of the patients with PFT who are taking part in this study are seen at least two years post-surgery and it is predicted that after this time there will be no more major changes in the brain.

(ii) Patients with AS

- Patients with AS will have difficulties compared to control participants with:

- **Literacy.** Patients with AS are predicted to be impaired on the tests of basic reading and spelling from the WORD because the results of the developmental questionnaire showed that 9 out of 14 patients were reported by their parents to have difficulties with language. Furthermore, patients with AS are predicted to be impaired on the test of reading comprehension because abnormal communication is one of the principal characteristics of autism.
- **Attention.** This is because attention relies on intact frontal lobe function and there is evidence to suggest that the frontal lobes are abnormal in individuals with autism.
- **Working memory:** Executive functions depend to a certain degree on intact working memory abilities (Berman et al., 1995) and because of the strong predictions concerning impairments in executive function in individuals with autism, it should be informative to investigate the level of working memory abilities in individuals with AS. Previous studies have found that working memory abilities are intact in individuals with autism. Nevertheless, the results of the developmental questionnaire showed that out of 14 individuals with AS, 8 were reported by their parents to have difficulties with memory, and the possibility that these memory problems are problems with working memory in particular in individuals with AS therefore requires investigation.
- **Face matching.** This ability is tested by the Benton Test of Facial Recognition and the face-sorting task. Patients with AS are predicted to be impaired on tests of face matching because previous studies have found that individuals with autism have particular difficulties with the recognition of faces and of facial expressions (Deruelle et al., 2004; Kracke, 1994; Szatmari et al. 1990) and because difficulties with face processing are likely to be associated with the socio-emotional impairments characteristic of autism. It is predicted that face matching will be the only area of visual perception on which individuals with AS will show an impairment compared to controls; they are not predicted to have difficulties with the Benton test of line judgment, nor with the test of visuo-motor integration (VMI).
- **Executive functions.** These functions are subserved by the frontal lobes and include the ability to maintain set and the ability to avoid perseverance in the face-sorting task. Patients with AS are predicted to be impaired on tests of executive

function because previous studies have identified abnormalities in the frontal lobes in autism (Carper and Courchesne, 2000; Minshew et al., 1993; Bailey et al., 1998; Hughes et al., 1994) and because in some respects individuals with autism have been found to perform in a similar way to patients with pathology of the frontal lobes (Shallice, 1988). Furthermore, the theory of executive dysfunction maintains that problems with executive function can explain the pattern of abnormalities seen in individuals with autism. In addition, a previous study found that individuals with Asperger's Syndrome were impaired on two tests of executive function: the Tower of Hanoi and the Wisconsin Card Sorting Task (Ozonoff et al. 1991).

4.3.3 Statistical analyses

The main statistical methods employed in this study were detailed in Section 2.2.3. In order to assess main effects of group, statistical analyses were carried out between patients with PFT and their matched controls and between patients with AS and their matched controls using independent sample t-tests. In addition, for tests that did not have standardized scores, ANCOVA analyses were carried out with age as a covariate in order to determine whether the age of the participants had any effect on the results. ANOVAs were carried out in order to investigate whether there were any within-group differences in the patients with PFT related to the location of the tumour (left hemisphere, right hemisphere or midline tumour), and in order to determine whether there were any effects of age at pathology or time since pathology, correlation analyses (Pearson's) were carried out separately between each of these measures and each of the measures of cognitive function.

As explained in Section 2.2.3, multiple comparison adjustment was not performed in this thesis. Instead a cut-off of $p<0.05$ was chosen as a mechanism for flagging potential problematic cognitive functions in the patient groups which will require further investigation in future studies. Any significant findings at this level (p-values <0.05) will be interpreted with caution and where there were strong expectations of effects, p values in the range 0.05 - 0.1 will also be commented upon (these will be referred to as weak evidence for an effect).

4.4 Results

The methods and results for each of the cognitive tests for both the patients with PFT and the patients with AS are detailed in this section.

4.4.1 Academic attainment

4.4.1.1 Wechsler Objective Reading Dimensions (WORD)

The WORD (Rust et al., 1993) was administered to assess reading and spelling abilities. This test comprises three sub-tests (Basic Reading, Spelling, Reading Comprehension) each of which is scored separately as well as producing a combined score (the WORD composite standard score) for the whole test. This is a standardized test and therefore age-adjusted standardized scores were calculated and used in the analyses of the results. The WORD is designed for children between the ages of 6 years 0 months and 16 years 11 months; however it was administered to all participants in this study as the patient groups in particular were unlikely to reach ceiling values. For participants over 16 years 11 months of age, the age-adjusted scores for the highest age group (16 years 8 months to 16 years 11 months) were used.

a) Patients with PFT: WORD

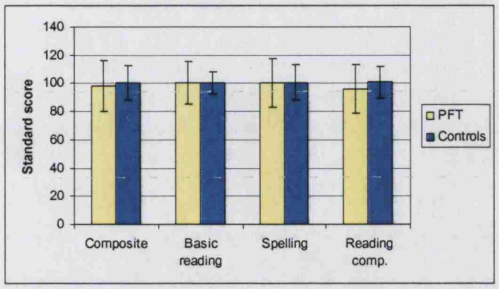
Table 4.1 and Figure 4.1 show the mean standard scores on the subtests of the WORD as well as the composite standard score for patients with PFT and their controls.

Table 4.1: Mean standard scores on the WORD for patients with PFT and controls

Group	Composite	Basic reading	Spelling	Reading Comp.
PFT	98.27 (17.93)	100.07 (15.08)	100.20 (17.11)	95.93 (17.24)
Controls	100.40 (12.04)	100.30 (8.27)	100.40 (12.63)	100.80 (11.12)

Mean (sd)

Figure 4.1: Mean standard scores on the WORD for patients with PFT and controls



Statistical analysis showed that patients with PFT performed significantly more poorly than controls on the reading comprehension subtest of the WORD (Mann-Whitney U-test: z = -1.974, p = 0.048). However, the score for patients with PFT was still a good score for this test indicating that although they performed more poorly than controls, reading comprehension does not appear to be particularly problematic for these patients. In addition, the standard deviations are very large, indicating that there is much variation in performance between individual patients with PFT. There was no significant difference between patients and controls for the other measures of the WORD (reading, spelling and composite score): WORD composite score (t = -0.329; df = 23; p = 0.745), basic reading (t = -0.044; df = 23; p = 0.965), spelling (t = -0.032; df = 23; p = 0.975).

ANCOVA analyses revealed that the difference on the reading comprehension subtest could not be accounted for by differences in levels of verbal IQ (ANCOVA F(1,25) = 4.988, p = 0.036.)

Further analysis within the PFT group (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no interaction between tumour location and performance on any of the measures of the WORD.

b) Patients with AS: WORD

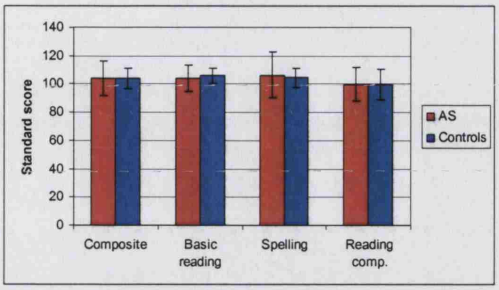
Table 4.2 and Figure 4.2 show the mean standard scores on the subtests of the WORD as well as the composite standard score for patients with AS and their controls.

Table 4.2: Mean standard scores on the WORD for patients with AS and controls

Group	Composite	Basic reading	Spelling	Reading Comp.
AS	103.71 (12.29)	103.64 (9.38)	106.21 (16.15)	99.93 (11.74)
Controls	103.60 (7.23)	106.00 (5.40)	104.40 (6.84)	99.40 (10.71)

Mean (sd)

Figure 4.2: Mean standard scores on the WORD for patients with AS and controls



Statistical analysis showed that there was no significant difference between patients with AS and their controls on any of the measures of the WORD: WORD composite standard score ($t = 0.026$; $df = 22$; $p = 0.979$), basic reading ($t = -0.712$; $df = 22$; $p = 0.484$), spelling ($t = 0.333$; $df = 22$; $p = 0.742$), reading comprehension ($t = 0.113$; $df = 22$; $p = 0.911$).

Because there were strong predictions that individuals with AS would be impaired on the language abilities tested by the WORD, differences in VIQ levels were partialled out using ANCOVAs. This did not, however, affect the results.

It should be noted that although the mean levels of performance on the subtests of the WORD were similar for the patients with AS and the controls, individuals with AS show a greater variation in performance than do controls, particularly for the spelling subtest (as indexed by the standard deviations reported in Table 4.2). This suggests that it is possible that some patients with AS may have particular problems with language, but that others perform better than controls and this might explain why statistical analysis showed no significant differences between the two groups.

4.4.1.2 Wechsler Objective Numerical Dimensions (WOND)

The WOND (Rust, 1996) was administered to assess mathematical abilities. It comprises two sub-tests (mathematics reasoning and numerical operations) both of which are scored separately as well as producing a combined score (the WOND composite standard score) for the whole test. This is a standardized test and therefore age-adjusted standardized scores were calculated and used in the analyses of the results. As was the case for the WORD, the WOND was also designed for children between the ages of 6 years 0 months and 16 years 11 months; however, it was administered to all participants in this study as the patient groups in particular were unlikely to reach ceiling values. For participants over 16 years 11

months of age, the age-adjusted scores for the highest age group (16 years 8 months to 16 years 11 months) were used.

a) Patients with PFT: WOND

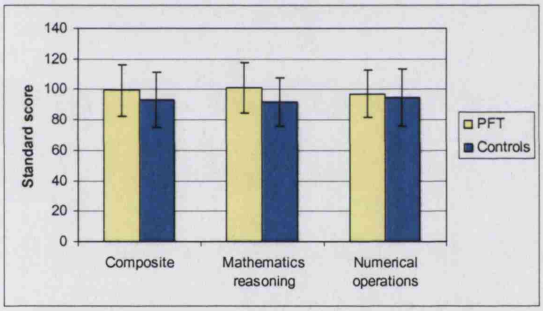
Table 4.3 and Figure 4.3 show the mean standard scores on the subtests of the WOND as well as the composite standard score for patients with PFT and their controls.

Table 4.3: Mean standard scores on the WOND for patients with PFT and controls

Group	Composite	Mathematics reasoning	Numerical operations
PFT	99.27 (17.14)	100.93 (16.74)	97.00 (15.26)
Controls	93.00 (17.98)	91.60 (15.88)	94.20 (18.78)

Mean (sd)

Figure 4.3: Mean standard scores on the WOND for patients with PFT and controls



Statistical analysis showed that there was no significant difference between patients with PFT and their controls on any of the measures of the WOND: composite standard score ($t = 0.879$; $df = 23$; $p = 0.389$), mathematical reasoning ($t = 1.393$; $df = 23$; $p = 0.177$), numerical operations ($t = 0.410$; $df = 23$; $p = 0.685$).

Further analysis within the PFT group (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no interaction between tumour location and performance on the WOND.

b) Patients with AS: WOND

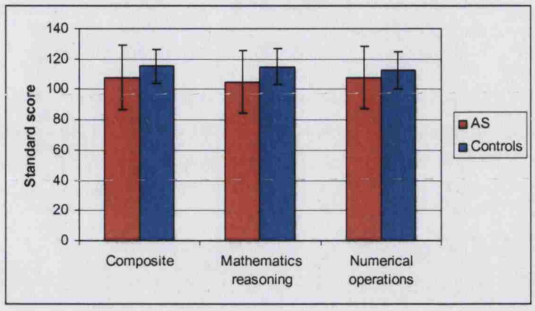
Table 4.4 and Figure 4.4 show the mean standard scores on the subtests of the WOND as well as the composite standard score for patients with AS and their controls.

Table 4.4: Mean standard scores on the WOND for patients with AS and controls

Group	Composite	Mathematics reasoning	Numerical operations
AS	107.79 (21.42)	105.00 (20.81)	107.64 (20.59)
Controls	115.40 (11.19)	114.90 (11.85)	112.40 (12.19)

Mean (sd)

Figure 4.4: Mean standard scores on the WOND for patients with AS and controls



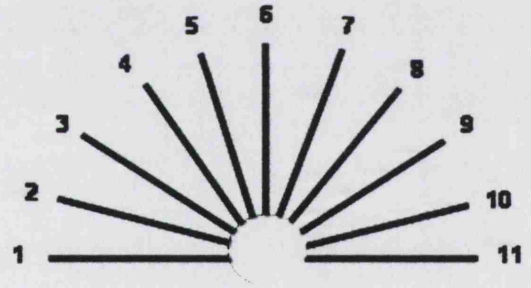
Statistical analysis showed there was no significant difference between patients with AS and their controls on any of the measures of the WOND: composite standard score (t = -1.024; df = 22; p = 0.317), mathematical reasoning (t = -1.351; df = 22; p = 0.190), numerical operations (t = -0.651; df = 22; p = 0.522).

4.4.2 Visual matching

4.4.2.1 Benton Judgment of Line Orientation

This is a test of visuospatial matching ability (Benton et al., 1978; Benton et al., 1983) which requires subjects to identify which two of eleven black lines presented in a semicircular pattern (see Figure 4.5) match the orientation and angle of two target lines. The test has thirty items in each of which there are two lines to be matched and the maximum total score is 30.

Figure 4.5: Stimuli from the Benton Judgment of Line Orientation test



(i) Patients with PFT: Benton judgment of line orientation

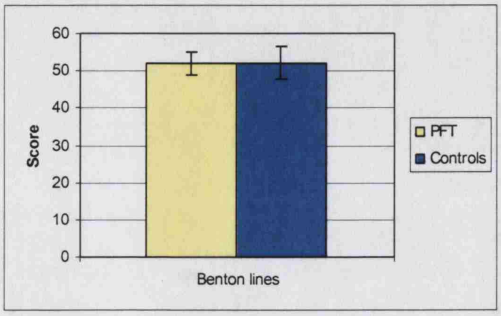
Table 4.5 and Figure 4.6 show the mean scores on the Benton lines test for the patients with PFT and their controls.

Table 4.5: Mean scores on the Benton lines test for patients with PFT and controls

Group	Benton lines
PFT	52.13 (3.09)
Control	52.10 (4.33)

Mean (sd)

Figure 4.6: Mean scores on the Benton lines test for patients with PFT and controls



Statistical analysis showed that there was no significant difference between the performance of patients with PFT and controls on the Benton lines test ($t = 0.023$, $df = 23$, $p = 0.982$, ANCOVA with age $F(1,25) = 0.053$, $p = 0.819$).

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the Benton lines test.

(ii) Patients with AS: Benton judgment of line orientation

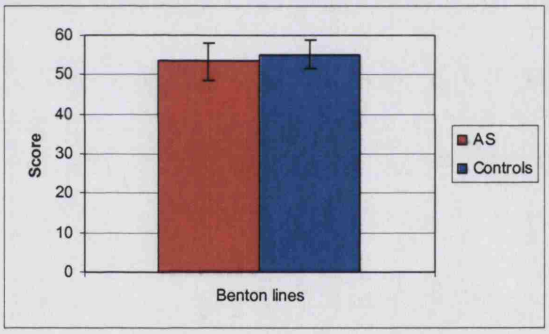
Table 4.6 and Figure 4.7 show the mean scores on the Benton lines test for the patients with AS and their controls.

Table 4.6: Mean scores on the Benton lines test for patients with AS and controls

Group	Benton lines
AS	53.36 (4.88)
Control	55.20 (3.62)

Mean (sd)

Figure 4.7: Mean scores on the Benton lines test for patients with AS and controls



Statistical analysis showed that there was no significant difference between the performance of patients with AS and controls on the Benton lines test ($t = -1.011$, $df = 22$, $p = 0.323$, ANCOVA with age $F(1,24) = 0.771$, $p = 0.390$).

4.4.2.2 Benton test of Facial Recognition

This test was designed by Benton and Van Allen (1968) and Benton et al. (1994) to assess the ability of subjects to match unfamiliar human faces in different orientations and under different lighting conditions. The 1983 version of the full test (long-form) was administered in this study (Benton et al. 1983). This consists of three sections:

a) **Matching identical face-on photographs**: A single face-on photograph is presented to the subject who is asked to choose which one of six face-on

photographs presented below the original, shows the same person. A total of six target faces (three male and three female) is presented in this section.

b) **Matching of face-on with three-quarter-view photographs:** A single face-on photograph is presented to the subject who is asked to choose which three of the six three-quarter-view photographs presented below the original, show the same person. A total of eight target faces (four male and four female) is presented in this section, requiring a total of 24 responses.

c) **Matching of face-on photographs under different lighting conditions:** A single face-on photograph taken under full lighting is presented to the subject who is asked to choose which three of six face-on photographs taken under different lighting conditions and presented below the original, show the same person. A total of eight target faces (four male and four female) is presented in this section, requiring a total of 24 responses.

(i) Patients with PFT: Benton test of face recognition

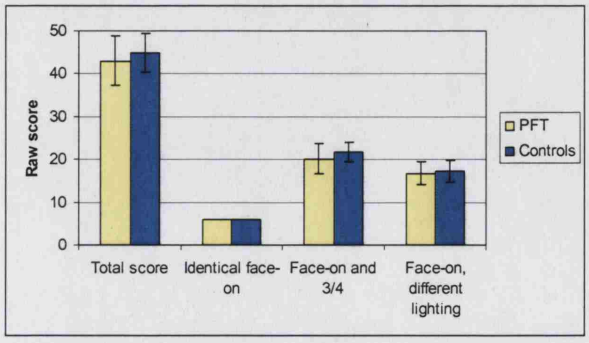
Table 4.7 and and Figure 4.8 show the mean scores on the Benton faces test for the patients with PFT and their controls.

Table 4.7: Mean scores on the Benton faces test for the patients with PFT and their controls

Group	Total score	Identical face-on	Face-on and ¾ view	Face-on under different lighting
PFT	43.00 (5.84)	6 (0)	20.17 (3.52)	16.73 (2.66)
Control	44.90 (4.46)	6 (0)	21.70 (2.31)	17.20 (2.62)

Mean (sd)

Figure 4.8: Mean scores on the Benton faces test for patients with PFT and controls



Both patients with PFT and controls correctly matched all the identical face-on photographs and statistical analysis was therefore not carried out on these scores. For the remaining measures, statistical analysis showed that there was no significant difference between the performance of patients with PFT and controls: total score ($t = -0.871$, $df = 23$, $p = 0.393$, ANCOVA with age $F(1,25) = 0.387$, $p = 0.540$); face-on and ¾ view ($t = -1.133$, $df = 23$, $p = 0.269$, ANCOVA with age $F(1,25) =$

0.857, p = 0.365); face-on under different lighting (t = -0.433, df = 23, p = 0.669, ANCOVA with age F(1,25) = 0.035, p = 0.854).

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was a significant interaction between location of tumour and performance on the Benton faces total score (F(2,12) = 7.631, p = 0.007) and on matching the face-on and ¾ view photographs (F(2,12) = 7.350, p < 0.001) and weak evidence for a significant interaction between tumour location and performance on matching face-on photographs under different lighting conditions (F(2,12) = 2.479, p = 0.073).

The mean scores for each of the PFT groups on each of the Benton faces scores are shown in Table 4.8 below.

Table 4.8: Mean scores on the Benton faces test for PFT groups

Group	Total score	Face-on and ¾ view	Face-on under different lighting
LH damage	44.00 (5.24)	21.20 (2.17)	16.80 (3.27)
Midline damage	47.60 (1.52)	22.80 (0.84)	18.80 (0.84)
RH damage	37.40 (4.78)	16.80 (3.70)	14.60 (1.52)

Mean (sd)

Patients with right hemisphere damage performed most poorly on the Benton faces test, and patients with midline damage performed best. Patients with right hemisphere damage had particular difficulties with matching face-on photographs with ¾ view ones. Post hoc analysis (Tukey's test) showed that there was a significant difference between those with midline and those with right hemisphere damage for the total score (p = 0.006), for matching face-on and ¾ view photographs (p = 0.007) and for matching face-on photographs under different lighting (p = 0.023). There was a significant difference between those with left hemisphere and those with right hemisphere damage for matching face-on and ¾ view photographs (0.043), weak evidence for a significant difference between these groups for the total score (p = 0.068) and no evidence for a significant difference on matching face-on photographs under different lighting conditions (p = 0.272). There was no significant difference between those with left hemisphere and those with midline damage on any of the measures of this test. These results indicate that individuals

with right hemisphere damage may have particular difficulties with this task compared to individuals with pathology affecting other areas of the cerebellum. However, there were large standard deviations for both patients with left hemisphere and patients with right hemisphere pathology on this test, indicating that there was much variation in the performance of patients with damage to similar regions of the cerebellum. These findings will therefore be interpreted with caution.

(ii) Patients with AS: Benton test of face recognition

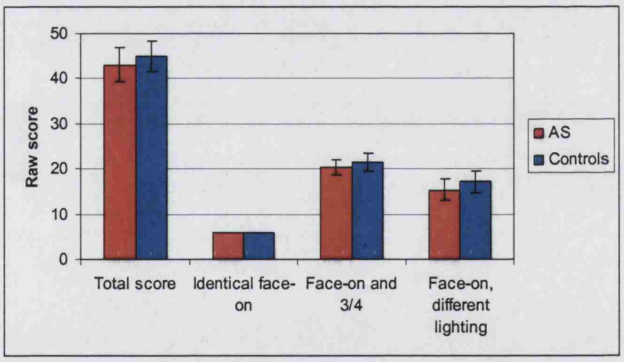
Table 4.9 and Figure 4.9 show the mean scores on the Benton faces test for the patients with AS and their controls.

Table 4.9: Mean scores on the Benton faces test for the patients with AS and their controls

Group	Total score	Identical face-on	Face-on and ¾ view	Face-on under different lighting
AS	41.43 (3.82)	6 (0)	20.29 (1.68)	15.29 (2.40)
Control	44.50 (3.31)	6 (0)	21.40 (1.96)	17.10 (2.47)

Mean (sd)

Figure 4.9: Mean scores on the Benton faces test for patients with AS and controls



Both patients with AS and controls correctly matched all the identical face-on photographs and statistical analysis was therefore not carried out on these scores. For the remaining measures of this test, statistical analysis showed that there was weak evidence for a significant difference between patients with AS and controls for the total score ($t = -2.051$, $df = 22$, $p = 0.052$, ANCOVA with age $F(1,24) = 4.242$, $p = 0.052$) and for the matching of face-on photographs under different lighting ($t = -1.804$, $df = 22$, $p = 0.085$, ANCOVA with age $F(1,24) = 3.128$, $p = 0.092$). There was no significant difference between the performance of patients with AS and controls on the matching of face-on and ¾ view photographs ($t = -1.495$, $df = 22$, $p = 0.149$, ANCOVA with age $F(1,24) = 1.915$, $p = 0.181$).

There was a strong hypothesis that individuals with AS would be impaired on this task and further analyses were therefore carried out on the results. ANCOVA analysis showed that when differences in freedom from distractibility levels were covaried out, the difference between the performance of patients with AS and controls reached significance for the total score (ANCOVA $F(1,24) = 5.383$, $p = 0.030$), the matching of face-on with ¾ view photographs became non-significant (ANCOVA $F(1,24) = 2.881$, $p = 0.104$) and the matching of face-on photographs under different lighting conditions reached weak levels of significance (ANCOVA $F(1,24) = 3.985$, $p = 0.059$). Further ANCOVA analysis showed that when performance on the Benton test of line judgment was co-varied (in order to control for differences in basic visual matching), none of the differences were significant (Benton lines total ($F(1,24) = 2.952$, $p = 0.101$), face-on and ¾ view ($F(1,24) = 1.388$, $p = 0.252$), different lighting ($F(1,24) = 2.324$, $p = 0.142$). This suggests that it was not face processing in particular that was impaired in individuals with AS, but rather that their difficulties with this task were due to more general problems with visual matching. The differences in the way that individuals with AS process visual information compared to controls are considered in some more detail in the discussion in Section 4.5.2.

4.4.3 Copying and drawing

4.4.3.1 The test of Visuo-motor integration (VMI)

The VMI is a drawing and copying test produced by Beery (1967) based on Frostig et al.'s (1966) visual perception test. It requires subjects to copy a set of increasingly complex geometric figures into specified squares of exactly the same dimensions as the original. Although this test was intended for children up to the age of 14 years 11 months, it has been argued that it remains valid for older children and adults as well (Beery, 1982) and was therefore administered to all participants in the current study. The revised version produced in 1997 which incorporates a new scoring system (Beery, 1989) and new norms, is the version used here (Beery, 1997).

(i) Patients with PFT: VMI

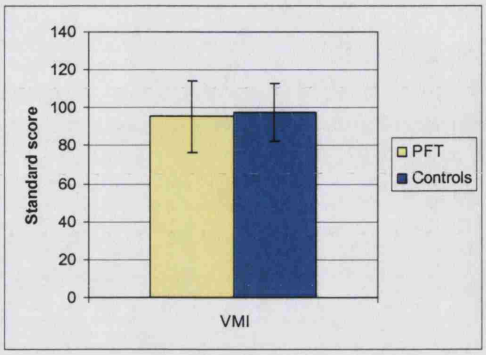
Table 4.10 and Figure 4.10 show the mean standard scores on the VMI for the patients with PFT and their controls.

Table 4.10: Mean standard scores on the VMI task for patients with PFT and controls

Group	VMI standard score
PFT	95.27 (18.89)
Control	97.50 (14.98)

Mean (sd)

Figure 4.10: Mean standard scores on the VMI task for patients with PFT and controls



Statistical analysis showed that there was no significant difference between the performance of patients with PFT and controls on the VMI (Mann-Whitney U-test: $z = -0.534$, $p = 0.593$). Age was not co-varied for the VMI as standardized scores were used in the analyses for this test. In order to investigate whether there were any differences between patients with PFT in the motoric aspects of copying, the visual perceptual parts of the task were partialled out by carrying out an ANCOVA with Benton lines (a purely visual matching task) as a covariate. The results showed that there were still no significant differences between the two groups (ANCOVA $F(1,25) = 0.095$, $p = 0.760$), indicating that individuals with PFT are not impaired on copying and drawing skills per se.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the VMI.

(ii) Patients with AS: VMI

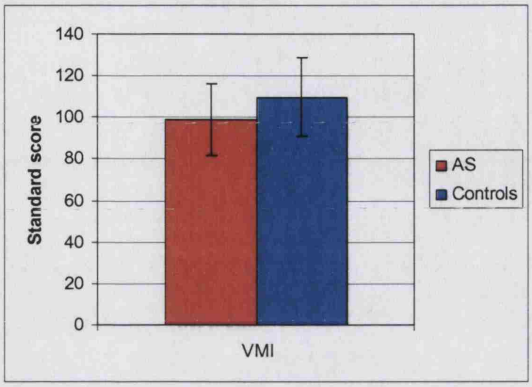
Table 4.11 and Figure 4.11 show the mean standard scores on the VMI for the patients with AS and their controls.

Table 4.11: Mean standard scores on the VMI task for patients with AS and controls

Group	VMI standard score
AS	98.71 (17.14)
Control	109.60 (18.99)

Mean (sd)

Figure 4.11: Mean standard scores on the VMI task for patients with AS and controls



Statistical analysis showed that there was no significant difference between the performance of patients with AS and controls on the VMI (after log transformation, $t = -1.472$, $df = 22$, $p = 0.155$). Age was not co-varied for the VMI as standardized scores were used in the analyses for this test. As was the case for the patients with PFT, in order to investigate whether there were any differences between patients with AS in the motoric aspects of copying, the visual perceptual parts of the task were partialled out by carrying out an ANCOVA with Benton lines (a purely visuo-spatial task) as a covariate. The results showed that there were still no significant differences between the two groups (ANCOVA $F(1,24) = 1.545$, $p = 0.228$), indicating that individuals with AS are not impaired on copying and drawing skills.

4.4.4 Executive functions

4.4.4.1 Attention

a) Letter and number cancellation

The letter and number cancellation tasks were designed to assess visual scanning and tracking aspects of attention as well as motoric speed. For the letter cancellation task, subjects are presented with a sheet containing 140 three-letter clusters (presented as a 10 by 14 grid). They are instructed to mark off every appearance of a particular letter cluster as quickly as they can and to inform the examiner when they think they have found them all. There are two scores for this test: the time taken to complete the task and the number of target letter clusters correctly identified (out of a total of 14). The number cancellation task is identical to the letter task except that the sheet contains three-number clusters rather than letters and the target cluster that they must look for is a cluster of three numbers.

(i) Patients with PFT: Letter and number cancellation

Table 4.12 and Figures 4.12 and 4.13 show the mean scores on the letter and number cancellation tests for patients with PFT and their controls.

Table 4.12: Mean scores on the letter and number cancellation tests for patients with PFT and controls

Group	Letter cancellation		Number cancellation	
	Time (s)	Number correct	Time (s)	Number correct
PFT	68.37 (23.28)	12.60 (1.64)	83.74 (26.46)	12.20 (1.94)
Controls	58.56 (25.45)	13.70 (0.48)	75.06 (23.47)	13.00 (1.05)

Mean (sd)

Figure 4.12: Mean time taken on the letter and number cancellation tests for patients with PFT and controls

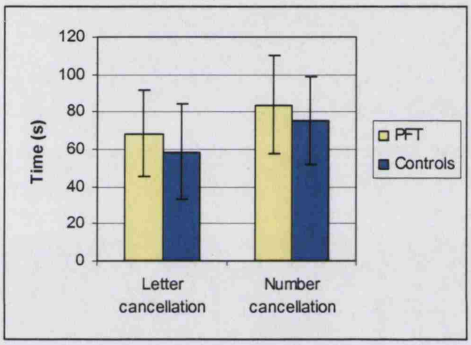
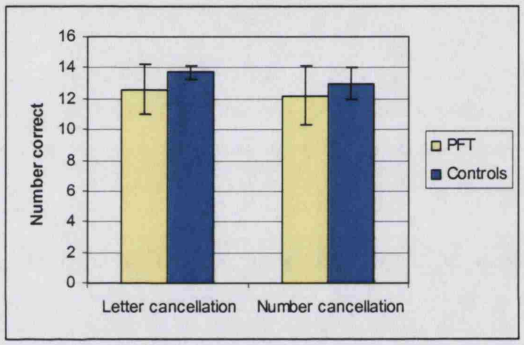


Figure 4.13: Mean number correct on the letter and number cancellation tests for patients with PFT and controls



Statistical analysis showed that there was no significant difference between patients with PFT and their controls in the time taken to complete the letter cancellation task (after log transformation, $t = 1.285$, $df = 23$, $p = 0.211$, ANCOVA with age $F(1,25) = 1.229$, $p = 0.280$), nor between the number correct (Mann Whitney U test $z = -1.628$, $p = 0.104$, ANCOVA with age $F(1,25) = 3.707$, $p = 0.067$). The same was true for the number cancellation task. There was no significant difference between patients with PFT and their controls in the time taken to complete the task (after log transformation, $t = 0.917$, $df = 23$, $p = 0.369$, ANCOVA with age $F(1,25) = 0.442$, $p = 0.513$), nor between the number correct (Mann Whitney U test $z = -0.977$, $p = 0.328$, ANCOVA with age $F(1,25) = 1.047$, $p = 0.317$).

Because there were strong predictions that individuals with PFT would be impaired on these tests of attention, the results were investigated further. In order to determine whether there were any differences in attention abilities between the groups when freedom from distractibility levels were partialled out, ANCOVA analyses were carried out. The results

showed that the only result that changed was for the number correct on letter cancellation ($F(1,25) = 4.215$, $p = 0.052$) for which there was weak evidence that patients with PFT performed more poorly than controls. When differences in PIQ were co-varied, the results showed that there were no significant differences between the groups.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the letter and number cancellation tests.

(ii) Patients with AS: Letter and number cancellation

Table 4.13 and Figures 4.14 and 4.15 show the mean scores on the letter and number cancellation tests for patients with AS and their controls.

Table 4.13: Mean scores on the letter and number cancellation tests for patients with AS and controls

Group	Letter cancellation		Number cancellation	
	Time (s)	Number correct	Time (s)	Number correct
AS	69.05 (22.55)	13.29 (0.91)	79.95 (25.79)	13.29 (0.91)
Controls	53.75 (15.76)	13.00 (0.94)	60.97 (9.13)	12.60 (1.58)

Mean (sd)

Figure 4.14: Mean time taken on the letter and number cancellation tests for patients with AS and controls

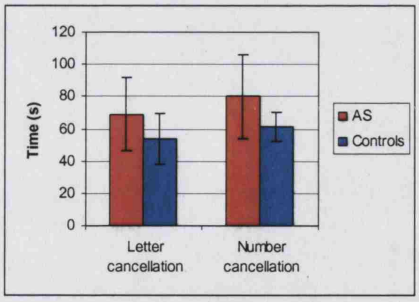
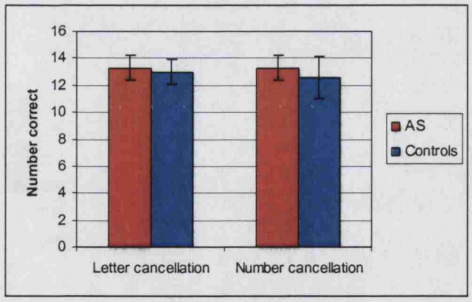


Figure 4.15: Mean number correct on the letter and number cancellation tests for patients with AS and controls



Statistical analysis showed that there was weak evidence for a significant difference between patients with AS and their controls in the time taken to complete the letter cancellation task (after log transformation, $t = 2.050$, $df = 22$, $p = 0.052$, ANCOVA with age $F(1,24) = 3.779$, $p = 0.065$), but no significant difference between the number correct (Mann Whitney U test $z = -0.886$, $p = 0.376$, ANCOVA with age $F(1,24) = 0.405$, $p = 0.531$). For the number cancellation task, there was a significant difference between

patients with AS and their controls in the time taken to complete the task ($t = 2.217$, $df = 22$, $p = 0.037$, ANCOVA with age $F(1,24) = 4.892$, $p = 0.038$), but no significant difference between the number correct (Mann Whitney U test $z = -1.158$, $p = 0.247$, ANCOVA with age $F(1,24) = 1.540$, $p = 0.228$).

ANCOVA analyses showed that the results did not change when differences in PIQ were co-varied, nor when differences in freedom from distractibility levels were co-varied.

4.4.4.2 Working memory

a) Digit Span

The results from the digit span were reported in Chapter 2 as this is one of the sub-tests of the WISC and the WAIS assessments that were administered to measure intelligence levels. The results are investigated in more detail here: the raw scores rather than the standardized scores are examined, and these scores are looked at separately for the digit span as a whole as well as for the two sub-parts (forward and backward span).

(i) Patients with PFT: Digit span

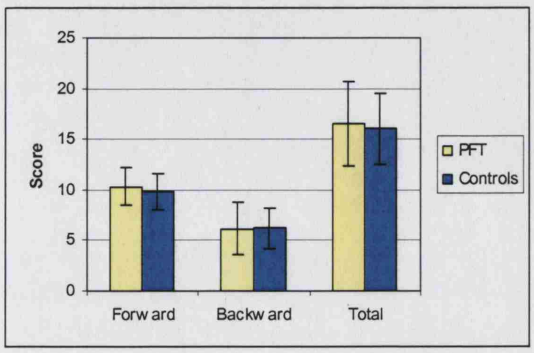
Table 4.14 and Figure 4.16 show the mean raw scores on digit span for the patients with PFT and their controls.

Table 4.14: Mean raw scores on the digit span for patients with PFT and controls

Group	Digit span forward	Digit span backward	Digit span total
PFT	10.33 (1.80)	6.13 (2.62)	16.47 (4.17)
Controls	9.80 (1.81)	6.20 (2.04)	16.00 (3.46)

Mean (sd)

Figure 4.16: Mean raw scores on the digit span for patients with PFT and controls



Statistical analysis showed that there was no significant difference between the performance of patients with PFT and controls on any of the measures of digit span: digit span forward (Mann Whitney U-test $z = -0.654$, $p = 0.513$, ANCOVA with age $F(1,25) = 0.813$, $p = 0.377$), backward (Mann Whitney U-test z = -

0.395, p = 0.693, ANCOVA with age F(1,25) = 0.002, p = 0.961), total (t = 0.292, df = 23, p = 0.773, ANCOVA with age F(1,25) = 0.197, p = 0.662).

Because there was a strong hypothesis that patients with PFT would be impaired on digit span, the results from this test were further investigated. There were no effects on the results when VIQ, PIQ or freedom from distractibility levels were excluded from the analyses using ANCOVAs. Furthermore, plots of the data showed that the distribution of the scores for each of the two groups was very similar, indicating that contrary to predictions, individuals with PFT were not impaired on this measure of verbal working memory.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the Digit span test.

(ii) Patients with AS: Digit span

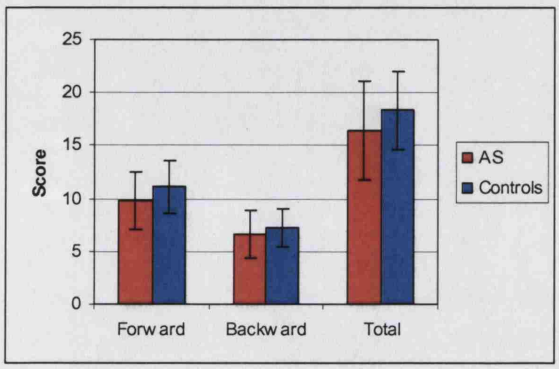
Table 4.15 and Figure 4.17 show the mean raw scores on digit span for the patients with AS and their controls.

Table 4.15: Mean raw scores on the digit span for patients with AS and controls

Group	Digit span forward	Digit span backward	Digit span total
AS	9.79 (2.75)	6.64 (2.21)	16.43 (4.65)
Controls	11.10 (2.47)	7.20 (1.81)	18.30 (3.68)

Mean (sd)

Figure 4.17: Mean raw scores on the digit span for patients with AS and controls



Statistical analysis showed that there was no significant difference between the performance of patients with AS and their controls on any of the measures of digit span: digit span forward (t = -1.203, df = 22, p = 0.242, ANCOVA with age F(1,24) = 1.469, p = 0.239), backward (t = -0.655, df = 22, p = 0.519, ANCOVA with age

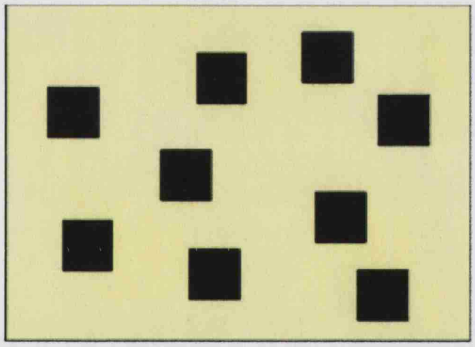
$F(1,24) = 0.545$, $p = 0.469$), total ($t = -1.055$, $df = 22$, $p = 0.303$, ANCOVA with age $F(1,24) = 1.217$, $p = 0.282$).

Because individuals with autism have been shown to have difficulties with working memory, the results from this test were further investigated. As was the case for the patients with PFT, there were no effects on the results when VIQ, PIQ or freedom from distractibility levels were excluded from the analyses using ANCOVAs. Furthermore, plots of the data showed that the distribution of the scores for each of the two groups was very similar, indicating that individuals with AS do not appear to have problems with this measure of verbal working memory.

b) Corsi block span

The Corsi Block Span is a test of visuo-spatial working memory (Corsi, 1972, reported in Isaacs & Vargha-Khadem, 1989). This test features a board onto which nine cubes are affixed in random positions (see Figure 4.18). The experimenter uses a pointer to tap a sequence of blocks that must then be copied by the subject. The sequences start at just two blocks in length and increase by one block each time two consecutive trials at one sequence length are achieved. The maximum sequence length is nine blocks and the test is discontinued after failure of both trials on any sequence length. Once this part of the test has been completed (block span forward), the second half (block span backward) is administered. This involves the experimenter tapping out a sequence of blocks again; however this time the subject is asked to tap the blocks back in the reverse order (i.e. backwards). Again the first sequence is just two blocks but the maximum sequence length in this part is eight blocks.

Figure 4.18: Top-down view of the Corsi block span test



(i) Patients with PFT: Corsi block span

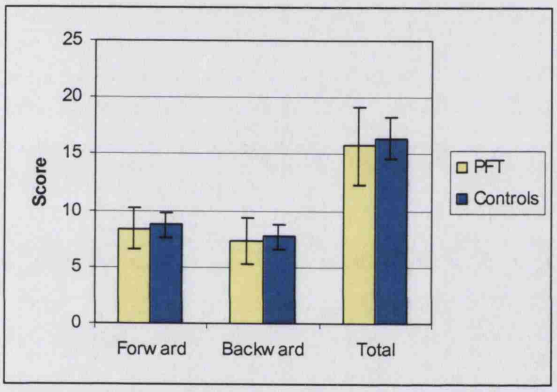
Table 4.16 and Figure 4.19 show the mean raw scores on the Corsi block span for the patients with PFT and their controls.

Table 4.16: Mean raw scores on the Corsi block span for patients with PFT and controls

Group	Block span forward	Block span backward	Block span total
PFT	8.40 (1.77)	7.33 (2.09)	15.73 (3.39)
Controls	8.70 (1.16)	7.70 (1.06)	16.40 (1.84)

Mean (sd)

Figure 4.19: Mean raw scores on the Corsi block span for patients with PFT and controls



Statistical analysis showed that there was no significant difference between the performance of patients with PFT and controls on any of the measures of block span: block span forward ($t = -0.472$, $df = 23$, $p = 0.641$, ANCOVA with age $F(1,25) = 0.160$, $p = 0.693$), backward ($t = -0.510$, $df = 23$, $p = 0.721$, ANCOVA with age $F(1,25) = 0.131$, $p = 0.721$) and block span total ($t = -0.566$, $df = 23$, $p = 0.577$, ANCOVA with age $F(1,25) = 0.192$, $p = 0.666$).

As was the case for digit span, because there was a strong hypothesis that patients with PFT would be impaired on this test of working memory, the results from the block span test were further investigated. ANCOVA analyses showed that there were no effects on the results when VIQ, PIQ or freedom from distractibility levels were excluded from the analyses. Contrary to predictions, therefore, individuals with PFT were not impaired on this measure of spatial working memory.

Further analysis within the patient group with PFT (one-way ANOVA between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the Corsi block-span test.

(ii) Patients with AS: Corsi block span

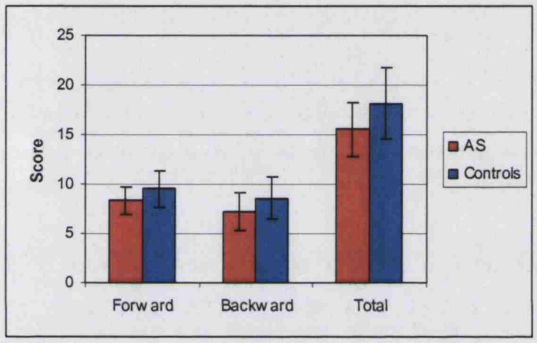
Table 4.17 and Figure 4.20 show the mean raw scores on the Corsi block span for the patients with AS and their controls.

Table 4.17: Mean raw scores on the Corsi block span for patients with AS and controls

Group	Block span forward	Block span backward	Block span total
AS	8.36 (1.39)	7.21 (1.85)	15.57 (2.71)
Controls	9.50 (1.78)	8.60 (2.07)	18.10 (3.60)

Mean (sd)

Figure 4.20: Mean raw scores on the Corsi block span for patients with AS and controls



Statistical analysis showed that there was weak evidence for a significant difference between the performance of patients with AS and controls on all of the measures of block span: block span forward ($t = -1.767$, $df = 22$, $p = 0.091$, ANCOVA with age $F(1,24) = 3.142$, $p = 0.091$), backward ($t = -1.726$, $df = 22$, $p = 0.098$, although this was not significant when age was covaried, ANCOVA with age $F(1,24) = 2.850$, $p = 0.106$) and block span total ($t = -1.966$, $df = 22$, $p = 0.062$, ANCOVA with age $F(1,24) = 3.782$, $p = 0.065$).

Given that working memory function in individuals with AS was of particular interest, this finding was investigated further. Two measures involving spatial perception (block design and object assembly from the WISC/WAIS) and a measure of verbal working memory (digit span) were partialled out in order to investigate whether the difference was associated with spatial problems or with working memory problems. The results showed that the problem appeared to be with working memory in particular because when tasks involving spatial ability were co-varied, the p-values decreased (ANCOVA with block design: block span forwards $F(1,24) = 4.819$, $p = 0.040$; backwards $F(1,24) = 3.155$, $p = 0.090$; total $F(1,24) = 4.958$, $p = 0.037$; ANCOVA with object assembly: block span forwards $F(1,24) = 3.759$, $p = 0.066$; backwards $F(1,24) = 3.256$, $p = 0.086$; total $F(1,24) = 4.944$, $p = 0.037$), whereas when a measure of working memory (digit span) was co-varied, the p-values

increased (ANCOVA with digit span: block span forwards $F(1,24) = 2.523$, $p = 0.127$; backwards $F(1,24) = 2.727$, $p = 0.114$; total $F(1,24) = 3.337$, $p = 0.082$).

It is important to note, however, that the differences between patients with AS and controls on the block span could be accounted for by differences in levels of freedom from distractability (ANCOVA with Freedom from distractibility: block span forwards $F(1,24) = 0.901$, $p = 0.353$; backwards $F(1,24) = 1.353$, $p = 0.258$; span total $F(1,24) = 1.504$, $p = 0.234$).

c) Word and non-word repetition

This is a test of phonological short-term memory where a list of 40 non-words is read out loud and subjects are asked to repeat each word as it is said (Gathercole and Baddeley, 1989). The control measure is for subjects to repeat a list of 40 words. The words range in length from two to five syllables and the non-words range from one to four syllables. There are ten words and nonwords at each syllable length. Both word lists are marked out of a total of 40 points.

(i) Patients with PFT: Word and non-word repetition

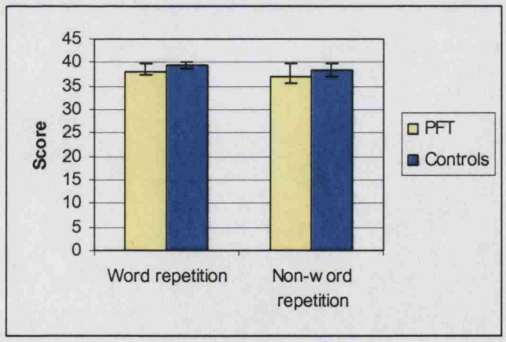
Table 4.18 and Figure 4.21 show the mean scores on the word and non-word repetition tests for the patients with PFT and their controls.

Table 4.18: Mean raw scores on the word and non-word repetition test for patients with PFT and controls

Group	Word repetition	Non-word repetition
PFT	38.13 (1.51)	37.13 (2.80)
Controls	39.40 (0.70)	38.30 (1.42)

Mean (sd)

Figure 4.21: Mean raw scores on the word and non-word repetition test for patients with PFT and controls



Statistical analysis showed that patients with PFT performed significantly more poorly than controls on the word repetition test (Mann-Whitney U-test, $z = -2.142$, $p = 0.032$, ANCOVA with age $F(1,25) = 5.547$, $p = 0.028$). However, although statistically significantly lower than the controls, the mean score for the patients with PFT (38.13) was still a high score for this test, and this implies that the patients with PFT do not have

impaired phonological working memory. There was no significant difference on the non-word repetition test (Mann-Whitney U-test, z = -0.847, p = 0.397, ANCOVA with age F(1,25) = 1.251, p = 0.275).

ANCOVA analyses revealed that the difference on word repetition could not be accounted for by differences in freedom from distractibility levels (ANCOVA F(1,25) = 6.009, p = 0.023), nor by differences in VIQ (ANCOVA F(1,25) = 6.353, p = 0.019).
Further analysis within the patient group with PFT (one-way ANOVA) showed that there was no significant interaction between location of tumour and performance on the word and non-word repetition test.

(ii) Patients with AS: Word and non-word repetition

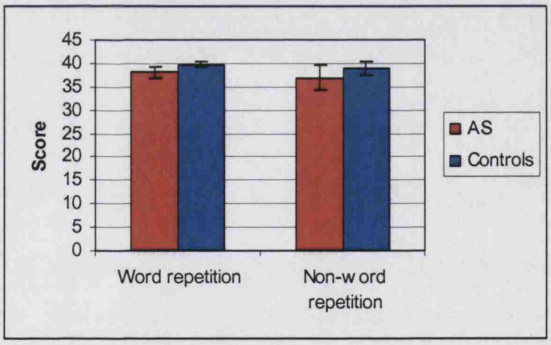
Table 4.19 and Figure 4.22 show the mean scores on the word and non-word repetition tests for the patients with AS and their controls.

Table 4.19: Mean scores on the word and non-word repetition test for patients with AS and controls

Group	Word repetition	Non-word repetition
AS	38.00 (1.30)	36.79 (2.75)
Controls	39.70 (0.48)	38.80 (1.40)

Mean (sd)

Figure 4.22: Mean scores on the word and non-word repetition test for patients with AS and controls



Statistical analysis showed that patients with AS performed significantly more poorly than controls on both the word and non-word repetition: word repetition (Mann-Whitney U-test, z = -3.417, p = 0.001, ANCOVA with age F(1,24) = 14.646, p = 0.001); non-word repetition (Mann-Whitney U-test, z = -2.158, p = 0.031, although there was only weak evidence for a difference when age was co-varied: ANCOVA with age F(1,24) = 4.139, p = 0.055). Although the patients with AS performed significantly more poorly than controls on the word and non-word repetition tests, the mean scores for the patients with AS on these tests were still high scores for this test, and this implies that the patients with AS do not have impaired phonological working memory.

ANCOVA analyses revealed that the difference on word repetition could not be accounted for by differences in freedom from distractibility levels (ANCOVA $F(1,24) = 13.809$, $p = 0.001$), nor by differences in VIQ levels (ANCOVA $F(1,24) = 14.689$, $p = 0.001$) and the difference on non-word repetition could not be accounted for by differences in VIQ (ANCOVA $F(1,24) = 5.421$, $p = 0.030$) but could be accounted for by differences in freedom from distractibility levels (ANCOVA $F(1,24) = 2.439$, $p = 0.133$).

4.4.4.3 Face-sorting

This is an adapted version of the Wisconsin Card Sorting Task designed by Vargha-Khadem and Isaacs (unpublished). The WCST evaluates problem solving and set-shifting abilities. It has typically been used with patients who have undergone frontal lobectomy or have suffered selective frontal lobe damage (Milner, 1963). Results of these studies typically reveal that patients with dorsolateral prefrontal lesions are impaired on certain aspects of the tests (e.g. number of categories achieved or number of perseverative errors – Stuss et al. 2000), whereas those with orbitofrontal damage are impaired on set maintenance of categories (Milner, 1963). In the face sorting task, subjects are required to sort up to 128 cards against four "cue" cards (shown in Figure 4.23 below) according to an unknown rule, being required to match on one of three categories: emotion, race or age. For each card placed by the subject, the examiner tells them if the card is correct or not, i.e. feedback is provided at every step. Once subjects complete one correct series of matches (10 matches of the specific category in a row), unknown to the subject, the examiner changes the "rule" so that subjects are required to match on the next category. Then once they have realized the change and matched 10 of the next category in a row, the examiner changes the rule again so that they have to match on the third category. This continues until subjects have completed six correct series or until all the cards (128) have been used up.

Figure 4.23: The four Cue cards from the Face Sorting task

Altogether five total scores are obtained for this test: the total number of categories completed, the level of failure to maintain set (the total number of cards correctly matched within a category but which are not part of a string of 10 correct matches in a row), the number of perseverative errors (where cards are matched according to the previously correct category), the number of non-perseverative errors (where cards are incorrectly matched, but not to the previous category) and the number of unique errors (where cards are not matched on either emotion, race or age).

In addition to these scores, it is possible to calculate scores for failure to maintain set, number of perseverative errors and number of non-perseverative errors relating to each of the three variables (emotion, race and age) individually in order to identify exactly where any difficulties lie.

This test of executive function draws on a number of cognitive skills that are thought to be subserved by the prefrontal cortex.

(i) Patients with PFT: Face sorting

Table 4.20 and Figures 4.24 and 4.25 show the mean total scores on the face-sorting task for the patients with PFT and their controls.

Table 4.20: Mean total raw scores on the face-sorting task for patients with PFT and controls

Group	Number of categories	Failure to maintain set	Perseverative errors	Non-perseverative errors	Unique errors
PFT	2.36 (1.50)	34.21 (10.30)	41.07 (18.51)	16.50 (11.85)	9.00 (10.14)
Controls	4.10 (2.08)	25.10 (13.15)	26.60 (22.37)	9.80 (8.57)	9.10 (8.67)

Mean (sd)

Figure 4.24: Face sorting: Number of categories completed by PFT and controls

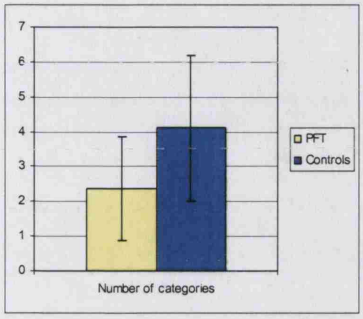
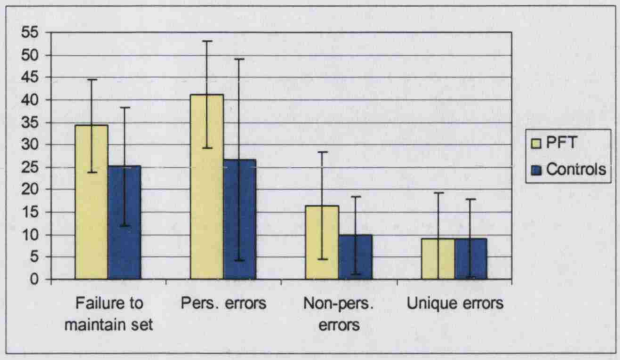


Figure 4.25: Face sorting: Total correct, total errors, perseverative errors, non-perseverative errors and unique errors for PFT and controls



Patients with PFT had some difficulty with the face-sorting task, as they succeeded in completing significantly fewer categories than controls ($t = -2.392$, $df = 22$, $p = 0.026$, ANCOVA with age $F(1,24) = 5.127$, $p = 0.034$). ANCOVA analyses showed that this difference could not be accounted for by differences in performance IQ (ANCOVA $F(1,24) = 4.480$, $p = 0.046$) nor by differences in freedom from distractibility levels (ANCOVA $F(1,24) = 6.029$, $p = 0.023$).

There was weak evidence for a difference in failure to maintain set ($t = 1.905$, $df = 22$, $p = 0.070$, which became significant when age was co-varied: ANCOVA with age $F(1,24) = 4.590$, $p = 0.044$). ANCOVA analyses revealed that the difference in failure to maintain set could be accounted for by differences in levels of performance IQ (ANCOVA $F(1,24) = 2.873$, $p = 0.105$) but not by differences in freedom from distractibility levels (ANCOVA $F(1,24) = 3.616$, $p = 0.071$).

There was weak evidence for a difference in the number of perseverative errors (Mann-Whitney U-test: $z = -1.905$, $p = 0.057$, but this was not significant when age was co-varied: ANCOVA with age $F(1,24) = 2.440$, $p = 0.133$). Furthermore, ANCOVA analyses showed that this difference in the number of perseverative errors could be accounted for by differences in freedom from distractibility levels (ANCOVA $F(1,24) = 2.862$, $p = 0.105$) but not by differences in levels of performance IQ (ANCOVA $F(1,24) = 3.512$, $p = 0.075$).

There was no evidence for a significant difference in the number of non-perseverative errors (after log transformation, t = 1.283, df = 22, p = 0.213, ANCOVA with age F(1,24) = 1.483, p = 0.206) or in the number of unique errors (after log transformation, t = -0.546, df = 22, p = 0.591, ANCOVA with age F(1,24) = 0.116, p = 0.737).

Each of the three sub-categories of the face-sorting task (emotion, race and age) were analysed separately. The results for the emotion category are shown in Table 4.21 below.

Table 4.21: Mean scores for the emotion category of the face-sorting task for patients with PFT and controls

Group	Failure to maintain set	Perseverative errors	Non-perseverative errors
PFT	6.07 (7.71)	27.57 (20.59)	7.14 (10.05)
Controls	1.50 (1.65)	15.20 (23.88)	6.60 (6.75)

Mean (sd)

Statistical analysis for the emotion category showed that there was weak evidence for a significant difference between patients with PFT and their controls for failure to maintain set (Mann-Whitney U-test: z = -1.679, p = 0.093, ANCOVA with age F(1,24) = 3.074, p = 0.094), but this could be explained by differences in PIQ (ANCOVA F(1,24) = 0.130, p = 0.722) or by differences in freedom from distractibility levels (ANCOVA F(1,24) = 0.193, p = 0.665). There was no significant difference between patients with PFT and their controls in the number of perseverative errors for emotion (t = 1.358, df = 22, p = 0.188, ANCOVA with age F(1,24) = 1.435, p = 0.244), nor on the number of non-perseverative errors for emotion (t = 0.148, df = 22, p = 0.884, ANCOVA with age F(1,24) = 0.021, p = 0.887). The results for the race category are shown in Table 4.22 below.

Table 4.22: Mean scores for the race category of the face-sorting task for patients with PFT and controls

Group	Failure to maintain set	Perseverative errors	Non-perseverative errors
PFT	17.71 (15.84)	12.07 (13.69)	7.07 (12.30)
Controls	8.70 (10.57)	10.40 (8.91)	2.30 (2.98)

Mean (sd)

Statistical analysis for the race category showed that there was no significant difference between the performance of patients with PFT and controls on any of the measures: failure to maintain set (t = 1.563, df = 22, p = 0.132, ANCOVA with age F(1,24) = 2.597, p = 0.122); number of perseverative errors for race (t = 0.337, df = 22, p = 0.739, ANCOVA

with age F(1,24) = 0.078, p = 0.783); number of non-perseverative errors for race (Mann-Whitney U-test: z = -0.271, p = 0.796, ANCOVA with age F(1,24) = 1.255, p = 0.275). The results for the age category are shown in Table 4.23 below.

Table 4.23: Mean scores for the age category of the face-sorting task for patients with PFT and controls

Group	Failure to maintain set	Perseverative errors	Non-perseverative errors
PFT	10.43 (10.44)	1.43 (3.20)	2.29 (2.89)
Controls	14.90 (14.84)	1.00 (2.00)	0.90 (0.88)

Mean (sd)

Statistical analysis for the age category showed that there was no significant difference between the performance of patients with PFT and controls on any of the measures: failure to maintain set (t = -0.869, df = 22, p = 0.394, ANCOVA with age F(1,24) = 0.570, p = 0.459); number of perseverative errors for race (t = 0.373, df = 22, p = 0.713, ANCOVA with age F(1,24) = 0.086, p = 0.772); number of non-perseverative errors for race (Mann-Whitney U-test: z = -0.521, p = 0.625, ANCOVA with age F(1,24) = 2.171, p = 0.155).

Further analyses within the patient group with PFT (one-way ANOVAs between patients with left hemisphere, right hemisphere and midline pathology) showed that there was no significant interaction between location of tumour and performance on the face-sorting test as a whole or for any of the sub-categories (emotion, race and age).

(i) Patients with AS: Face sorting

Table 4.24 and Figures 4.26 and 4.27 show the mean scores on the face-sorting task for the patients with AS and their controls.

Table 4.24: Mean scores on the face-sorting task for patients with AS and controls

Group	Number of categories	Failure to maintain set	Perseverative errors	Non-perseverative errors	Unique errors
AS	4.43 (1.95)	26.50 (21.08)	19.21 (18.31)	8.93 (7.69)	5.21 (6.46)
Controls	4.20 (1.75)	25.80 (16.80)	21.90 (12.56)	11.20 (7.76)	6.00 (6.90)

Mean (sd)

Figure 4.26: Face sorting: Number of categories completed by AS and controls

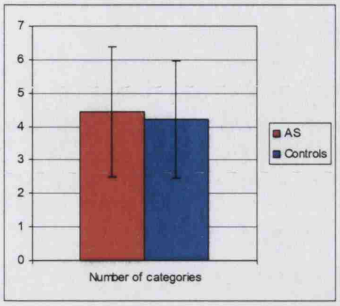
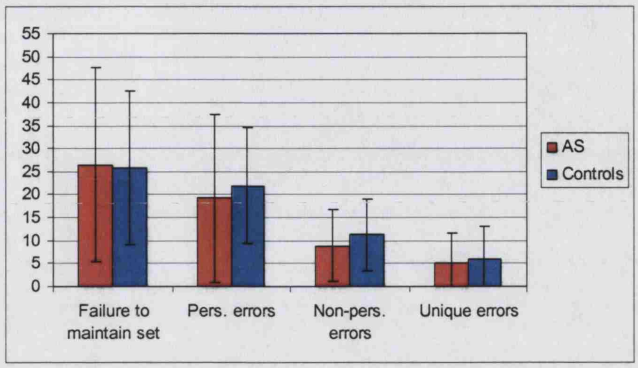


Figure 4.27: Face sorting: Total correct, total errors, perseverative errors, non-perseverative errors and unique errors for AS and controls



Statistical analysis showed that there was no significant difference between patients with AS and controls on any of the measures of the face sorting task, even after age was co-varied: number of categories (Mann Whitney U-test: $z = -0.378$, $p = 0.705$, ANCOVA with age $F(1,24) = 0.232$, $p = 0.635$), failure to maintain set (Mann Whitney U-test: $z = -0.088$, $p = 0.930$, ANCOVA with age $F(1,24) = 0.004$, $p = 0.952$), perseverative errors (Mann Whitney U-test: $z = -0.851$, $p = 0.395$, ANCOVA with age $F(1,24) = 0.435$, $p = 0.516$), non-perseverative errors (Mann Whitney U-test: $z = -0.881$, $p = 0.378$, ANCOVA with age $F(1,24) = 0.7$, $p = 0.412$), unique errors (Mann Whitney U-test: $z = -0.297$, $p = 0.767$, ANCOVA with age $F(1,24) = 0.226$, $p = 0.639$).

There were strong predictions that individuals with AS would be impaired on the face-sorting test and the results were therefore analysed in more detail. ANCOVA analyses showed that there were no effects on the results when either PIQ, freedom from distractibility, block span or digit span were excluded from the analyses. Furthermore, when performance on the Benton test of facial recognition was excluded from the analyses, there were no effects on the results, they remained non-significant, indicating that there were no significant differences in performance even when any difficulties with face recognition were removed from the analyses.

Each of the three sub-categories of the face-sorting task (emotion, race and age) were analysed separately. The results for the emotion category are shown in Table 4.25 below.

Table 4.25: Mean scores for the emotion category of the face-sorting task for patients with AS and controls

Group	Failure to maintain set	Perseverative errors	Non-perseverative errors
AS	7.00 (9.87)	8.71 (13.67)	5.86 (6.60)
Controls	4.60 (5.60)	12.00 (10.91)	7.40 (6.13)

Mean (sd)

Statistical analysis for the emotion category showed that there was no significant difference between the performance of patients with AS and controls on any of the measures: failure to maintain set ($t = 0.691$, $df = 22$, $p = 0.497$, ANCOVA with age $F(1,24) = 0.439$, $p = 0.515$); number of perseverative errors for emotion ($t = -0.629$, $df = 22$, $p = 0.536$, ANCOVA with age $F(1,24) = 0.878$, $p = 0.359$); number of non-perseverative errors for race ($t = -0.581$, $df = 22$, $p = 0.567$, ANCOVA with age $F(1,24) = 0.403$, $p = 0.532$).

Because emotion recognition was of particular interest in patients with AS, these results were investigated in more detail. In order to investigate whether there were any differences in performance when differences in face recognition abilities were removed from the analysis, ANCOVA analyses with Benton faces were carried out. The results showed that there was no change in the significance levels of the results: failure to maintain set (ANCOVA $F(1, 24) = 0.191$, $p = 0.667$), number of perseverative errors (ANCOVA $F(1,24) = 1.752$, $p = 0.200$), number of non-perseverative errors (ANCOVA $F(1,24) = 0.897$, $p = 0.354$). The results for the race category are shown in Table 4.26 below.

Table 4.26: Mean scores for the race category of the face-sorting task for patients with AS and controls

Group	Failure to maintain set	Perseverative errors	Non-perseverative errors
AS	6.64 (7.91)	8.50 (11.46)	2.29 (3.36)
Controls	9.30 (9.73)	7.30 (5.81)	1.40 (2.41)

Mean (sd)

Statistical analysis for the race category showed that there was no significant difference between the performance of patients with AS and controls on any of the measures: failure to maintain set (Mann-Whitney U-test: $z = -0.149$, $p = 0.886$, ANCOVA with age $F(1,24) = 0.652$, $p = 0.428$); number of perseverative errors for race ($t = 0.303$, $df = 22$, $p = 0.765$, ANCOVA with age $F(1,24) = 0.046$, $p = 0.833$); number of non-perseverative errors for race ($t = 0.711$, $df = 22$, $p = 0.485$, ANCOVA with age $F(1,24) = 0.321$, $p = 0.577$). The results for the age category are shown in Table 4.27 below.

Table 4.27: Mean scores for the age category of the face-sorting task for patients with AS and controls

Group	Failure to maintain set	Perseverative errors	Non-perseverative errors
AS	12.79 (11.79)	2.29 (3.87)	0.86 (1.17)
Controls	11.90 (11.62)	2.60 (3.69)	2.40 (2.91)

Mean (sd)

Statistical analysis for the age category showed that there was no significant difference for failure to maintain set or for the number of perseverative errors, but there was weak evidence for a significant difference for the number of non-perseverative errors: failure to maintain set ($t = 0.183$, $df = 22$, $p = 0.857$, ANCOVA with age $F(1,24) = 0.041$, $p = 0.841$); number of perseverative errors for age ($t = -0.200$, $df = 22$, $p = 0.843$, ANCOVA with age $F(1,24) = 0.015$, $p = 0.905$); number of non-perseverative errors for age (Mann-Whitney U-test: $z = -1.057$, $p = 0.341$, ANCOVA with age $F(1,24) = 3.093$, $p = 0.093$).

Effects of age at surgery for patients with PFT

Correlation analyses were performed between age in months at surgery and the results of each of the cognitive tests described above for the patients with PFT. The results showed that the only significant result was a positive correlation between age at surgery and performance on the Benton test of facial recognition (Pearson correlation coefficient = 0.523, $p = 0.045$).

There was a specific hypothesis that patients who had early pathology of the cerebellum (age five and younger) would perform better than patients who had later pathology (age six and above) on measures of basic cognitive abilities (including the WORD, the WOND, the letter and number cancellation task, the word and non-word repetition, digit span and Corsi block span tests) due to the compensatory mechanisms which ensure that such functions are rescued. In order to investigate this possibility, independent sample t-tests were carried out between the performance of patients with PFT who had pathology at age five and younger and patients with PFT who had pathology at age six and older on each of the cognitive tests considered above. The results showed that the only test on which the two groups differed was the WOND. The mean scores of the two groups on the subtests from the WOND are shown in table 4.28 below.

Table 4.28: Mean scores for patients with early and late pathology on the WOND

Group	WOND composite	Mathematical reasoning	Numerical operations
Early	108.00 (17.09)	110.00 (16.53)	104.71 (12.93)
Late	91.63 (13.93)	93.00 (13.12)	90.25 (14.51)

Mean (sd)

Statistical analysis showed that the late group was significantly impaired on mathematical reasoning ($t = 2.221$, $df = 13$, $p = 0.045$). Furthermore, there was weak evidence that the late group were significantly impaired on numerical operations ($t = 2.025$, $df = 13$, $p = 0.064$) and on the composite score ($t = 2.046$, $df = 13$, $p = 0.062$) from the WOND. However, it should be emphasized that these results should be treated with caution because the large number of statistical tests carried out here means that there is a high probability of achieving false positive results.

Effects of time since surgery for patients with PFT

Correlation analyses were also performed between time in months since surgery and the results of each of the cognitive tests described above. The results showed that there were no significant correlations.

4.5 Discussion

As stated in the methods section, adjustment for multiple comparisons was not performed in this thesis. Instead, a cut-off was chosen in order to flag problematic cognitive functions in each of the two patient groups that will require further investigation in future studies. Therefore, as was the case for the results from the motor tests, it is important to re-iterate that the results from the cognitive tests should also be interpreted with some caution.

4.5.1 Patients with PFT

The performance of patients with PFT on each of the cognitive tests is summarized in table 4.29 below.

Table 4.29: Summary of the performance of patients with PFT on each of the cognitive tests

	Domains	Test	Performance by patients with PFT
GENERAL COGNITIVE DOMAINS	1. Academic attainment	WORD	Not impaired
		WOND	Patients with late pathology impaired compared to patients with early pathology
	2. Visual matching	Benton test of line judgment	Not impaired
		Benton test of facial recognition	Not impaired
	3. Copying and drawing	Test of visuo-motor integration	Not impaired
EXECUTIVE FUNCTIONS	4. Attention	Letter cancellation	Not impaired
		Number cancellation	Not impaired
	5. Working memory	Digit span	Not impaired
		Corsi block span	Not impaired
		Word and non-word repetition	Not impaired
	6. Face matching	Face sorting task	Significantly impaired on task as a whole (completed fewer categories) and also had problems with set maintenance and set-shifting

1. Academic attainment

Results from the baseline tests of literacy (WORD) and numeracy (WOND) showed that patients with PFT performed significantly more poorly than controls on the reading comprehension subtest of the WORD. However, they still achieved high scores on this test indicating that, although they did not score quite as highly as controls, reading comprehension is not particularly impaired in patients with PFT. There were no significant differences between the two groups on any of the other measures of literacy or numeracy. This indicates that academic function is relatively intact in patients with PFT and that pathology of the cerebellum does not necessarily affect these basic functions. It is interesting to note that the mean scores for patients with PFT on the WOND were actually up to nine points higher than those for controls, which suggests that mathematical ability may not be affected by damage to the cerebellum.

2. Visual matching

Patients with PFT were not predicted to be impaired on tests of visual matching because there is little evidence to indicate that cerebellar pathology is associated with problems with visual matching. The results were consistent with this. There were no significant group differences between patients with PFT and their controls on either the Benton test of line

judgment or the Benton test of facial recognition. These results indicate that an intact cerebellum may not be essential for visual matching abilities.

3. Copying and drawing

Patients with PFT were not predicted to be impaired on the test of visuo-motor integration (VMI), which is used to assess copying and drawing abilities. This task depends on similar visuo-perceptual abilities to those required in the Benton test of line judgment considered above, but it also requires subjects to carry out motor functions in that they have to draw copies of visually presented shapes. The results showed that there were no significant group differences between patients with PFT and their controls on the VMI. This is consistent with the finding that these patients were not impaired on the simple visual matching skills required in the Benton test of line judgment. In addition, these results show that patients with PFT do not have difficulty executing the motor functions necessary to be able to satisfactorily copy visually presented shapes.

4. Attention

It was predicted that patients with PFT would be impaired on the tests of attention, but this prediction was not supported. There was no significant difference between the performance of patients with PFT and controls on either the time to complete the letter and number cancellation tasks, or the number correct, even after differences in freedom from distractibility levels or performance IQ levels were partialled out. This indicates that patients with PFT are not impaired on the particular aspect of attention (which is only one aspect of executive functioning) tested by these tasks. Given that there is evidence to suggest that the cerebellum is involved in attention, it is important to consider why the current results are not in line with this possibility. One possible explanation is that the patients with PFT may have difficulties with different aspects of attention to those tested by the letter and number cancellation tasks. Many of the functional imaging studies of attention have used shifting attention paradigms (e.g. Allen et al. 1997; Le et al., 1998) and it is possible that the cerebellum may be particularly involved in attention shifting rather than in simply attending to stimuli. It would be interesting to investigate this possibility in future studies by administering both simple attention tasks and tasks testing attention

shifting abilities in patients with PFT. If patients with PFT do not have problems with tests of shifting attention either, then the possibility must be considered that the cerebellum may not in fact subserve attention abilities. It is possible that the activity in the cerebellum reported in functional imaging studies of attention may be related to the fact that the cerebellum has strong connections with areas of the brain that are known to subserve attention, such as the prefrontal cortex, rather than to activity in the cerebellum itself.

5. Working memory

Contrary to predictions, patients with PFT were not found to be impaired on tests of working memory (one aspect of executive functioning). Given that previous studies have found that cerebellar damage is associated with working memory deficits (Silveri et al. 1998), it is important to determine why the current results were not in line with these findings.

One possibility is that there were differences in the particular aspects of working memory being tested. For example, in a functional imaging study of working memory carried out by Desmond et al. (1997) where they found activation in the right cerebellum, participants were required to remember visually presented letters over a short delay. This differed from the tests of verbal working memory used in the current study where the stimuli were presented audiologically.

Another way in which previous studies have differed is in the level of complexity of the working memory task. A study by Castro-Sierra et al. (2003) used the Boucher and Lewis Test where participants are given visual or auditory instructions that relate to the positions in which they must place a variety of small toys. They found that patients with lesions of the lateral regions of the cerebellum were significantly impaired on this test. However, the Boucher and Lewis Test is much more complicated than the simple recall of numbers or of spatial sequences used in this study. It is therefore possible that an intact cerebellum is important for more complex tasks, but not for simple tests of working memory.

One final possibility is that an intact cerebellum may not in fact be essential for working memory. It is possible that, as was suggested for attention above, the activity in the

cerebellum reported in functional imaging studies of working memory may be due to the strong connections between the cerebellum and regions of the brain (such as the prefrontal cortex) known to subserve working memory, rather than due to an active role of the cerebellum itself.

6. Face matching

In line with the predictions, patients with PFT were found to be impaired on the face-sorting task (a modified version of the WCST), which is a test of executive function that is believed to be subserved by the frontal lobes. On this task, patients with PFT succeeded in completing significantly fewer categories than controls, indicating that these patients had difficulties that prevented them from successfully completing the task. Furthermore, when differences in age were partialled out, there was evidence that patients with PFT failed to maintain set more frequently than controls. In addition, there was weak evidence that they produced more perseverative errors than controls. Both the ability to maintain set and the ability to avoid perseverance are executive functions that are subserved by the orbitofrontal cortex (Milner, 1963). Set maintenance in the face sorting tasks depends on the ability to keep information in mind while simultaneously selecting on what basis to match a particular card. The ability to avoid perseverance, on the other hand, is essentially the ability to set-shift, to alter behaviour when external rules change. The finding that individuals with PFT had problems with these executive functions suggests that their cerebellar pathology may have had a knock-on effect on areas of the frontal lobes including the orbitofrontal cortex, compromising normal function.

These results are in line with Schmahmann and Sherman's cerebellar cognitive affective syndrome detailed in Section 1.4.3.1.4. Schmahmann and Sherman (1998) highlighted executive function as one of four areas in which patients with cerebellar damage have particular difficulties.

In the current investigations, patients with PFT did not perform significantly more poorly than controls on either the number of non-perseverative or the number of unique errors. This indicates that the patients were following internal rules and not simply matching

haphazardly. That is to say that they did not simply fail to perform the task due to a limited understanding or a limited ability to match information; instead it seems that the patients approached the task in a similar way to normal controls, but they had difficulties with the intricacies of the task.

7. **Associations between tumour location and functional impairment:**

Comparisons between the performance of patients with PFT on the basis of the location of their tumour (left hemisphere, right hemisphere or midline) showed that the only test on which the groups differed significantly was the Benton test of Facial Recognition on which individuals with right hemisphere damage performed particularly poorly. A previous functional imaging study found that the cerebellum was activated during face recognition (Paller et al., 2003) and the present results suggest that it may be the right cerebellar hemisphere in particular that is involved in normal face recognition abilities.

It had been predicted that individuals with pathology of the right cerebellum would have difficulties with tasks involving language, and individuals with pathology of the left cerebellum would be impaired on tasks involving spatial abilities (in line with Riva and Giorgi, 2000). This prediction was not supported by the results. Individuals with right cerebellar pathology actually performed better than individuals with midline or left cerebellar pathology on all measures of the WORD (which assesses language and literacy abilities), and patients with pathology of the left cerebellum performed at very similar levels to patients with pathology in other cerebellar regions on the Corsi block span (which depends on spatial perceptual abilities as well as working memory). It is possible that this lack of support for the predictions is associated with the fact that there is much variation between the particular lobules that are damaged in each of the individual patients with PFT. It is therefore possible that particular regions or lobules within the right cerebellum are involved in language and particular regions or lobules within the left cerebellum are involved in spatial abilities. However, these may not have shown up in the current investigations if the patients with PFT did not have pathology in those particular regions. The particular cerebellar lobules damaged in each of the patients with PFT are detailed in Chapter 5.

8. Effects of age at pathology

The possible effects of age at pathology on cognitive outcome were investigated with correlation analyses between the age at surgery and the results of each of the neuropsychological tests reported above. The only significant finding was that surgery carried out at a younger age has negative effects on the ability to carry out the Benton Test of Facial Recognition (a test of visual perceptual abilities). This is in line with the prediction that patients with early pathology would perform more poorly on tests of high-level functions due to the effects of compensatory factors which ensure that basic functions are intact, often at the expense of the normal development of high-level cognitive functions. However, given the large number of statistical tests carried out, it is possible that this is a false positive result and should therefore be interpreted with caution until further investigations have been carried out to substantiate the finding.

Direct comparisons were also carried out between the performance of patients with early (age five and younger) and late (age six and older) pathology using independent sample t-tests. The results showed that individuals with late pathology performed poorly on the WOND (particularly on the mathematical reasoning subtest), which provides a measure of numeracy skills. This finding provides preliminary support for the idea that individuals who have pathology at an early age may have relatively intact numeracy skills, whereas patients who have pathology at a later age tend to have selective deficits on functions subserved by the region of the brain that is damaged. That is to say that after functions have developed through modularization, they are no longer dependent on the brain areas subserving the basic functions on which they are built, but instead rely on the brain structure which has come to subserve that function. In this case, the results suggest that the cerebellum (or areas with which the cerebellum has strong connections and which would be affected by cerebellar damage) may subserve aspects of numeracy abilities and that the damage to the cerebellum in the patients with late pathology has resulted in selective difficulties in the ability to carry out these abilities. Furthermore, these differences in numeracy ability are likely to be associated with compensatory mechanisms being less effective at a later age (see Section 1.1). Again, it is important to emphasize that due to the large number of statistical tests carried out, the probability of obtaining false positive

results is high and these findings should therefore be interpreted cautiously. Nevertheless, it is possible that differences do exist between patients with pathology at different ages, and this study has started to identify the cognitive domains that may be of particular interest for future investigations.

9. Effects of time since surgery

The possible effects of time elapsed since surgery on cognitive outcome were investigated with correlation analyses between the time since surgery and the results of each of the neuropsychological tests reported above. As predicted, there were no significant correlations between time since surgery and performance on any of the cognitive tests. This is most likely to be because all of the patients with PFT who participated in the study were seen at least two years post-surgery, by which time most of the major changes in the brain would have been completed.

4.5.2 Patients with AS

The performance of patients with AS on the cognitive tests is summarized in table 4.30 below.

Table 4.30: Summary of the performance of patients with AS on each of the cognitive tests

	Domains	Test	Performance by patients with AS
GENERAL COGNITIVE DOMAINS	1. Academic attainment	WORD	Not impaired
		WOND	Not impaired
	2. Visual matching	Benton test of line judgment	Not impaired
		Benton test of facial recognition	Some difficulties matching face-on photographs under different lighting conditions
	3. Copying and drawing	Test of visuo-motor integration	Not impaired
EXECUTIVE FUNCTIONS	4. Attention	Letter cancellation	Not impaired.
		Number cancellation	Impaired on time taken but not on accuracy
	5. Working memory	Word and non-word repetition	Not impaired
		Digit span	Not impaired
		Corsi block span	Not impaired
	6. Executive function	Face sorting task	Not impaired

1. Academic attainment

Results from the baseline tests of literacy (WORD) and numeracy (WOND) showed that there were no significant differences between the performance of patients with AS and controls on either of these tests. It was predicted that individuals with AS would be impaired on tests of language ability; however, the results of the WORD showed that they performed at very similar levels to controls on all the measures of this test. Nevertheless, individuals with AS did show more variation in the level of performance than controls, as indexed by the large standard deviations for the patients with AS, which suggests that some patients with AS may have particular problems with language, but that this is not the case for all of the patients as some even performed better than controls on measures of the WORD.

2. Visual matching

Patients with AS were not predicted to be impaired on tests of basic visual perception, but were predicted to have significant difficulties with the perception and processing of facial information. These predictions were partially supported. The results showed that there was no significant difference between patients with AS and their controls on a test of simple visual processing (the Benton test of line judgment) indicating that basic visual perceptual skills are intact in this patient population.

For face processing, however, there was partial support for the prediction that patients with AS would be impaired on tests of face-matching (the Benton test of Facial Recognition and the face-sorting task). For the Benton test of Facial Recognition, there was weak evidence that patients with AS were impaired on the matching of face-on photographs under different lighting conditions; however they were not significantly impaired on the matching of face-on and ¾ view photographs. Further investigation revealed that the problems on this task are likely to be associated with differences in the way in which individuals with AS perceive visual information. This is because the differences in performance on this task were removed when performance on the Benton test of line judgment (i.e. basic visual perceptual abilities) was partialled out.

A study by Deruelle et al. (2004) tested individuals with autism on a task where they had to match faces based either on local or global facial features. They found that in contrast to the controls, individuals with autism performed better on the matching of local features than on the matching of global features. It is therefore likely that the current results reflect the increased tendency to focus on local rather than global features of an image in patients with AS. The matching of faces under different lighting conditions will have been difficult for individuals with AS because some of the local features of the face on which they rely in order to match correctly, could not be seen because of shadows. In contrast, for matching face-on and ¾ view photographs, none of the local features were missing; there was just a decrease in the number of local features that could be seen because of the angle at which the photograph was taken. The fact that individuals with AS did not have problems with this aspect of the task thus suggests that the local features on which they match faces were present here, but may have been missing or less obvious in the task with different lighting conditions.

The results of the face-sorting task are considered in some detail in the section on executive functions below. However, it is important to briefly consider them here because the results from this task showed that patients with AS were not impaired even though it required the processing of faces. A possible explanation for this finding is that the stimuli in the face sorting task were line drawings, not photographs and patients with AS were not impaired on the face sorting task because they did not process these line drawings of faces in the same way that they would normally process "real" faces. This possibility is supported by the results from the Benton test of Facial Recognition as the faces used in this task are black and white photographs of faces, not line drawings, and patients with AS did have some difficulties with this task.

There is evidence in the literature to support the idea that individuals with autism do not process faces in the same way as controls. Dawson and Zanolli (2003), for example, carried out an investigation of the development of face processing and found that 3-year old children with autism did not produce different ERPs when shown photographs of their mother's compared to a stranger's face. They argued that these results showed that the

normal specialized face processing system does not develop properly in individuals with autism because these individuals do not attend to faces and therefore do not acquire the necessary expertise for face processing and accurate face recognition.

In summary, individuals had some difficulties with face processing and this is likely to be due to the fact that they focus on local rather than global features of faces. Furthermore, their difficulties may be related to the fact that the normal specialized processing system for faces does not develop properly in individuals with autism.

3. Copying and drawing

Patients with AS were not predicted to be impaired on the test of visuo-motor integration (VMI) which assesses copying and drawing abilities. As was explained in the discussion for patients with PFT, the VMI depends on essentially the same visuo-perceptual abilities as the Benton test of line judgment, but is a slightly higher-level function as it also involves motor output. The results showed that there was no significant difference between the performance of patients with AS and their controls on the VMI. This indicates that in addition to not having problems with simple visual perceptual abilities (as shown by the results of the Benton test of line judgment), patients with AS also do not have problems with the motor functions needed to copy visually presented shapes.

4. Attention

The prediction that patients with AS would be impaired on tests of attention (the letter and number cancellation tasks) was partially supported by the results. Patients with AS seemed to make a sacrifice in the time taken to complete the number cancellation task in order to get as many correct as possible because they were significantly slower than controls to complete the task but did not differ significantly from controls in the number of correct cancellations. It may be difficult for individuals with AS to process information efficiently because they do not have the systems in place that enable them to simultaneously process or consider multiple inputs and therefore are slower to attend to stimuli. There is evidence in the literature that there are abnormalities in the way that individuals use attention. Allen and Courchesne (2003), for example, carried out an fMRI study of attention and found that

individuals with autism showed significantly less activation in the regions of the cerebellum thought to be involved in attention than did controls.

Furthermore, this finding of abnormalities in attention abilities is interesting in light of the fact that attention is subserved by the frontal lobes and that there is evidence that the frontal lobes are abnormal in autism (Carper and Courchesne 2000; Minshew et al. 1993; Bailey et al. 1998; Hughes et al. 1994).

5. Working memory

The results of the tests of working memory showed that patients with AS were not significantly impaired on phonological working memory or on digit span. There was weak evidence that patients with AS were impaired on spatial working memory (the Corsi block span) and further investigation suggested that it is the working memory aspect of this task that is problematic for the patients with AS rather than aspects related to spatial abilities. The finding that individuals with AS had difficulties with the test of spatial working memory is consistent with a study carried out by Morris et al. (1999) who found that patients with AS were significantly impaired on a test of spatial working memory. Morris et al. (1999) found similar, but less severe difficulties with spatial working memory in a group of patients with left frontal excisions. These results indicate that the abnormalities present in the brains of patients with AS result in more substantial difficulties with spatial working memory than the difficulties that result when regions of the frontal lobe are excised. This is likely to be associated with the fact that patients with AS have abnormalities not only in the frontal lobes, but also in additional regions of the brain (for example, the cerebellum) because the neural connections of the brain during early development are abnormal.

It is interesting to note that previous studies have found that working memory is intact in individuals with autism (Minshew and Goldstein, 2001; Ozonoff and Strayer, 2001) and the current results might therefore suggest that individuals with AS may have difficulties with some forms of working memory that are not problematic in individuals at the less able end of the autistic spectrum. This is in line with previous work that has argued that different

working memory systems are dissociable. A study by Pickering et al. (1998), for example, found little relation between the performance of normally developing children on tests of verbal working memory and on tests of visuospatial working memory, indicating that there are likely to be dissociations between these memory systems.

Furthermore, the results indicate that the problems with memory in patients with AS reported by parents in the developmental questionnaire (see Chapter 2) may involve difficulties with working memory.

6. Face matching

Contrary to predictions, individuals with AS were not found to be impaired on the executive functions tested by the face-sorting task. This is an unexpected result. There is much evidence in the literature to show that individuals with AS have difficulties with executive functions (Ozonoff et al. 2004; Ozonoff et al., 1991; Geurts et al., 2004). Furthermore, there is evidence that these patients have difficulties with the WCST in particular (e.g. Shu et al., 2001; Ozonoff et al. 2001) on which the face-sorting test was based. This suggests that there is something about the face-sorting task that makes it relatively easy for individuals with AS to perform well. In order to work out what this might be, it is necessary to contrast this test with the WCST. The most fundamental difference is that the face-sorting task uses faces rather than shapes. It might be the case that this provides an advantage for patients with AS because the faces provide more cues by which they can match. A number of studies have shown that individuals with high functioning autism are particularly good at tasks which depend on good local processing such as the identification of embedded figures (Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983; Mottron et al. 2003), but perform at normal levels on tasks which depend on global processing (e.g. Mottron et al. 1999; Ozonoff et al. 1994). This is also the case for face processing. A study by Deruelle et al. (2004) considered in the section on visual processing above, found that individuals with autism were better at matching on high frequency than on low frequency facial information (i.e. on local rather than global facial features). Thus, the lack of problems with the face-sorting task may be associated with the fact that these

individuals with AS are able to focus on the local features of the faces in order complete the task.

However, it is important to remember that patients with AS are known to have difficulties matching faces, a fact that is linked to their socio-emotional impairment and their problems with communication and theory of mind (see Section 1.4.3.2.1). Therefore the fact that they do not have problems matching faces in this task might appear unexpected. Nevertheless, as explained in the section on visual perception above, it is important to remember that the faces in the face-sorting task are 2-dimensional line drawings. This means that it is possible that individuals with AS do not process these pictures in the same way that they process faces and therefore do not have the same difficulties with these 2-d line drawings.

The effects on cognitive function of neurodevelopmental versus acquired damage to the cerebellum

It is commonly believed that there is a fundamental difference between brains affected by neurodevelopmental abnormalities and brains affected by acquired pathology (see Section 1.1). Those affected by neurodevelopmental damage are thought to have been abnormal from the beginning of inter-utero development so that there are abnormalities in their connections and neural networks. Brains affected by acquired pathology, on the other hand, are not believed to have been abnormal from the beginning. These brains are thought to have normal, intact, neural connectivity and until the onset of the acquired pathology, they also had normal potential. Thus there are likely to be differences in the performance of patient groups with neurodevelopmental versus acquired pathology of the same brain region.

In the current investigation, the cerebellum is affected in the two patient populations and the results show that there are a number of differences in the intact and impaired cognitive functions that may be associated with this cerebellar damage. The patients with PFT, who have acquired pathology of the cerebellum, have particular difficulties with the executive functions of set maintenance and set-shifting as assessed by the face-sorting task, and with reading comprehension as assessed by the WORD. The patients with AS, on the other hand,

who have developmental abnormality of the cerebellum in addition to a number of other brain regions, were found to have particular difficulties with verbal (and to a lesser degree, spatial) working memory, with some aspects of attention and with the visual perceptual task of face matching. It is possible that these differences in performance could be explained by differences in the way that the two patient groups approach cognitive tasks as a result of their different brain abnormalities. That is to say that the abnormal neural connectivity of the brain in patients with AS could mean that they do not approach cognitive tasks in the normal way. This was in fact demonstrated for face recognition where it appeared that patients with AS focussed on local rather than global features. It is possible that comparable differences in approach could explain the impairments in working memory that were found in patients with AS, although this clearly requires further investigation in order to determine what mechanisms these patients use to retain information in memory and whether these are substantially different from those used by normal controls. For the patients with PFT, who have normal neural connectivity and whose early development is believed to have been normal, it is likely that they approach cognitive functions in the same way as normal controls. However, because sections of their cerebella are damaged or even missing, they are likely to have particular difficulties with the functions that are subserved by those cerebellar areas.

To summarise, patients with AS may have difficulties with cognitive functions because they do not approach the tasks in the conventional way as a result of abnormalities in the connections of the brain which form during early development and which affect a number of different brain areas, one of which is the cerebellum. The difficulties of patients with PFT, on the other hand, may not be related to differences in the approach to tasks, but to actual problems with the normal completion of the tasks due to damage to the regions of the cerebellum (and the knock-on effects on other regions of the brain with which the cerebellum has strong connections) that normally subserve a particular function.

4.6 Summary

The investigations into cognitive function in patients with PFT and patients with AS have revealed that patients with PFT have difficulties with executive function and reading

comprehension, but have intact verbal and spatial working memory, visual perception, numeracy and copying and drawing abilities. Patients with pathology of the right hemisphere of the cerebellum appear to have particular problems with face recognition, but patients with midline or left hemisphere pathology do not have particular difficulties with any of the cognitive tests administered. Patients with AS appear to have difficulties with verbal working memory, with some aspects of attention and spatial working memory and with visual perceptual face matching, but do not have problems with literacy, numeracy, copying and drawing, or the executive functions of set maintenance and set-shifting assessed by the face-sorting task.

CHAPTER 5: MR CHARACTERIZATION OF THE PATIENTS WITH PFT

In this chapter, the MR characteristics of the brains of the individuals with PFT who participated in this study are reported. Detailed analyses using voxel-based morphometric analyses are reported in Chapter 6, however this chapter focuses on the obvious abnormalities in the brain that can be seen from conventional neuroradiological assessment. For each individual patient, the precise location of the tumour and the particular cerebellar lobules affected by surgery are described. This tumour location information is then used in analyses with the results from the motor and cognitive tests reported in Chapters 3 and 4 in order to investigate the nature of functional organization within the cerebellum.

Previous structure/function studies of patients with PFT have not focused on the particular location or extent of pathology of the cerebellum. Instead, these studies have tended to focus on the functions of the cerebellum as a whole or on more general distinctions between the right and left hemisphere and the vermis. Such studies have shown that the right cerebellum is particularly involved in auditory sequential memory and language processing (Riva and Giorgi, 2000), the left hemisphere in spatial and visual sequential memory (Riva and Giorgi, 2000) and the vermis in modulation of affect (Levisohn et al. 2000; Steinlin et al. 2003). However, while these studies have provided important information about the functions in which the cerebellum is involved, the precise nature of functional localisation within the cerebellum is still unclear.

The publication of an MRI atlas of the human cerebellum (Schmahmann et al. 2000), has enabled the accurate identification of individual cerebellar lobules from MRI scans and hence the identification of lobules that are damaged or missing in patients who have undergone surgery to remove posterior fossa tumours. This is an important step in the understanding of functional localisation in the cerebellum. If patients with damage to particular cerebellar lobules are impaired on a given task, then it is possible that that particular lobule is involved in the function which is impaired. If, on the other hand, there is no clear association between the particular lobule that is damaged and impaired

functioning, then this might suggest that the cerebellum operates more as a whole rather than individual lobules having their own individual functions. The functional organization of the cerebellum will be investigated in Section 5.4 below.

The chapter begins with a description of the selection criteria for the patients with PFT who participated in the study. Details of the MR imaging methods are then reported, followed by a description of the methods used to identify the precise location and extent of cerebellar damage in each individual patient with PFT. Flattened maps of the cerebellar cortex are provided for each patient to show the location of the pathology in each individual, for the tumour location subgroups and for the group with PFT as a whole. Once the precise regions of damage have been identified, investigations (independent sample t-tests) will be carried out to examine whether there are any differences in the performance of patients with PFT on the motor and cognitive tests reported in Chapters 3 and 4 depending on which particular cerebellar lobules are damaged. Finally, in order to investigate whether there is any association between the extent of cerebellar pathology (the number of lobules damaged) and performance on any of the motor or cognitive tests reported in Chapters 3 and 4, correlation analyses will be carried out.

5.1 Methods

5.1.1 Participants

As detailed in Chapter 2, all of the patients with PFT had been treated for cerebellar astrocytomas at Great Ormond Street Hospital in London between the years of 1986 and 2001. Individuals were excluded from the study if they had undergone any chemotherapy or radiation treatment, if they had any abnormal development prior to the symptoms of the tumour, if they had any additional neurological or psychiatric diagnosis (including epilepsy, attention deficit hyperactivity disorder (ADHD) and autism) and if their tumours, and post-surgical brain abnormalities, were not limited to the cerebellum alone. In addition, patients were only recruited at least two (and up to 16) years post-surgery in order that any major changes in the brain caused by the tumour and surgery would have dissipated.

5.1.2 Data Acquisition

MRI scans of the brain were obtained for all of the participants described in Section 2.3.1 with the exception of one patient: patient 9 was not scanned because she still had a brain reservoir (Rickham's Reservoir) in situ and it was unclear whether or not this was MR compatible.

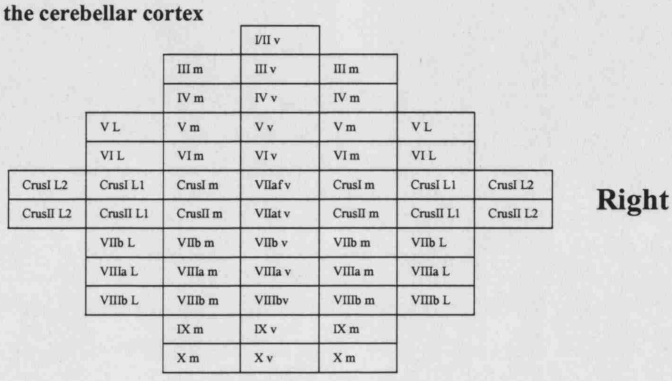
MRI data were acquired on a 1.5 Tesla Siemens Vision system. A T1 weighted 3D-FLASH sequence was carried out with the following parameters: TR = 16.8ms, TE = 5.7ms, flip angle = 12°, matrix size = 256 x 256, field of view = 200mm, partition thickness = 1mm, 160 sagittal partitions, voxel size = 0.78mm x 0.78mm x 1.00mm, acquisition time = 8.59 minutes.

T2 weighted Turbo Spin Echo (TSE) sequences were acquired in the coronal and in the axial planes with the following parameters: TR = 3458ms, TE = 96ms, matrix size = 196 x 512, field of view = 210mm, partition thickness = 5mm.

5.1.3 Tumour localisation

In order to determine the location and extent of pathology in each individual patient, it was necessary to first produce a common reference map of the cerebellum. The anatomical distinctions between the different cerebellar lobules adopted by Schmahmann et al. (2000) in their MRI atlas of the human cerebellum are used in this thesis. In line with these distinctions, a simplified flattened map of the cerebellar cortex was produced showing each of the ten lobules and their divisions into vermal (v), intermediate (m) and lateral (L1 and L2) zones (see Figure 5.1).

Figure 5.1: Flattened map of the cerebellar cortex



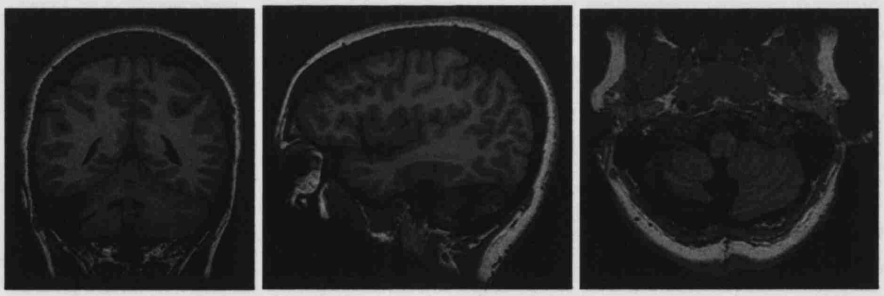
T1-weighted images were then visually inspected in the sagittal, axial and coronal planes in conjunction with both the Schmahmann et al. (2000) atlas and the Angevine et al. (1961) atlas in order to identify which lobules were damaged or missing in each individual patient. T2-weighted images were also inspected in the axial and coronal planes in order to confirm that the correct lobules had been identified. Once the missing and damaged lobules had been identified, these were marked on the flattened maps of the cerebellar cortex. The lobules were shaded dark grey if the whole of the lobule was missing or damaged and were shaded light grey if only small sections of the lobule were missing or damaged. In this way it was possible to record which particular lobules were affected by the pathology and which lobules were essentially intact.

5.2 Results

The particular location of the cerebellar pathology for each individual patient with PFT is reported below.

Patient PFT 1

Female
Left hemisphere tumour
12y 11m at surgery
17y 16m at MRI scan
4y 6m since surgery



		I/II v			
	III m	III v	III m		
	IV m	IV v	IV m		
V L	V m	V v	V m	V L	
VI L	VI m	VI v	VI m	VI L	
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
VIIb L	VIIb m	VIIb v	VIIb m	VIIb L	
VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L	
VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L	
	IX m	IX v	IX m		
	X m	X v	X m		

Patient PFT 1 has pathology limited to the lateral zone of the left hemisphere of the cerebellum. The lobules that are affected are Crus I (only the lateral portion), Crus II and lobule VIIb.

Patient PFT 2

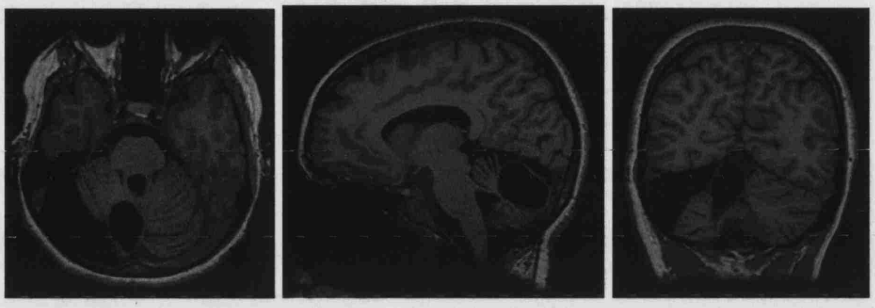
Female

Left hemisphere tumour

7y 3m at surgery

11y 6m at MRI scan

4y 2m since surgery



		I/II v				
	III m	III v	III m			
	IV m	IV v	IV m			
V L	V m	V v	V m	V L		
VI L	VI m	VI v	VI m	VI L		
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
VIIb L	VIIb m	VIIb v	VIIb m	VIIb L		
VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L		
VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L		
	IX m	IX v	IX m			
	X m	X v	X m			

Patient PFT 2 has pathology affecting a large portion of the left hemisphere of the cerebellum as well as approximately half of the vermis. Both the intermediate and lateral zones of the left hemisphere are affected: in the intermediate zone, lobules V to VIIb are missing and in the lateral zone, Crus I and II and lobules VI and VIIb are no longer present. In the vermis, lobules V through to VIIb are missing. No regions of the right cerebellar hemisphere appear to be damaged.

Patient PFT 3

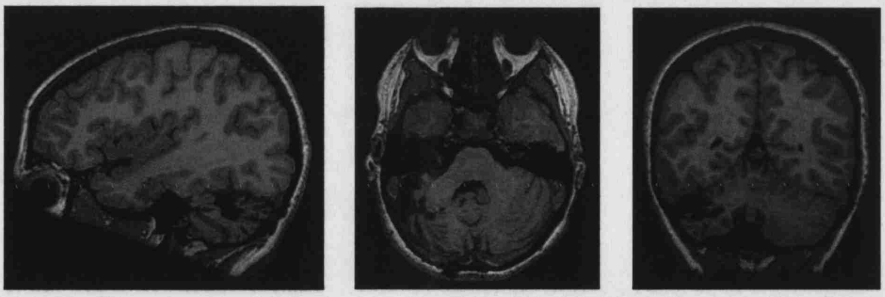
Female

Left hemisphere tumour

5y 6m at surgery

13y 9m at MRI scan

8y 3m since surgery



		I/II v				
	III m	III v	III m			
	IV m	IV v	IV m			
V L	V m	V v	V m	V L		
VI L	VI m	VI v	VI m	VI L		
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
VIIb L	VIIb m	VIIb v	VIIb m	VIIb L		
VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L		
VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L		
	IX m	IX v	IX m			
	X m	X v	X m			

Patient PFT 3 has pathology limited to the lateral zone of the left hemisphere of the cerebellum. The lobules that are affected are Crus I and II and lobule VI, although Crus II appears to be intact in the more medial portion of the lateral zone.

Patient PFT 4

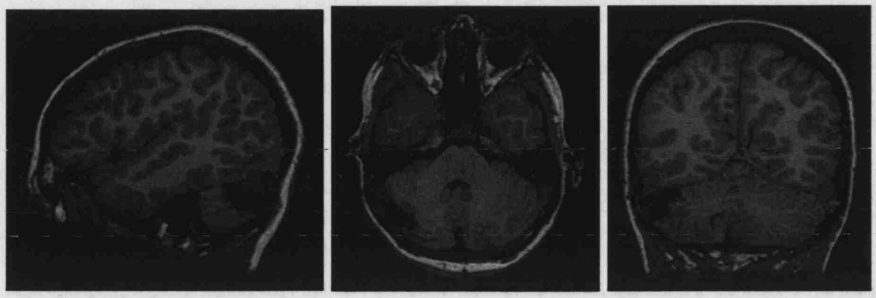
Male

Left hemisphere tumour

5y 6m at surgery

13y 8m at MRI scan

8y 1m since surgery



			I/II v			
		III m	III v	III m		
		IV m	IV v	IV m		
	V L	V m	V v	V m	V L	
	VI L	VI m	VI v	VI m	VI L	
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
	VIIb L	VIIb m	VIIb v	VIIb m	VIIb L	
	VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L	
	VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L	
		IX m	IX v	IX m		
		X m	X v	X m		

Patient PFT 4 has pathology limited to the lateral zone of the left hemisphere of the cerebellum. The lobules that are affected are Crus I and II and lobule VIIb.

Patient PFT 5

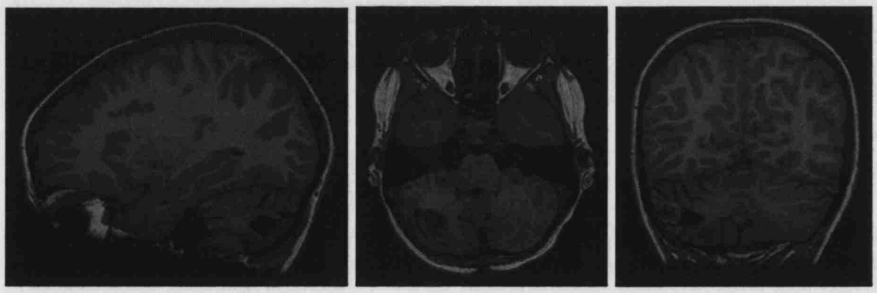
Male

Left hemisphere tumour

7y 7m at surgery

9y 11m at MRI scan

1y 3m since surgery



			I/II v			
		III m	III v	III m		
		IV m	IV v	IV m		
	V L	V m	V v	V m	V L	
	VI L	VI m	VI v	VI m	VI L	
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
	VIIb L	VIIb m	VIIb v	VIIb m	VIIb L	
	VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L	
	VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L	
		IX m	IX v	IX m		
		X m	X v	X m		

Patient PFT 5 has fairly localized pathology affecting lateral regions of the left hemisphere of the cerebellum only. The particular lobules that are damaged are Crus II and lobules VIIb and VIIIa.

Patient PFT 6

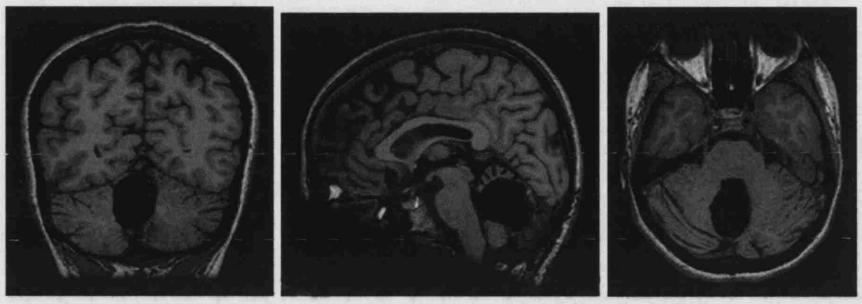
Female

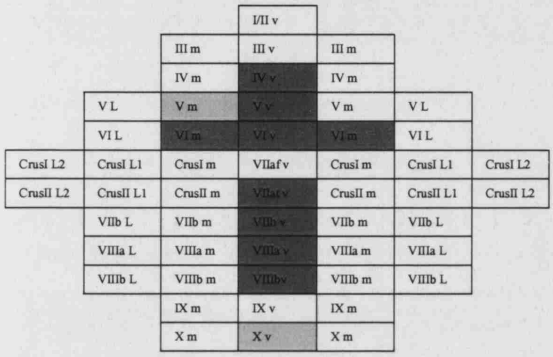
Midline tumour

15y 2m at surgery

18y 10m at MRI scan

3y 8m since surgery





Patient PFT 6 has pathology affecting a large section of the vermis from lobules IV through to VIIIb. The pathology has also encroached into the intermediate zone adjacent to the vermis in lobule VI bilaterally. There is some abnormality in lobule V in the intermediate zone on the left, and in lobule X of the vermis.

Patient PFT 7

Patient PFT 7 could not be scanned because she had a Rickham's Reservoir in situ and it was unclear whether this was MR-compatible.

Patient PFT 8

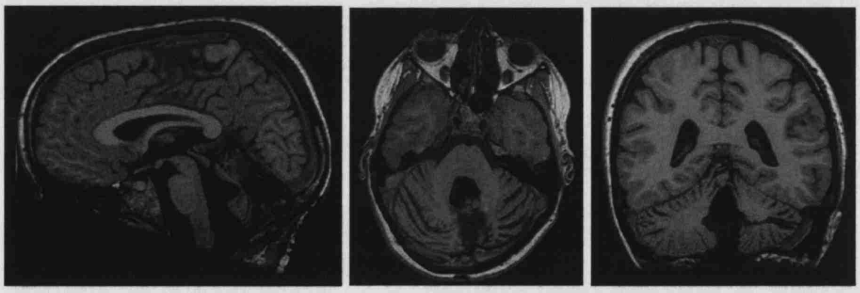
Female

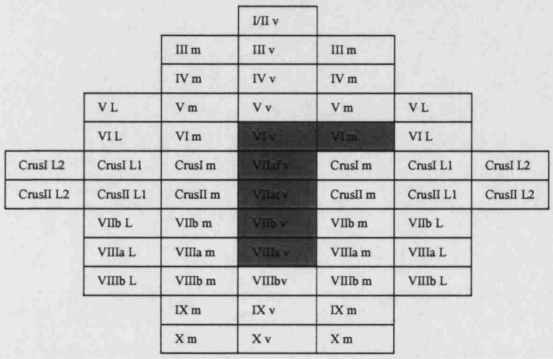
Midline tumour

4y 7m at surgery

12y 11m at MRI scan

8y 4m since surgery





Patient PFT 8 has pathology which has affected a section of the vermis from lobules VI through to VIIIa. The pathology has also encroached into the intermediate zone adjacent to the vermis in lobule VI on the right. There is no damage to the lateral zone of the right hemisphere or to any sections of the left hemisphere.

Patient PFT 9

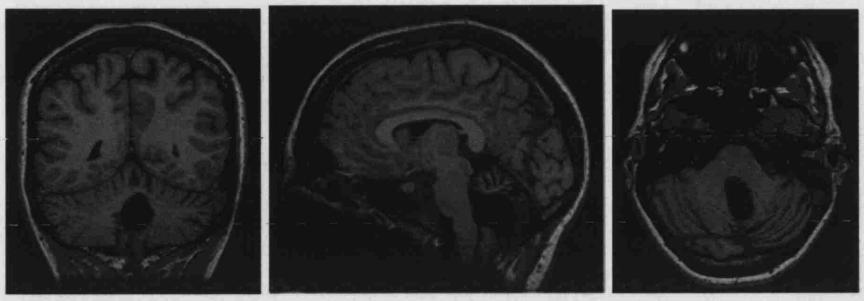
Female

Midline tumour

11y 10m at surgery

20y 0m at MRI scan

8y 1m since surgery



		I/II v				
		III m	III v	III m		
		IV m	IV v	IV m		
	V L	V m	V v	V m	V L	
	VI L	VI m	VI v	VI m	VI L	
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
	VIIb L	VIIb m	VIIb v	VIIb m	VIIb L	
	VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L	
	VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L	
		IX m	IX v	IX m		
		X m	X v	X m		

Patient PFT 9 has pathology affecting a large section of the vermis from lobule III through to lobule VIIIa. In addition, the pathology has encroached into the intermediate zone on the right, affecting a small medial portion of lobules V, VI and VIIIa.

Patient PFT 10

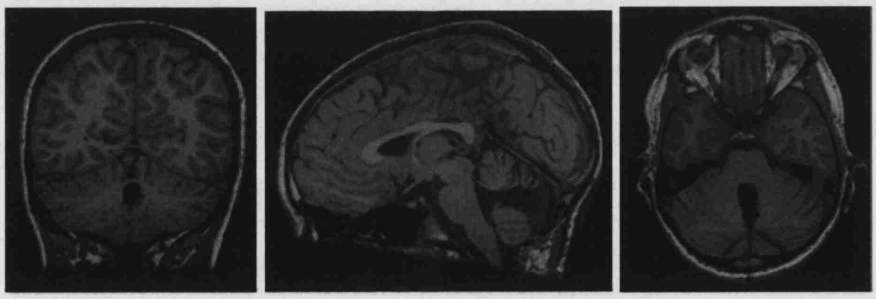
Male

Midline tumour

11y 2m at surgery

13y 3m at MRI scan

2y 1m since surgery



		I/II v				
		III m	III v	III m		
		IV m	IV v	IV m		
	V L	V m	V v	V m	V L	
	VI L	VI m	VI v	VI m	VI L	
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
	VIIb L	VIIb m	VIIb v	VIIb m	VIIb L	
	VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L	
	VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L	
		IX m	IX v	IX m		
		X m	X v	X m		

Patient PFT 10 has pathology limited to a small area of the vermis. Lobules VIIat and VIIb are missing and lobule VI is damaged. There does not appear to be any pathology in either of the cerebellar hemispheres.

Patient PFT 11

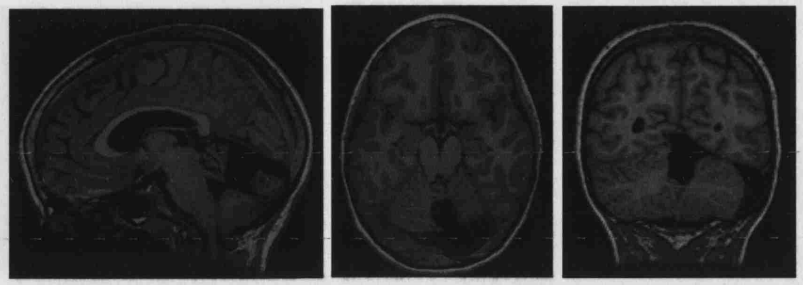
Female

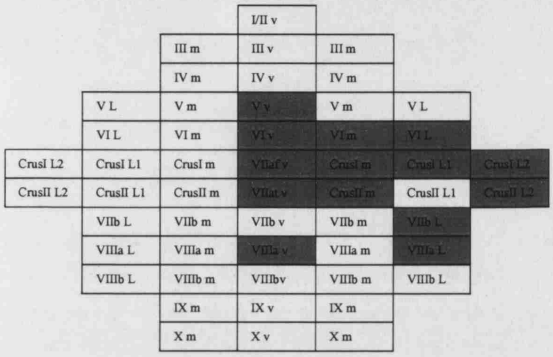
Right hemisphere tumour

6y 3m at surgery

8y 8m at MRI scan

2y 5m since surgery





Patient PFT 11 has fairly diffuse pathology affecting a number of lobules in the intermediate and lateral zones of the right hemisphere of the cerebellum as well as a large proportion of the vermis. In the intermediate zone, Crus I and II and lobule VI are affected. In the lateral zone, lobules VI, VIIb, VIIIa and Crus I are missing, but Crus II appears to be present in the more medial regions of the lateral zone. In the vermis, lobules V through to VIIIa are missing. No regions of the left cerebellar hemisphere appear to be damaged.

Patient PFT 12

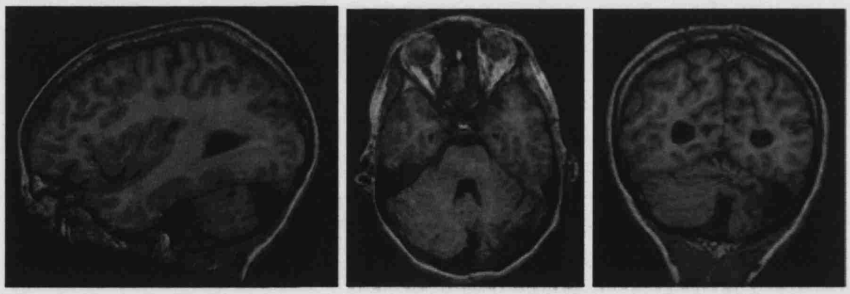
Male

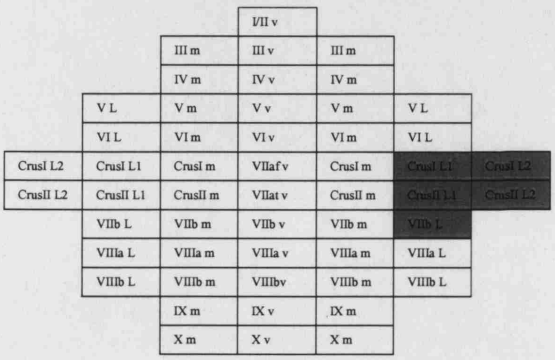
Right hemisphere tumour

2y 2m at surgery

12y 9m at MRI scan

10y 7m since surgery





Patient PFT 12 has pathology limited to the lateral zone of the right hemisphere of the cerebellum. The lobules that are affected are Crus I and II and lobule VIIb.

Patient PFT 13

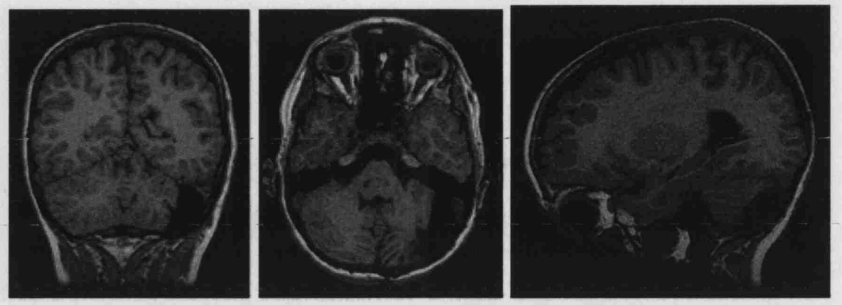
Male

Right hemisphere tumour

1y 9m at surgery

8y 10m at MRI scan

7y 1m since surgery



		I/II v				
	III m	III v	III m			
	IV m	IV v	IV m			
V L	V m	V v	V m	V L		
VI L	VI m	VI v	VI m	VI L		
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
VIIb L	VIIb m	VIIb v	VIIb m	VIIb L		
VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L		
VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L		
	IX m	IX v	IX m			
	X m	X v	X m			

Patient PFT 13 has pathology limited to the lateral zone of the right hemisphere of the cerebellum. The lobules that are affected are Crus I and II and lobule VIIb.

Patient PFT 14

Male

Right hemisphere tumour

11y 7m at surgery

15y 0m at MRI scan

3y 5m since surgery

		I/II v				
	III m	III v	III m			
	IV m	IV v	IV m			
V L	V m	V v	V m	V L		
VI L	VI m	VI v	VI m	VI L		
CrusI L2	CrusI L1	CrusI m	VIIaf v	CrusI m	CrusI L1	CrusI L2
CrusII L2	CrusII L1	CrusII m	VIIat v	CrusII m	CrusII L1	CrusII L2
VIIb L	VIIb m	VIIb v	VIIb m	VIIb L		
VIIIa L	VIIIa m	VIIIa v	VIIIa m	VIIIa L		
VIIIb L	VIIIb m	VIIIbv	VIIIb m	VIIIb L		
	IX m	IX v	IX m			
	X m	X v	X m			

Patient PFT 14 has pathology limited to the intermediate zone of the right hemisphere of the cerebellum. Lobules VIIIb and IX are affected as well as the medial portions of intermediate lobules Crus II, VIIb and VIIIa.

Patient PFT 15

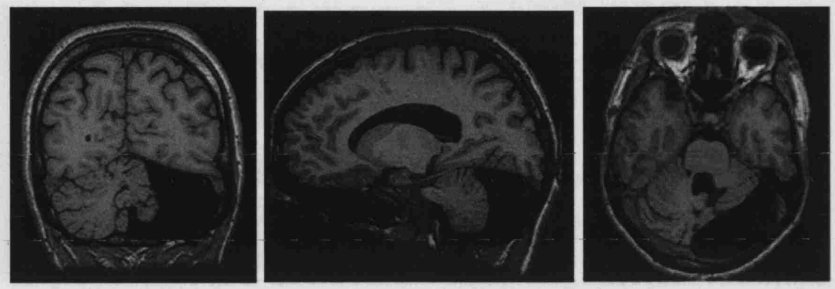
Male

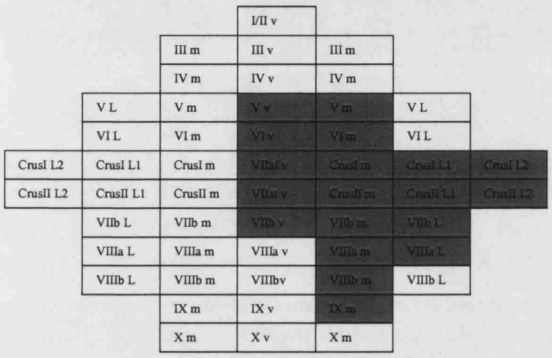
Right hemisphere tumour

4y 2m at surgery

14y 8m at MRI scan

10y 6m since surgery





Patient PFT 15 has pathology affecting a large portion of the right hemisphere of the cerebellum as well as approximately half of the vermis. Both the intermediate and lateral zones of the right hemisphere are affected: in the intermediate zone, lobules V to IX are missing and in the lateral zone, Crus I and II and lobules VIIb and VIIIa are no longer present. In the vermis, lobules V through to VIIb are missing. No regions of the left cerebellar hemisphere appear to be missing.

These flattened maps of the cerebellar cortex show that there are a variety of different lobules that are damaged in the patients with PFT, but that it is possible to broadly divide the patients into those who have pathology affecting the left hemisphere, the right hemisphere or the vermis. As detailed in Section 2.3.1, the criterion adopted in this thesis for allocating individuals to the tumour location subgroups was that patients were allocated to the midline pathology group only if they had damage limited to the midline alone. If there was any pathology of either of the cerebellar hemispheres, then patients were allocated to the relevant hemisphere pathology subgroup.

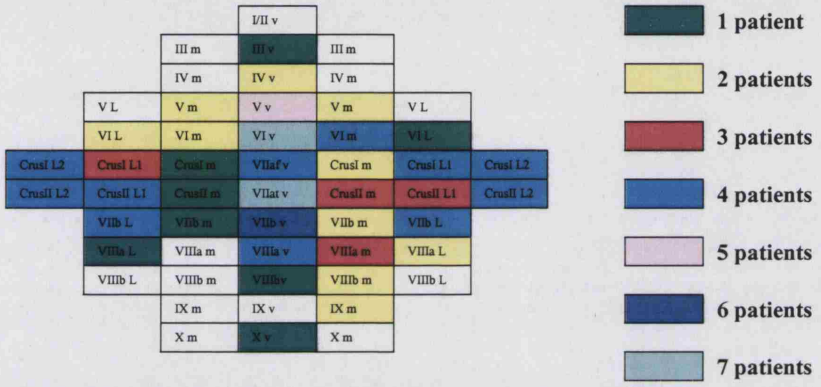
5.3 Lesion overlap

Having identified the particular cerebellar lobules that are affected by pathology in each of the individual patients with PFT, these areas of pathology can be overlapped in order to gain an idea of the overall extent of pathology affecting the group as a whole, and that affecting each of the three tumour location subgroups (left hemisphere, right hemisphere and midline pathology).

5.3.1 All patients with PFT

The flattened map of the cerebellar cortex in Figure 5.2 shows all of the sections of lobules that are damaged in one or more of the patients with PFT. Patients are counted if they have any damage to a particular lobule, not only if the whole of that lobule is missing, as it is predicted that any abnormality in a lobule will have an impact on normal functioning. The lobules are colour-coded to show the number of patients who have damage to each region.

Figure 5.2: Flattened map of the cerebellar cortex showing lobules damaged in patients with PFT

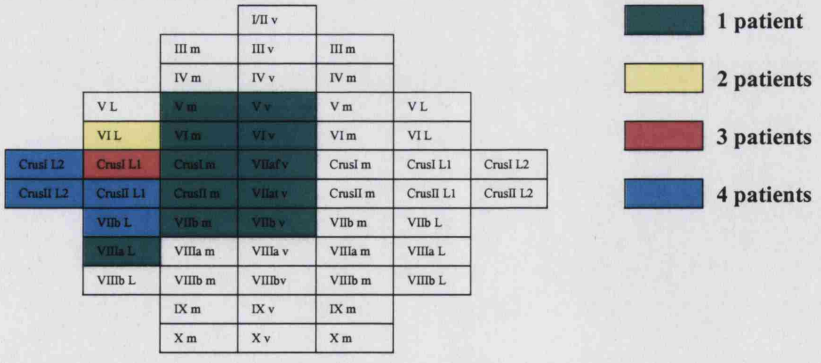


This map shows that there are very few lobules that are not damaged in any of the patients with PFT who participated in the study.

5.3.2 Patients with left hemisphere pathology

The flattened map of the cerebellar cortex in Figure 5.3 shows the lobules that are damaged in one or more of the five patients with left hemisphere pathology.

Figure 5.3: flattened map of the cerebellar cortex showing lobules damaged in patients with left hemisphere pathology



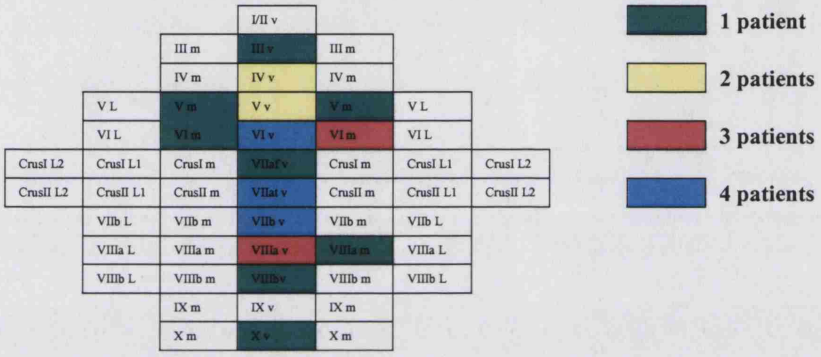
This map shows that the pathology in patients with left hemisphere damage was principally located in lobules V through to VIIb. There was very little pathology of the anterior lobe which is the region of the cerebellum that has been particularly implicated in motor

functions. The fact that lobules I-IV of the anterior lobe were intact in the individuals with left hemisphere pathology is consistent with the finding that these patients performed relatively well on the tests of motor function reported in Chapter 3.

5.3.3 Patients with midline pathology

The flattened map of the cerebellar cortex in Figure 5.4 shows the lobules that are damaged in one or more of the four patients with midline pathology for whom MRI scans were obtained.

Figure 5.4: flattened map of the cerebellar cortex showing lobules damaged in patients with midline pathology

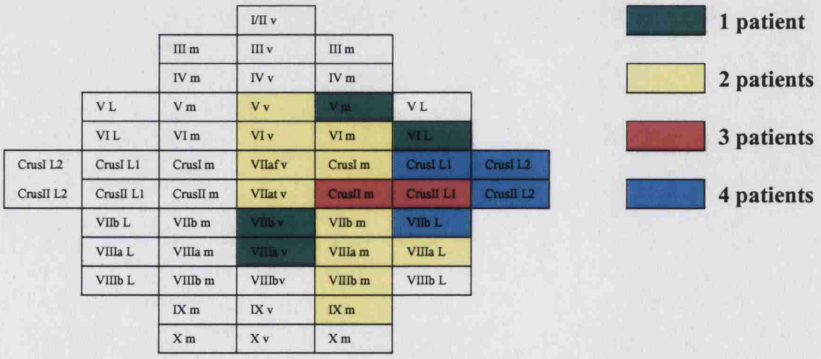


This map shows that the pathology in patients with midline damage affected an extensive amount of the vermis. The only vermal lobules that were not damaged were lobules I and II of the anterior lobe and lobule IX of the posterior lobe.

5.3.4 Patients with right hemisphere pathology

The flattened map of the cerebellar cortex in Figure 5.5 shows the lobules that are damaged in one or more of the five patients with right hemisphere pathology.

Figure 5.5: flattened map of the cerebellar cortex showing lobules damaged in patients with right hemisphere pathology



This map shows that the pathology in patients with right hemisphere damage was principally located in lobules VI through to VIIIa. There was also some pathology of

vermal lobule V of the anterior lobe and of medial lobules VIIIb and IX of the posterior lobe. These damaged regions are similar to those damaged in patients with left hemisphere pathology; however the damage in patients with right hemisphere pathology extends further to the posterior, affecting lobules VIIIa medially and laterally in addition to the vermis, and affecting lobules VIIIb and IX which were not affected in patients with left hemisphere pathology. The only lobule of the anterior lobe that was damaged in patients with right hemisphere pathology was lobule V of the vermis. This means that their anterior lobe pathology was even more minor than that of patients with left hemisphere pathology. This finding is unexpected given that the patients with right hemisphere pathology were found to perform significantly more poorly than the other tumour location subgroups on a number of motor tests. This indicates that it may not simply be the case that motor function is subserved by the anterior lobe of the cerebellum, but that other regions of the cerebellum (possibly in the right hemisphere) may be essential for intact motor abilities. However, it is also possible that there were other medical variables (such as hydrocephalus) in the patients with right hemisphere pathology and their difficulties with motor function could be related to such factors. Alternatively, it is possible that patients with right hemisphere pathology had additional damage to other areas of the brain involved in motor functions (for example the motor cortex) that could explain their difficulties with motor function. This possibility will be considered in Chapter 6 when subtle abnormalities in grey and white matter densities over the whole brain will be reported.

5.4 Investigating functional localisation in patients with PFT

Having identified the particular cerebellar lobules damaged in each patient with PFT, it is possible to carry out investigations into the possibility that there is functional localisation in the cerebellum. Two different methods will be employed to investigate the functional organization of the cerebellum:

(i) **Investigating functional localisation at a lobular level:** The first method is to look at whether damage to individual lobules has any effect on the performance of any of the motor or cognitive tasks reported in Chapters 3 and 4. This involves carrying out independent sample t-tests for each cerebellar lobule between patients with PFT who have pathology of that lobule and patients with

PFT who do not have pathology of that lobule. If patients with pathology of a particular lobule perform significantly more poorly on a particular motor or cognitive test than patients who do not have pathology of that lobule then this indicates that that particular lobule may play a role in that particular motor or cognitive function.

(ii) **Investigating cerebellum-wide functions:** The second method is to investigate whether the cerebellum might function more as a coordinated whole than as a mosaic of sub-parts each with their own role in behaviour. This involves carrying out correlation analyses between the number of lobules damaged in patients with PFT and the scores obtained on each of the motor and cognitive tests reported in Chapters 3 and 4. This method will test Lashley's theory of mass action detailed in Section 1.1.2 which states that the amount of brain that is damaged is critical to the level of functioning. It is predicted that if the cerebellum functions as a whole, and if Lashley's theory of mass action is correct, then negative correlations will be found between the number of lobules damaged and scores on the neuropsychological tests, reflecting a decrease in performance with an increase in the amount of pathology of the cerebellum.

5.4.1 Investigating functional localisation at a lobular level

Tables 5.1 and 5.2 below show the results of independent sample t-tests carried out for each cerebellar lobule between patients who did and did not have damage to that lobule for a number of motor and cognitive tests. Given the small number of patients, it was not possible to consider each section of each lobule (middle, intermediate and lateral); instead each of the lobules was considered as a whole, so that patients with any damage to a particular lobule (irrespective of whether the damage was in the right or left hemisphere, or in the midline) were included in the analyses. Only the tests on which there was a significant difference are reported. Given the extensive number of comparisons carried out here, it may be considered necessary to apply a Bonferroni correction. However, the present analyses were approached as an exploratory investigation in order to show the types of functions with which patients with different regions of cerebellar damage had problems. Therefore any comparisons which reached uncorrected significance of $p < 0.05$ are reported

here. It should be noted that the analyses were only carried out for lobules for which there were at least five patients in both the groups with and without pathology. This meant that the only lobules for which it was possible to carry out statistical analyses were lobules V, VI, Crus I and VIIIa. Altogether, six patients had damage to lobule V, eight patients had damage to lobule VI, eight patients had damage to Crus I (hemisphere) or lobule VIIaf (midline), and six patients had damage to lobule VIIIa.

Table 5.1: Motor tests on which patients with damage to different cerebellar lobules experienced significant problems (p values are given in the table). DH = dominant hand, NDH = non-dominant hand.

	V (6 patients)	VI (8 patients)	Crus I or VIIaf (8 patients)	VIIIa (6 patients)
Annett Pegs NDH	0.012	0.033		0.037
Grooved Pegs DH	0.021			
Grooved Pegs NDH	0.002			
Big blue beads	0.030			
Simple tapping NDH	0.003			
Bimanual tapping				0.043
Rotary pursuit fast learning		0.018		
Rotary pursuit slow learning		0.025		
Posting task full gap DH 45 degrees				0.011
Posting task full gap NDH 45 degrees	0.011			0.011
Posting task full gap NDH 135 degrees	0.034			0.045
Posting task quarter gap NDH 45 degrees	0.014			

These results provided preliminary support for the claim that the anterior lobe of the cerebellum is particularly involved in motor functions, as patients with damage to lobule V were significantly impaired on a number of tests of motor function. However, patients with damage to lobules in the posterior lobe also experienced some difficulties with motor function, indicating that some regions of the posterior lobe may also be important for motor functions. This is in line with a functional imaging study (PET) by Inoue et al. (1998) who found some activation in lobules VIII and IX during reaching movements with the shoulder (Inoue et al. 1998).

The results for the comparisons between patients with damage to different lobules on the cognitive tests are provided in Table 5.2 below.

Table 5.2: Cognitive test on which patients with damage to different cerebellar lobules experienced significant problems (p values are given in the table)

	V (6 patients)	VI (8 patients)	Crus I or VIIaf (8 patients)	VIIIa (6 patients)
Test of visuo-motor-integration (VMI)	0.033			

The only significant finding was that patients with damage to lobule V have problems with the VMI. This test actually has a significant motor component (participants are required to copy a series of increasingly complex geometric figures) and it is therefore possible that patients with damage to lobule V have particular problems with the motor, rather than the cognitive, components of this test, in line with the findings above that these patients have difficulties with a number of motor functions.

These results do not support the claims that the posterior lobe is particularly involved in non-motor function (Schmahmann, 2000) as, if this were the case, it would be expected that there would be numerous problems with non-motor functions after damage to lobules located in the posterior lobe of the cerebellum. However, there are possible explanations for why such problems were not observed in these analyses. Firstly it could be because the cognitive tests administered did not directly tap into the functions in which the lobules of the posterior lobe of the cerebellum are particularly involved. Secondly, it is possible that regions in the posterior lobe work together to carry out non-motor functions and therefore that damage to an individual lobule is not sufficient to cause that function to be severely impaired, as it can still be supported by other intact lobules. Thirdly, it is possible that some of the lobules that could not be included in this analysis (for example Crus II) are particularly involved in cognitive functions, rather than the lobules that were included here. Finally, it is possible that there has been some reorganization of function after the acquired cerebellar pathology resulting in different lobules having slightly different functions in different individuals depending on the precise location, timing and extent of cerebellar damage.

5.4.2 Investigating cerebellum-wide functions

The total number of lobules that were damaged in each patient with PFT is shown in table 5.3 below (lobules with any amount of damage were included as it was decided that even the lobules that only had a small amount missing or damaged would not be able to function normally).

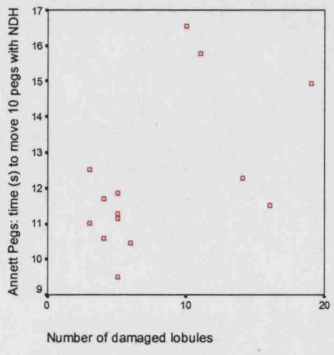
Table 5.3: Number of lobules damaged in each of the patients with PFT

Patient ID	Number of cerebellar lobules damaged
PFT 1	4
PFT 2	16
PFT 3	4
PFT 4	5
PFT 5	3
PFT 6	11
PFT 7	N/A
PFT 8	6
PFT 9	10
PFT 10	3
PFT 11	14
PFT 12	5
PFT 13	5
PFT 14	5
PFT 15	19

Correlation analyses were carried out between these scores for the number of damaged lobules and the scores for each of the motor and cognitive tests. The results showed that there were significant correlations between the number of damaged lobules and performance on the following motor and cognitive tests:

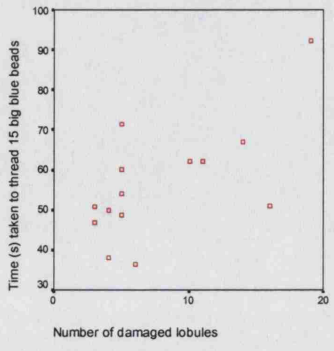
MOTOR TESTS

a) Annett Pegboard non-dominant hand



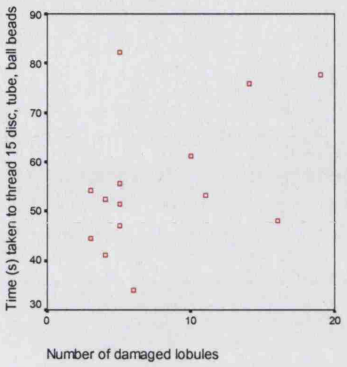
Pearson correlation = 0.535, p = 0.049board

b) Big blue beads



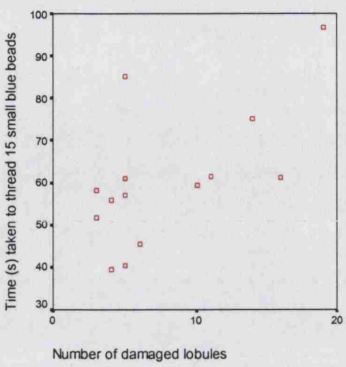
Pearson correlation = 0.646, p = 0.013

c) Disc, tube, ball beads



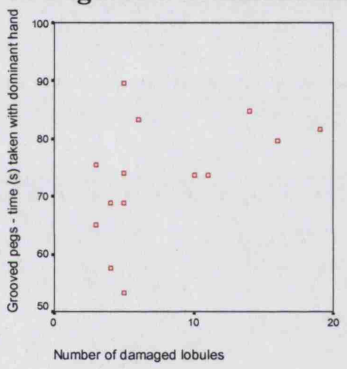
Pearson correlation = 0.459, p = 0.099

d) Small blue beads



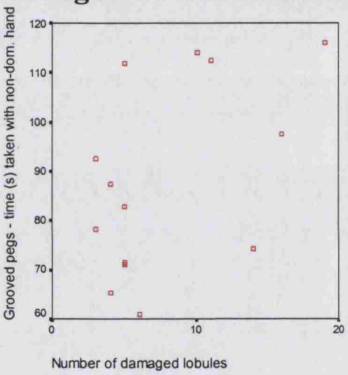
Pearson correlation = 0.622, p = 0.018

e) Grooved Pegboard dominant hand



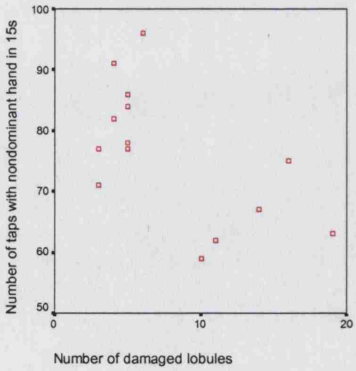
Pearson correlation = 0.467, p = 0.093

f) Grooved Pegboard non-dominant hand



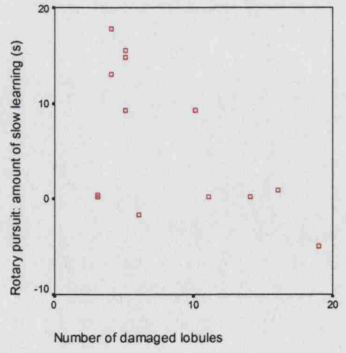
Pearson correlation = 0.492, p = 0.074

g) Non-dominant hand simple tapping



Pearson correlation = -0.595, p = 0.025

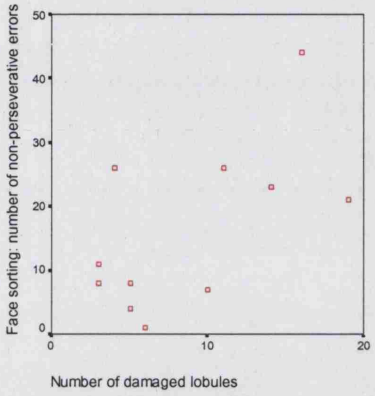
h) Rotary pursuit slow learning



Pearson correlation = -0.550, p = 0.051

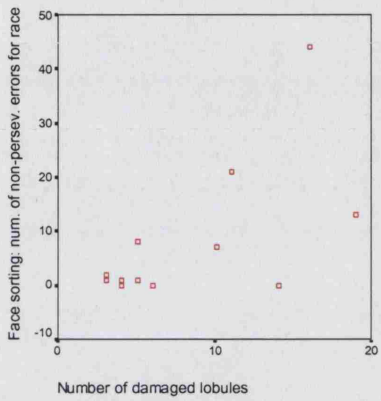
COGNITIVE TESTS

i) Face sorting non-perseverative errors



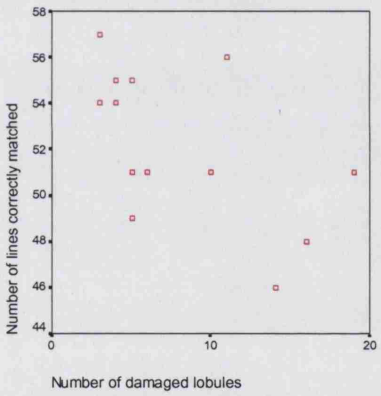
Pearson correlation = 0.543, p = 0.055

j) Face sorting non-perseverative errors (race)



Pearson correlation = 0.633, p = 0.020

k) Benton test of line judgment



Pearson correlation = -0.533, p = 0.050

The results show that for all of these tests, the greater number of cerebellar lobules that are damaged in an individual, the more poorly they perform. For the timed tests (the Annett pegboard, the Grooved Pegboard and the bead threading tasks), there were positive correlations, as patients showed a tendency to be slower to complete the tasks the more cerebellar lobules that were damaged. For the tests on which a high score indicated good performance, (for example the simple tapping task) there were negative correlations, as patients showed a tendency to gain a lower score, the more cerebellar lobules that were damaged. These findings provide preliminary evidence to suggest that the cerebellum may carry out at least some of its functions as a coordinated whole, so that it is not as important

exactly which lobules are damaged, but what is more important is the number of lobules or the actual extent of the damage to the cerebellum as a whole. This supports Lashley's theory of mass action, as there does appear to be an association between the amount of brain damage and the level of performance on a given test.

However, the fact that there were some differences in the performance of patients depending on which individual cerebellar lobules were damaged (see Section 5.4.1) indicates that there may be a certain degree of functional localisation within the cerebellum. It may be the case that certain regions of the cerebellum are specialized for particular functions (such as the anterior lobe being involved in motor actions) but that these regions do not function in isolation, but rather depend on other areas of the cerebellum processing information at the same time.

5.5 Summary

MRI scans (T1 and T2-weighted) were obtained for fourteen out of the fifteen patients with PFT who participated in this study. Out of these fourteen patients, five had pathology affecting the left hemisphere, five had pathology affecting the right hemisphere and four had pathology predominantly affecting the midline. By means of visual inspection of the MRI scans, the particular lobules that were damaged in each individual patient were identified and these were then plotted on flattened maps of the cerebellar cortex. In this way it was possible to show the extent and localisation of the pathology in each patient and also in the tumour location subgroups and the group with PFT as a whole.

Once the particular cerebellar lobules that were damaged in each patient with PFT had been identified, the extent of functional localisation in the cerebellum was investigated. This involved firstly comparing the performance of patients with PFT who have pathology of a particular cerebellar lobule with patients with PFT who do not have pathology of that lobule, and secondly, carrying out correlation analyses between the number of lobules damaged in patients with PFT and the scores obtained on each of the motor and cognitive tests reported in Chapters 3 and 4. The results showed that there were some differences in the performance of patients depending on which individual cerebellar lobules were

damaged and also that there was an association between the number of cerebellar lobules and performance on a number of motor and cognitive tasks. These findings indicate that there may be some localized specialization of function in the cerebellum, but that individual cerebellar lobules may not function in isolation; rather, these may be sub-components of a highly organized structure which operates as a coordinated whole. Further studies are needed with a larger number of patients in order to compare the performance of patients with damage to different regions of the cerebellum.

CHAPTER 6: MR INVESTIGATIONS

In the previous chapter, regions of brain abnormality that could be seen from visual inspection of MR images were reported for the patients with PFT. However, it is likely that there are also some more subtle abnormalities in the brains of the patients with PFT that would not be seen by visual inspection of MRI scans. In addition, subtle differences are likely to be found in the brains of the patients with AS who do not have any obvious regions of pathology that can be seen using conventional inspection of MRI scans. Autism and AS are neurodevelopmental disorders and are known to involve changes in the brain that stem from abnormalities in the network of connections at the very start of development. In order to uncover these subtle abnormalities, more sophisticated methods are required.

In this chapter, the results of voxel-based morphometric analyses of grey and white matter densities over the whole brain are reported. Voxel-based morphometry (VBM) is a computational method whereby statistical comparisons are carried out on individual voxels throughout the whole brain to identify any differences in grey and white matter densities between different groups of individuals. Using this method it might be possible to determine to what extent any abnormalities in the brains of patients with PFT are limited to the cerebellum alone, and to determine the pattern of abnormalities in different brain areas that is present in the patients with AS.

Previous neuroimaging studies of patients with PFT and patients with AS were described in Chapter 1. For patients with autism and AS, several studies have been carried out in an attempt to identify which regions of the brain show abnormalities that underlie the disorder. These studies have found that patients with autism and AS have abnormalities in the cerebellum, the medial temporal lobes (amygdala and hippocampus) and the frontal lobes (Zilbovicius et al., 1995; Piven et al. 1997; Aylward et al., 1999; Abell et al., 1999; Carper and Courchesne, 2000; Courchesne et al., 2001). For patients with PFT, however, there have been very few studies that have investigated additional brain abnormalities outside the cerebellum. Instead, those studies that have been carried out have tended to focus on the functions of the cerebellum and whether there is localisation of function in the cerebellar

hemispheres and the vermis. In this section of the thesis, investigations using voxel-based morphometric analysis methods will be reported with the aim of identifying the whole brain abnormalities that are present in either of the patient groups.

For the patients with PFT it is clear that the primary region of pathology is the cerebellum; however it is likely that this pathology has had knock-on effects on areas with which the cerebellum is intimately connected. These effects may not be visible on conventional MR images and it is therefore important to carry out investigations at a voxel level to examine any subtle differences in grey and white matter density that may be present in the patients with PFT compared to controls.

Similarly, for the patients with AS, it is not possible to identify any obvious regions of brain abnormality by simply looking at conventional MR images. Using voxel-based morphometry, it may be possible to determine whether the cerebellum is abnormal in these patients and furthermore, to determine whether there are any abnormalities in other regions of the brain that may be part of the complex network of connections of the cerebellum.

Once the particular abnormalities in the brains of both patients with PFT and patients with AS have been identified, correlation analyses can then be performed to investigate whether, within either of the patient groups, any of these brain abnormalities can be related to the motor or cognitive impairments reported in chapters 3 and 4.

The chapter begins with a description of the morphometric methods used to look at subtle differences in grey and white matter densities between the patient groups and their controls. The aims and predictions of the MR imaging investigations are then outlined for each of the two patient groups. In the results section which follows, differences in grey matter density are first reported, followed by any differences in white matter density revealed either through conventional MR imaging, or through the new method of diffusion tensor imaging (DTI) which is used to look at the integrity of white matter tracts in particular. In the final sections of this chapter, correlation analyses are carried out between the results of the VBM studies and the performance of the patients with PFT and the patients with AS on the motor

and cognitive tasks on which they performed particularly poorly (see Chapters 3 and 4). In this way it is anticipated that it will be possible to determine whether there are any particular brain abnormalities that may be related to any of the motor or cognitive problems encountered by either of the two patient groups.

6.1 Introduction to voxel based morphometry (VBM)

VBM is an automated computational approach to neuroanatomical investigations. This method enables the identification of subtle structural abnormalities in local amounts of brain tissue that may not be detectable through conventional neuroradiological examination. VBM is not biased to particular structures, but carries out statistical comparisons (t-tests) between grey (or white) matter density on individual voxels throughout the whole brain using statistical parametric mapping (SPM) techniques (Ashburner and Friston, 2000). In this way, it is possible to produce an objective measurement of grey and white matter differences between groups of individuals.

In the current study, VBM methods were used on both high resolution T1-weighted 3-D images, and on diffusion tensor images (see Section 6.3.3.3). Before MR images can be analysed using VBM, it is necessary for the data-sets to undergo a series of processing stages which are outlined below. These processing stages were carried out using SPM software (SPM99 and SPM2, developed by the Wellcome Department of Imaging Neuroscience).

Stage 1: Spatial normalization

In the first stage, the images are normalized into the same stereotactic space using a standard T1 template (this involves matching the images by estimating the optimal affine transformation and then correcting gross differences in non-linear shape using nonlinear transformation methods).

Stage 2: Segmentation

In the second stage, the normalised images are segmented into grey matter, white matter and cerebrospinal fluid (CSF) to produce three probability maps which indicate the

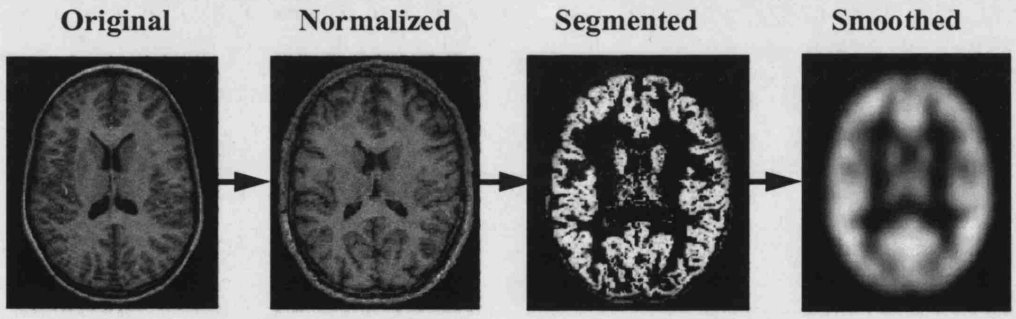
probability that each individual voxel is grey matter, white matter or CSF. The algorithm used to carry out the segmentation stage uses both the voxel intensities from the images and prior probabilities which are derived from data from the Montreal Neurological Institute.

Stage 3: Smoothing

In the third stage, the segmented images are smoothed using an isotropic Gaussian kernel. The smoothing process involves averaging each individual voxel with its neighbours (in essence filtering out high frequencies) in order to remove noise and to ensure that the data have a normal distribution (which increases the validity of subsequent statistical analyses). The smoothing can be sensitized to a particular brain structure by choosing a Gaussian kernel which has a similar size to this structure.

A diagram of images in each of these processing stages is shown below:

Figure 6.1: Image processing stages of VBM



In the final stage, the smoothed images are analysed statistically on a voxel-wise basis to produce statistical parametric maps that demonstrate those regions of the brain where there are statistically significant differences between the groups under investigation (for more information on each of the processing stages, see Ashburner and Friston, 2000).

The resulting statistical parametric maps are based on voxel-by-voxel comparisons and thus depend on large numbers of statistical tests. For this reason, it is necessary to correct for multiple comparisons in order to minimize the chance of obtaining false positive results (Ashburner and Friston, 2000). Throughout this chapter, correction for multiple comparisons across the whole brain is applied using the False Discovery Rate (FDR) correction.

6.1.1 The bilateral method

In addition to the method of VBM analysis described above (the "unilateral method"), a new bilateral method of analysis has recently been developed. The bilateral method identifies homologous regions of abnormality that are present in both hemispheres of the brain. This method offers increased sensitivity for the detection of symmetrical bilateral abnormalities. It involves flipping the data so that the two hemispheres occupy the same stereotactic space and can thus be analysed using a conjunction analysis. Two statistical parametric maps are produced, one which compares the standard images of each group and the other which compares the flipped images. In this way, it is possible to identify regions of significant differences between groups that are common to both statistical parametric maps (Salmond et al. 2000).

6.1.2 White matter abnormalities

Although the methods described above have tended to focus on grey matter abnormalities, these methods can also be used to examine abnormalities in white matter. Investigations of the integrity of white matter tracts are particularly important in studies of patients with brain damage as this can increase understanding of the re-organization of neuronal connectivity after pathology. There are two ways in which to investigate abnormalities in white matter tracts: by analysing the probability maps for the white matter produced in the segmentation stage described above, or by using the new imaging technique of diffusion tensor imaging which is described below.

6.1.3 Diffusion tensor imaging (DTI)

DTI is based on the random (Brownian) motion of water molecules and provides a means by which to investigate the integrity of white matter tracts within the brain. Whereas in free solution the diffusion of water molecules is isotropic (equal in all directions), in the white matter of the brain it is anisotropic: there is more diffusion along the unobstructed length of fibres than across the breadth of these tracts (Le Bihan et al. 2001). MRI methods can detect the amount of diffusion that is taking place in different directions and use this information to produce fractional (directional) anisotropy maps. These fractional anisotropy maps are then compared between groups and any differences found may be interpreted as differences in the integrity of white matter tracts. Within the brain, the

greatest levels of fractional anisotropy are found in white matter tracts which contain numerous parallel fibres, such as the corpus callosum (Shimony et al. 1999).

6.2 Aims and predictions

(i) Patients with PFT

Although predictions will be made as to areas that might be found to be abnormal in patients with PFT, because there are so many areas that could be associated with cerebellar damage, only the peaks for the areas that are significant or approach significance when corrected for multiple comparisons will be reported in this thesis. The unilateral method of voxel-based morphometry will be used for the analysis of the MRI scans of the patients with PFT and their controls.

a) Grey matter

- Because pathology of the cerebellum will affect not only the particular lobules that are removed during surgery, but also the neurons that originate in those lobules and thus the projections of the cerebellum to other areas of the brain, it is predicted that there will be a decrease in grey matter density in regions to which the cerebellum projects (the thalamus, the red nucleus, the inferior olive, the vestibular nucleus and the hypothalamus). This is in line with a study by Tecco et al. (1998) who found abnormalities in the thalamus after damage to the cerebellum.
- It is predicted that the decrease in grey matter in regions to which the cerebellum projects will be related to the particular region of the cerebellum that is damaged.
  - (i) Patients with pathology of the cerebellar hemispheres are predicted to have a decrease in grey matter density in the regions to which the intermediate (emboliform and globose) and dentate nuclei project as these are the nuclei that receive input from hemispheric lobules of the cerebellum. The particular regions predicted to be affected by pathology of the cerebellar hemispheres are the red nucleus, the ventrolateral nucleus of the thalamus, the pons and the inferior olive.
  - (ii) Patients with pathology of midline cerebellum (the vermis) are predicted to have a decrease in grey matter density in the regions to which the middle (fastigial) cerebellar nuclei project as these nuclei receive input from midline

lobules of the cerebellum. The particular regions predicted to be affected by pathology of the vermis are the lateral vestibular nucleus, the inferior olive and the ventrolateral nucleus of the thalamus.

- It is predicted that there will be no regions of increased grey matter density in individuals with PFT. Although it is possible that after damage to the cerebellum, other areas of the brain will take-over some of the functions normally subserved by the cerebellum (likely to be demonstrated by an increase in grey matter density in those regions), the fact that patients with PFT were found to have difficulties with a number of tests of motor and cognitive function indicates that such changes are unlikely to have been significant enough for successful recovery of function. It is therefore predicted that no significant regions of increased grey matter density will be found in patients with PFT compared to controls.

b) White matter

- It is predicted that there will be white matter tract abnormalities throughout the brain systems in which the cerebellum is involved, reflecting changes in the connections of the cerebellum after pathology. Only the areas that are significantly different or approach significance when corrected for multiple comparisons will be reported.

(ii) Patients with AS

As was the case for patients with PFT, because there are likely to be a number of different brain regions that are abnormal in the patients with AS, only the peaks for the areas that are significant or approach significance when corrected for multiple comparisons will be reported in this thesis. Furthermore, because the abnormalities in the patients with AS are likely to be very subtle, the bilateral method of voxel-based morphometry will be used for the analysis of the MRI scans of the patients with AS and their controls. It is important to note that in bilateral analyses, effects that span the midline must be discounted as these are not representative of a conjunction analysis (Salmond et al. 2000).

a) Grey matter

- Previous studies have found a number of different regions of increased grey matter density in individuals with AS. A study by Salmond et al. (2003), in which eleven of the fourteen patients with AS who participated in the current study also

participated, found increases in grey matter density in the cerebellum (lobules VIIIA and VIIIB), the fusiform gyrus, the dorsolateral prefrontal cortex, the peri-hippocampal cortex, the lateral occipitotemporal sulcus and the anterior hippocampal formation. In addition, a study by Abell et al. (1999) found increases in grey matter density in the amygdala, middle temporal gyrus, inferior temporal gyrus and the cerebellum. On the basis of these findings, it is predicted that increases in grey matter density in patients with AS compared to controls will be found in a number of different brain regions including the cerebellum, the amygdala, the fusiform gyrus, hippocampal regions and the inferior temporal gyrus.

- For regions of decreased grey matter density in patients with AS, studies have found decreases in grey matter density in the right paracingulate sulcus and in the left inferior frontal gyrus (Abell et al. 1999); in the medial frontal lobe and cingulate, the basal ganglia, thalamus and ventral striatum and in the cerebellum (McAlonan et al., 2002). On the basis of these previous studies, it is predicted that decreases in grey matter density in patients with AS may be found in the cerebellum, the basal ganglia, the cingulate, frontal and orbitofrontal regions, the inferior frontal gyrus and the superior temporal gyrus. Again, given the large number of areas that could be abnormal in patients with AS, only the peaks that are significant when corrected for multiple comparisons will be reported here.

b) White matter

- Very few studies have investigated white matter abnormalities in patients with AS; however a study by McAlonan et al. (2002) found decreases in white matter density in the left cerebellum and pons and in left fronto-temporal regions, possibly within the inferior and superior longitudinal fasciculi and the occipitofrontal fasciculus fibre tracts. Increases in white matter density, on the other hand, were found bilaterally in the region including the basal ganglia and the external capsule. On the basis of McAlonan et al.'s study, it is predicted that there may be decreases in white matter density in the pons, cerebellum and fronto-temporal regions of the patients with AS who participated in the current study, and increases in white matter density in the basal ganglia and external capsule. In addition, it is anticipated that using diffusion tensor imaging (DTI) methods it will be possible to determine whether it is

the longitudinal fasciculi and the occipitofrontal fasciculus fibre tracts in particular that have a decrease in white matter density in patients with AS.

6.3 Methods

6.3.1 Participants

MRI scans of the brain were obtained for all of the participants described in Chapter 2 with the exception of four subjects: two patients with AS (patient AS1 and patient AS9) were scanned but because of orthodontic braces these scans were not useable and had to be discarded, one of the AS control subjects could not be scanned because of problems with the scanner during his visit, and one patient with PFT (patient PFT7) was not scanned because she still had a brain reservoir (Rickham's Reservoir) in situ and it was unclear whether or not this was MR compatible. Thus altogether 45 MRI scans were included in the analyses (14 patients with PFT, 10 PFT controls, 12 patients with AS, 9 AS controls).

6.3.2 Data Acquisition

MRI data were acquired for all participants on a 1.5 Tesla Siemens Vision system. A T1 weighted 3D-FLASH sequence was carried out with the following parameters: TR = 16.8ms, TE = 5.7ms, flip angle = 12°, matrix size = 256 x 256, field of view = 200mm, partition thickness = 1mm, 160 sagittal partitions, voxel size = 0.78mm x 0.78mm x 1.00mm, acquisition time = 8.6 minutes.

T2 weighted Turbo Spin Echo (TSE) sequences were acquired in the coronal and in the axial planes with the following parameters: TR = 3458ms, TE = 96ms, matrix size = 196 x 512, field of view = 210mm, partition thickness = 5mm.

In the case of the patients with PFT, these T1 and T2-weighted scans are the same ones that were reported on in Chapter 5.

DTI data were acquired using a twice-refocused diffusion-weighted spin echo-planar (EPI) sequence with the following parameters: TE = 110ms, matrix size = 128 x 128, zero-filled to 256 x 256, pixel size = 1.5 x 1.5mm after zero-filling, slice thickness = 3mm. Forty

contiguous slices that covered the whole brain were acquired. In addition, 3 images with no diffusion weighting were collected at the start, middle and end of the diffusion-weighted scan acquisition and diffusion-encoding gradients (b = 1000s/mm^2) were applied in twenty directions that were non-collinear.

6.3.3 Image processing

6.3.3.1 T1-weighted MR scans

The T1-weighted 3d-FLASH images were analysed using SPM software (Wellcome Department of Imaging Neuroscience). As outlined in Section 6.1 above, the images were first normalized into the same stereotactic space, they were then segmented into grey matter, white matter and CSF and finally they were smoothed using an isotropic Gaussian kernel. The smoothing value of 12mm was chosen for both the patients with PFT and the patients with AS. For the patients with PFT, there were few a priori hypotheses and 12mm was chosen in order to minimize the possibility of false positive results. For the patients with AS, the brain area of particular interest in these investigations was the cerebellum and given that this is a large structure, 12mm was deemed to be an appropriate level of smoothing.

Statistical analysis was then carried out on the smoothed images using SPM2. A number of different pair-wise comparisons were carried out using the following contrasts:

(i) Patients with PFT

a) Patients with PFT (n = 14) versus PFT controls (n = 10)

b) Left hemisphere patients with PFT (n = 5) versus PFT controls (n = 10)

c) Midline patients with PFT (n = 4) versus PFT controls (n = 10)

d) Right hemisphere patients with PFT (n = 5) versus PFT controls (n = 10)

(ii) Patients with AS

a) Patients with AS (n = 12) versus AS controls (n = 9)

For the patients with PFT, unilateral analyses were carried out in SPM2. For each pair-

wise comparison, an interaction analysis was carried out with the contrasts entered as 1 –1 (increased grey or white matter in the PFT group of interest or in an individual PFT patient for contrast e) and –1 1 (decreased grey or white matter in the PFT group of interest or in an individual PFT patient for contrast e).

For the patients with AS, bilateral analyses were carried out in SPM99 as it was hypothesized that any abnormalities would be more subtle and might only show up using this bilateral method (which could not yet be carried out in the available version of SPM2). Furthermore, neurodevelopmental abnormalities of congenital origin are more likely to be bilateral, because a unilateral abnormality can generally be compensated for by its homologue in the other hemisphere. For each pair-wise comparison, a conjunction analysis was carried out on the four groups (patients with AS unflipped, patients with AS flipped, AS controls unflipped, AS controls flipped) with the contrasts entered as 1 –1 0 0 and 0 0 1 –1 (increased grey or white matter in the patients with AS) and –1 1 0 0 and 0 0 –1 1 (decreased grey or white matter in the patients with AS).

The peaks from the results from both the unilateral and bilateral analyses are reported at a significance level of $p < 0.05$ (strong evidence) and $p < 0.10$ (weak evidence) after FDR (false discovery rate) correction for multiple comparisons over the whole brain.

6.3.3.2 Correlations with performance on neuropsychological tests

Correlation analyses were carried out for each group separately in order to investigate whether there were any associations between regions of grey matter abnormality and performance on the motor and cognitive tests on which each of the patient groups had significant difficulties.

(i) Correlation analyses for patients with PFT

For the patients with PFT, unilateral analyses were carried out in SPM2. For each correlation, an interaction analysis was carried out with the contrasts entered as 1 0 (positive correlation between grey matter density and score on the neuropsychological test) and –1 0 (negative correlation between grey matter density and score on the neuropsychological test).

(ii) Correlation analyses for patients with AS

For the patients with AS, bilateral analyses were carried out in SPM99 in order to show up the more subtle abnormalities that may be present in this patient group. For each correlation, a conjunction analysis was carried out on the four data sets (grey matter density in patients with AS unflipped, score on the neuropsychological test, grey matter density in patients with AS flipped, score on the neuropsychological test) with the contrasts entered as 1 0 0 0 and 0 1 0 0 (positive correlation between bilateral grey matter density and score on the neuropsychological test) and -1 0 0 0 and 0 -1 0 0 (negative correlation between bilateral grey matter density and score on the neuropsychological test).

6.3.3.3 DTI scans

The DTI scans for the following eight participants had to be discarded because of problems caused by gross motion artifacts, CSF pulsation or spiking: three patients with PFT (patients PFT 13, PFT 15 and PFT 3), two patients with AS (patients AS 19 and AS 18), one PFT control and two AS controls.

Pre-processing

Before carrying out any analysis on the DTI scans, a number of pre-processing steps were completed in order to check the integrity of the scans. The first step was to assemble the base images. These were then checked manually, one slice at a time to look for any movement artifacts, CSF pulsation or spiking. Bad slices showing any of these artifacts were discarded and if more than five (out of twenty) base images were discarded for any one slice, then the whole of that patient's data-set was rejected. The next step was to assemble eigenvector maps to check that there was no directionality bias in grey matter (which can result if too many slices are rejected in a similar direction). Finally, fractional anisotropy (FA) maps were assembled and these were then analysed in order to look at differences in diffusion between the different participant groups.

Data analysis

For both the patients with PFT and the patients with AS, the FA maps were analysed using SPM2. The methods were broadly the same as those described above for T1-weighted

images, except for the normalisation and segmentation stages. For normalisation, the base images without diffusion weighting (b=0) were first normalised to an echo-planar image (EPI) template (MNI). The parameters produced in this stage were then used to normalise the FA maps. Because in FA maps the main contributor to image intensity is the white matter, there was no need to segment the images. Instead, following normalisation, the images were smoothed as described above using a 12mm Gaussian smoothing kernel. The same contrasts that were employed for the T1-weighted images were also employed for the DTI images:

(i) Patients with PFT

- PFT patients (n = 11) versus PFT controls (n = 8)
- Left hemisphere PFT patients (n = 4) versus PFT controls (n = 8)
- Midline PFT patients (n = 4) versus PFT controls (n = 8)
- Right hemisphere PFT patients (n = 3) versus PFT controls (n = 8)

(ii) Patients with AS

- AS patients (n = 10) versus AS controls (n = 7)

6.4 Results

6.4.1 Patients with PFT voxel-based morphometry: 3d-FLASH data sets

6.4.1.1 Comparison between the patient group with PFT (n=14) and their control group (n=10)

(i) Grey matter

There was one region of decreased grey matter density in the wall of the 4th ventricle in the patient group with PFT compared to their controls that reached corrected significance (see table 6.1 below). It is likely that the finding of decreased grey matter density in the wall of the 4th ventricle is due to the presence of scar tissue or oedematous white matter (which may have a similar appearance to grey matter on T1-weighted images) in this area that is associated with the surgical approach. There were no regions of increased grey matter density.

Table 6.1: Decreased grey matter density in patients with PFT compared to controls

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Wall of 4th ventricle	-3, -46, -34	4.96	0.026	12mm	6.2

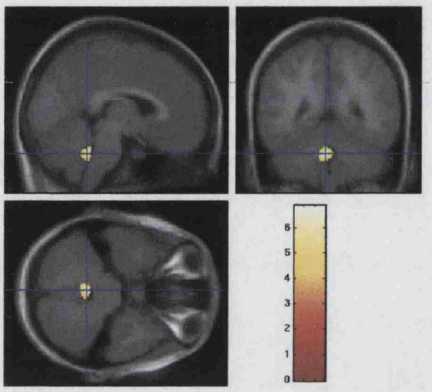


Figure 6.2: Decreased grey matter density in the wall of the 4th ventricle: -3, -46, -34

(i) White matter

There were no regions of increased or decreased white matter density in the patient group with PFT compared to their control group that reached corrected significance.

These results show that the only consistent abnormality in grey or white matter density in the patients with PFT compared to the control group was a decrease in grey matter density in the wall of the 4th ventricle.

6.4.1.2 Comparison between patients with left hemisphere damage (n=5) and the control group (n=10)

There were no regions of increased or decreased grey or white matter density in patients with left hemisphere damage compared to controls that reached corrected significance.

6.4.1.3 Comparison between patients with midline damage (n=5) and the control group (n=10)

a) Grey matter in patients with midline pathology

There were a number of regions of decreased grey matter in patients with midline damage compared to controls that reached corrected significance. These were located in lobules V, VI, VIII and Crus II of the cerebellum and are shown in table 6.2 below and in Figures 6.3-

6.7. In addition, in order to further investigate the precise nature of subtle abnormalities in grey matter density in patients with PFT, analyses were also carried out for a subgroup made up of any patient with damage to the vermis (midline). As was detailed in Section 2.3.1, throughout this thesis, patients were allocated to the midline pathology subgroup only if they had pathology that was limited to the vermis. If they had any pathology of either of the cerebellar hemispheres, then they were allocated to the relevant hemisphere pathology subgroup. By looking at patients with any damage to the vermis (the midline plus group, n=7) as well as the original midline pathology subgroup who had damage to the midline only (the midline only group, n=4), it might be possible to gain an idea of the extent to which any regions of abnormality are associated with damage to the vermis per se or with damage to regions in the cerebellar hemispheres. VBM analysis for the midline plus subgroup showed that there was a decrease in grey matter density in lobule VIII of the cerebellar vermis and in Crus II of the right cerebellar hemisphere (as was the case for the midline only subgroup), and there were additional regions of abnormality in the thalamus and the hypothalamus in the midline plus group. These regions are shown in Table 6.2 and in Figures 6.8-6.11. There were no regions of increased grey matter density in either the midline only or the midline plus pathology subgroups that reached corrected significance.

Table 6.2: Decreased grey matter density in patients with midline only and midline plus cerebellar pathology compared to controls

PFT group	Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Midline only pathology (n = 4)	Cerebellar vermis lobule VIII	0, -57, -33	5.83	0.000	12mm	6.3
	Right cerebellar hemisphere Crus II	44, -48, -46	3.80	0.020	12mm	6.4
	Left cerebellar hemisphere Lobule VI	-30, -72, -27	3.77	0.022	12mm	6.5
	Left cerebellar hemisphere Lobule VI	-46, -57, -22	3.62	0.030	12mm	6.6
	Left cerebellar hemisphere Lobule V	-16, -50, -18	3.43	0.047	12mm	6.7
Midline plus (n = 7)	Cerebellar vermis lobule VIII	2, -51, -33	5.46	0.001	12mm	6.8
	Right cerebellar hemisphere Crus II	46, -45, -46	4.05	0.008	12mm	6.9
	Thalamus	-3, -24, 9	3.95	0.010	12mm	6.10
	Hypothalamus	2, 3, -6	3.35	0.039	12mm	6.11

Decreased grey matter in patients with midline only pathology:

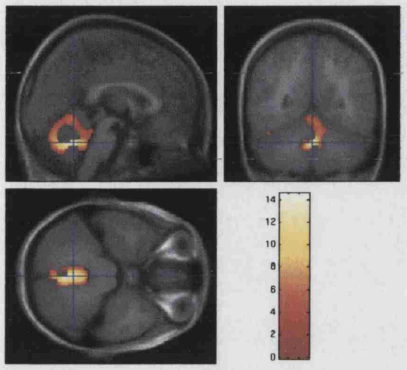


Figure 6.3: Decreased grey matter density in lobule VIII of the cerebellar vermis: 0, -57, -33

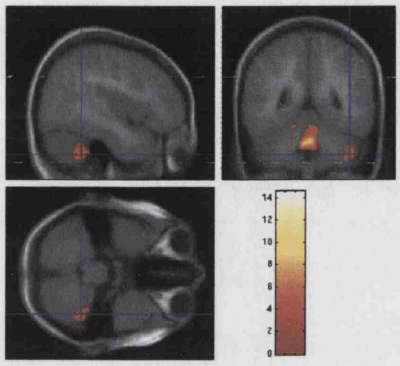


Figure 6.4: Decreased grey matter density in Crus II of the right cerebellar hemisphere: 44, -48, -46

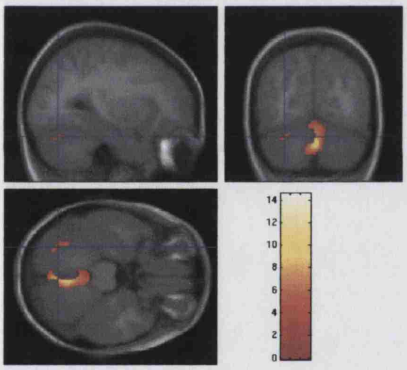


Figure 6.5: Decreased grey matter density in lobule VI of the left cerebellar hemisphere: -30, -72, -27

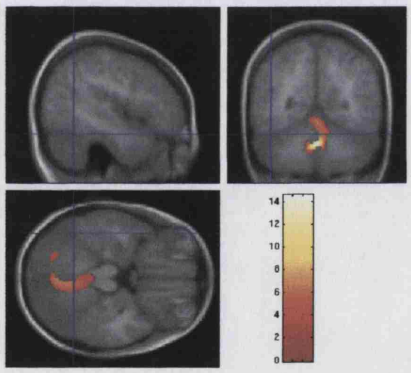


Figure 6.6: Decreased grey matter density in lateral regions of lobule VI of the left cerebellar hemisphere: -46, -57, -22

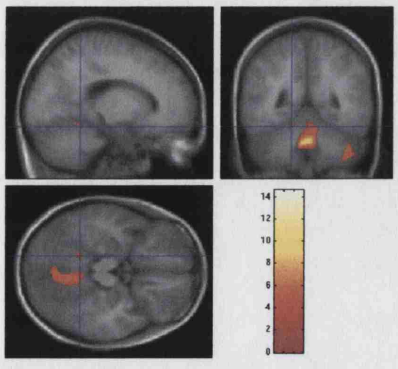


Figure 6.7: Decreased grey matter density in lobule V in the intermediate zone of the left cerebellar hemisphere: -16, -50, -18

Decreased grey matter in patients with midline plus pathology:

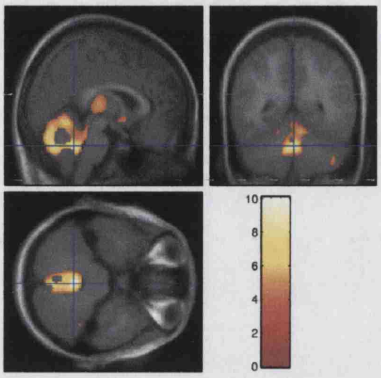


Figure 6.8: Decreased grey matter density in Lobule VIII of the cerebellar vermis: 2, -51, -33

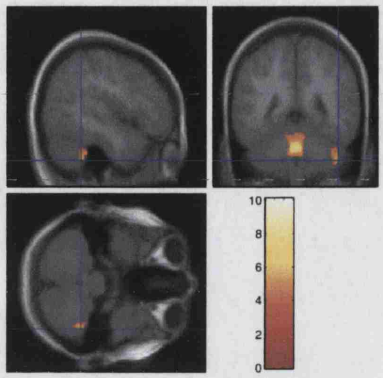


Figure 6.9: Decreased grey matter density in Crus II of the right cerebellar hemisphere: 46, -45, -46

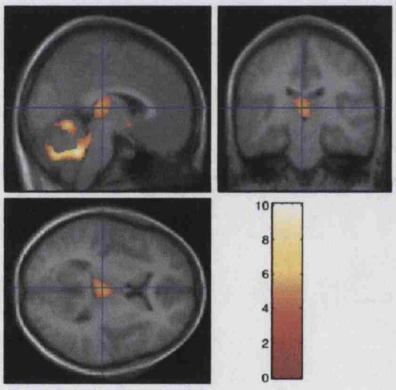


Figure 6.10: Decreased grey matter density in the thalamus: -3, -24, 9

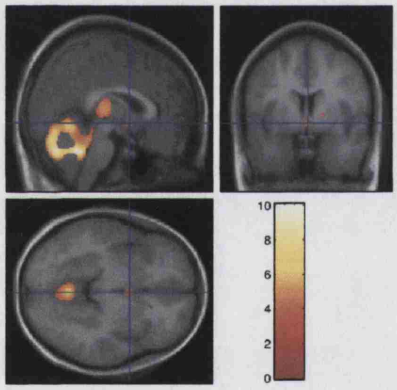


Figure 6.11: Decreased grey matter density in the hypothalamus: 2, 3, -6

b) White matter in patients with midline pathology

There were no regions of increased or decreased white matter density in patients with midline damage compared to controls that reached corrected significance.

6.4.1.4 Comparison between patients with right hemisphere damage (n=5) and the control group (n=10)

a) Grey matter in patients with right hemisphere pathology

There were a number of regions of decreased grey matter in patients with right hemisphere damage compared to controls that reached corrected significance. These were located in lobules VI, VIII, Crus I and Crus II of the cerebellum, the thalamus, hypothalamus and

globus pallidus and are shown in Table 6.3 below and in Figures 6.12-6.18. In addition, in order to further investigate the subtle abnormalities in grey matter density in patients with PFT, analyses were also carried out for a subgroup made up of patients with damage limited to the right cerebellar hemisphere. As was detailed in Chapter 2, throughout this thesis, patients were allocated to the right hemisphere pathology subgroup if they had any pathology of the right cerebellar hemisphere, irrespective of whether they also had damage to midline regions of the cerebellum. However, by looking at patients with damage limited to the right cerebellar hemisphere (the RH only group, n=3) as well as the original right hemisphere pathology subgroup (the right hemisphere plus group, n=5), it might be possible to gain an idea of the extent to which any regions of abnormality are associated with damage to the right hemisphere per se or with damage to regions in the midline cerebellum. VBM analysis for the RH only subgroup showed that there was a decrease in grey matter density in lobule VIII of the cerebellar vermis, in lobule VI of the right cerebellar hemisphere and in the thalamus. These regions are shown in Table 6.3 below and in Figures 6.19-6.21. There were no regions of increased grey matter density in either of the subgroups of patients with right hemisphere damage compared to the control group that reached corrected significance.

Table 6.3: Decreased grey matter density in patients with right hemisphere only and right hemisphere plus cerebellar pathology compared to controls

PFT group	Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Right hemisphere plus pathology (n = 5)	Thalamus	-9, -24, 16	5.53	0.001	12mm	6.12
	Cerebellar vermis lobule VIII	0, -45, -33	4.82	0.001	12mm	6.13
	Right cerebellar hemisphere Crus I/II	44, -44, -40	4.50	0.002	12mm	6.14
	Hypothalamus	0, 0, -9	3.36	0.034	12mm	6.15
	Left cerebellar hemisphere lobule VI	-33, -63, -30	3.31	0.038	12mm	6.16
	Right cerebellar hemisphere lobule VI	15, -58, -21	3.25	0.043	12mm	6.17
	Globus pallidus	20, 2, -14	3.24	0.044	12mm	6.18
Right hemisphere only (n = 3)	Right cerebellar hemisphere lobule VI	32, -66, -27	4.79	0.023	12mm	6.19
	Thalamus	-9, -24, 16	4.76	0.023	12mm	6.20
	Cerebellar vermis lobule VIII	0, -44, -32	4.42	0.023	12mm	6.21

Decreased grey matter in patients with right hemisphere plus pathology:

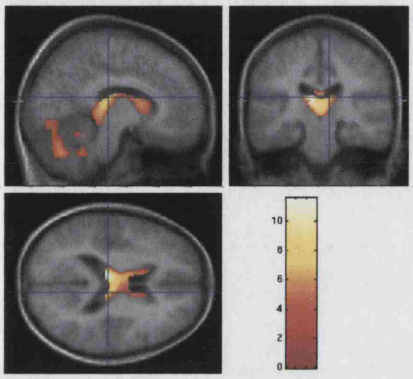


Figure 6.12: Decreased grey matter density in the thalamus: -9, -24, 16

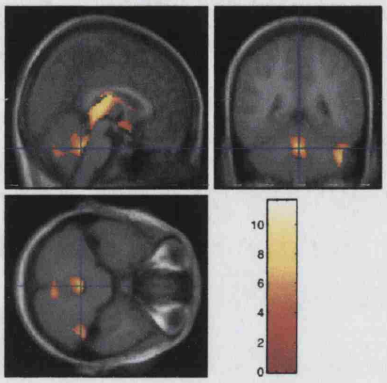


Figure 6.13: Decreased grey matter density in Lobule VIII of the cerebellar vermis: 0, -45, -33

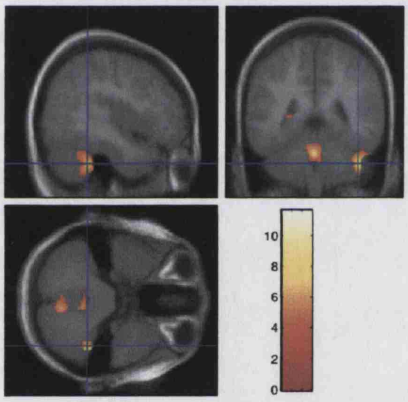


Figure 6.14: Decreased grey matter density in Crus I/II of the right cerebellar hemisphere: 44, -44, -40

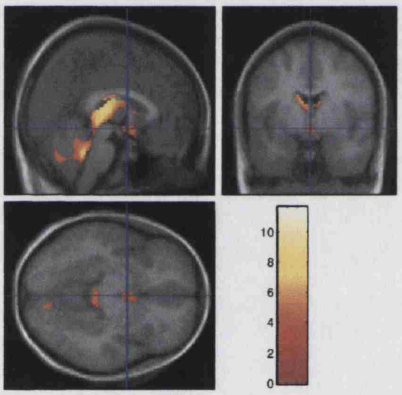


Figure 6.15: Decreased grey matter density in the hypothalamus: 0, 0, -9

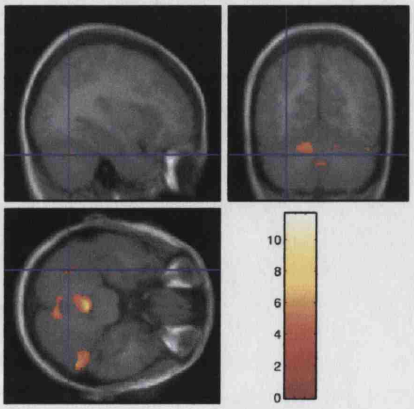


Figure 6.16: Decreased grey matter density in lobule VI of the left cerebellar hemisphere: -33, -63, -30

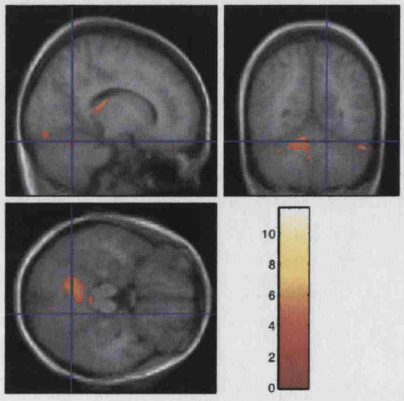


Figure 6.17: Decreased grey matter density in lobule VI of the right cerebellar hemisphere: 15, -58, -21

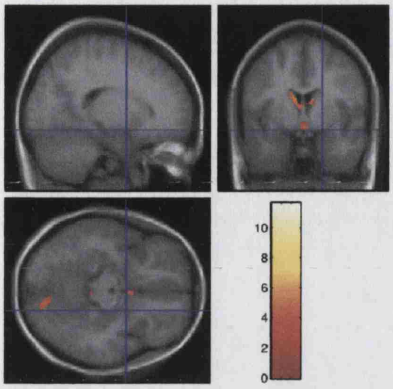


Figure 6.18: Decreased grey matter density in the globus pallidus: 20, 2, -14

Decreased grey matter in patients with right hemisphere only pathology:

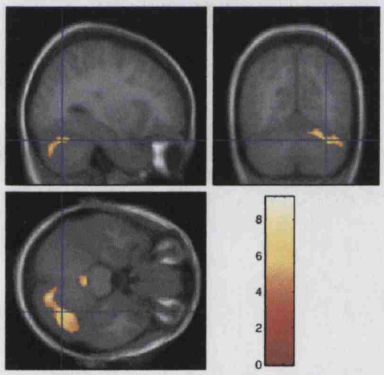


Figure 6.19: Decreased grey matter density in lobule VI of the right cerebellar hemisphere: 32, -66, -27

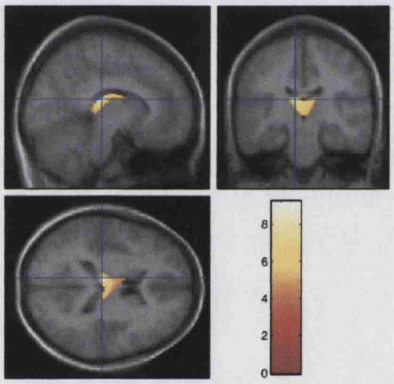


Figure 6.20: Decreased grey matter density in the thalamus: -9, -24, 16

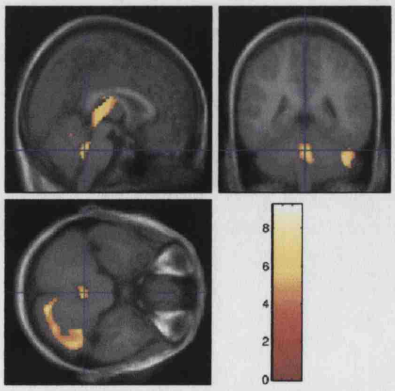


Figure 6.21: Decreased grey matter density in Lobule VIII of the cerebellar vermis: 0, -44, -32

b) White matter in patients with right hemisphere pathology

There were a number of regions of decreased white matter in the two subgroups of patients with right hemisphere damage compared to controls that reached corrected significance. These are shown in table 6.4 below and in Figures 6.22-6.36.

There were no regions of increased white matter density in either of the subgroups of patients with right hemisphere pathology compared to the controls.

Table 6.4: Regions of decreased white matter density in patients with right hemisphere pathology

PFT group	Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Right hemisphere plus pathology (n = 5)	Peri-trigonal white matter	-22, -36, 14	6.67	0.000	12mm	6.22
	Right subcortical inferior parietal white matter	60, -44, 28	4.11	0.001	12mm	6.23
	Left subcortical premotor white matter	-33, 14, 45	4.01	0.001	12mm	6.24
	Left subcortical parietal white matter	-24, -42, 48	3.54	0.003	12mm	6.25
	Right subcortical parietal white matter	9, -62, 54	3.40	0.005	12mm	6.26
	Right premotor frontal white matter	21, 0, 57	3.39	0.005	12mm	6.27
	Left occipital white matter	-28, -74, 2	3.98	0.009	12mm	6.28
	Right deep frontal white matter	24, 8, 30	3.92	0.010	12mm	6.29
	Inferior parietal white matter	-51, -48, 36	3.87	0.011	12mm	6.30
RH only (n =3)	Peri-trigonal white matter	26, -33, 20	5.90	0.000	12mm	6.31
	Left deep frontal white matter	-26, 16, 22	3.77	0.003	12mm	6.32
	Left inferior parietal white matter	48, -46, 33	3.65	0.004	12mm	6.33
	Left frontal subcortical white matter	-33, 14, 45	3.22	0.012	12mm	6.34
	Left occipital white matter	-32, -72, 0	3.20	0.013	12mm	6.35
	Left deep frontal white matter	-18, -9, 42	3.13	0.015	12mm	6.36

Decreased white matter in patients with right hemisphere plus pathology:

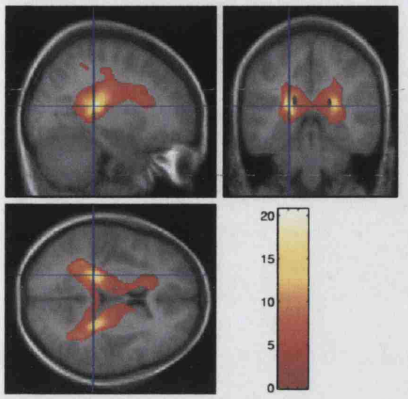


Figure 6.22: Decreased white matter density in peri-trigonal white matter: -22, -36, 14

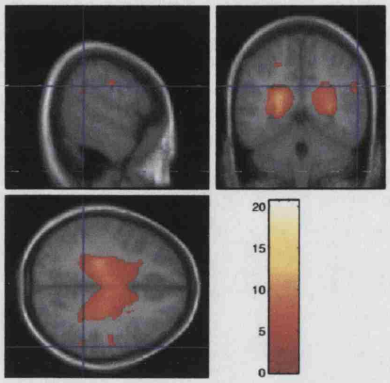


Figure 6.23: Decreased white matter density in right subcortical inferior parietal white matter: 60, -44, 28

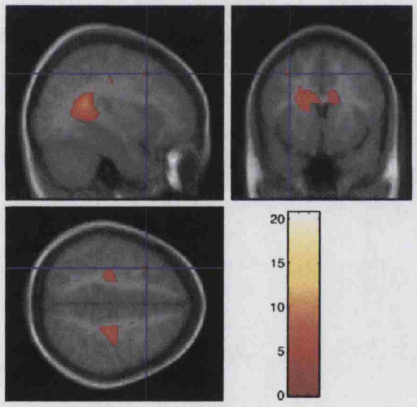


Figure 6.24: Decreased white matter density in left subcortical premotor white matter: -33, 14, 45

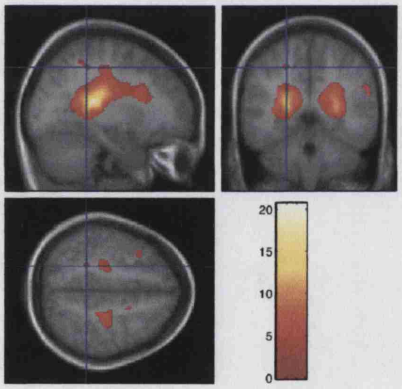


Figure 6.25: Decreased white matter density in left subcortical parietal white matter: -24, -42, 48

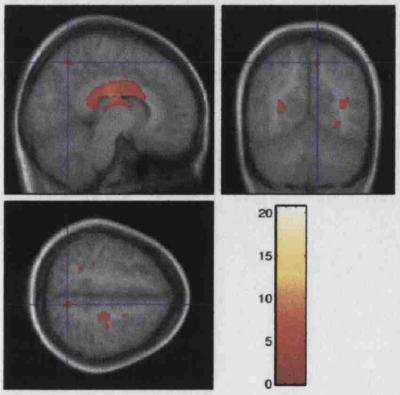


Figure 6.26: Decreased white matter density in right subcortical parietal white matter: 9, -62, 54

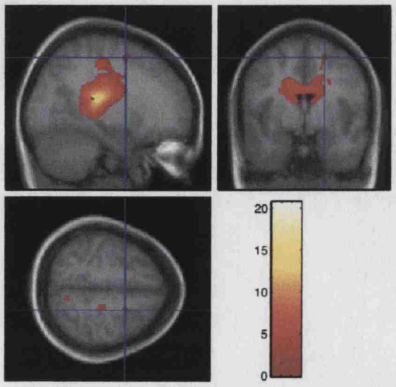


Figure 6.27: Decreased white matter density in right premotor frontal white matter: 21, 0, 57

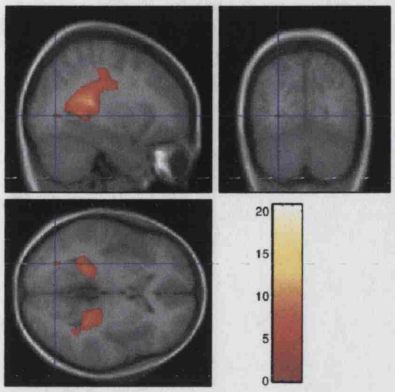


Figure 6.28: Decreased white matter density in left occipital white matter: -28, -74, 2

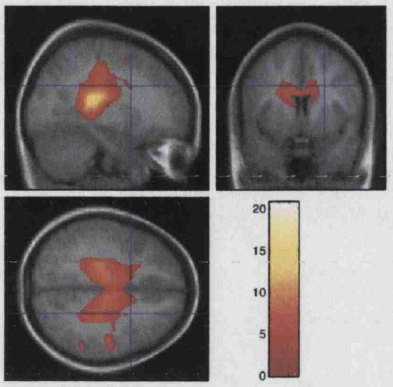


Figure 6.29: Decreased white matter density in right deep frontal white matter: 24, 8, 30

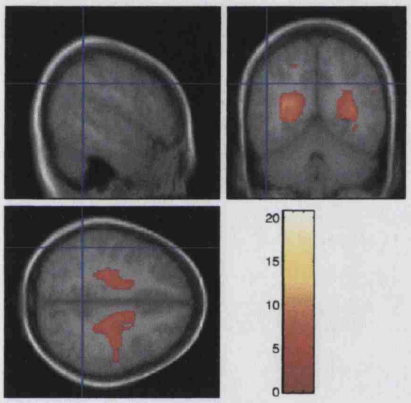


Figure 6.30: Decreased white matter density in inferior parietal white matter: -51, -48, 36

Decreased white matter in patients with right hemisphere only pathology:

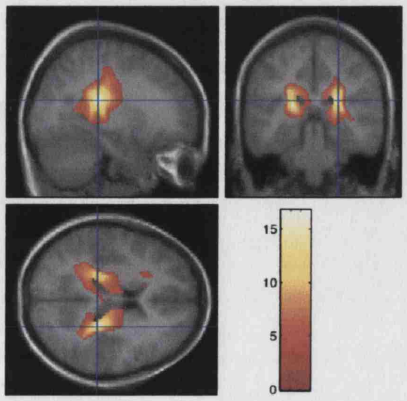


Figure 6.31: Decreased white matter density in peri-trigonal white matter: 26, -33, 20

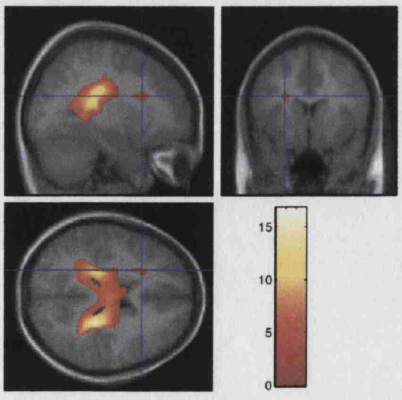


Figure 6.32: Decreased white matter density in left deep frontal white matter: -26, 16, 22

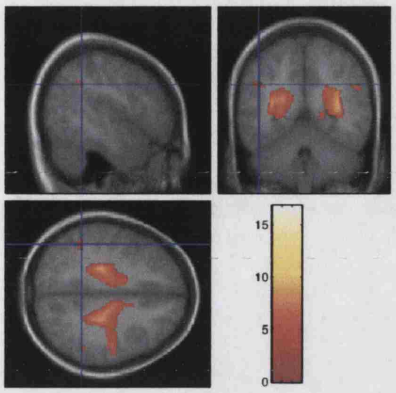


Figure 6.33: Decreased white matter density in left inferior parietal white matter: -48, -46, 33

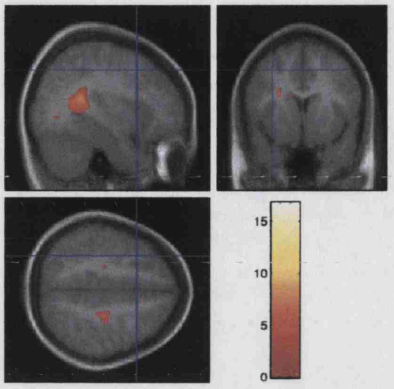


Figure 6.34: Decreased white matter density in left frontal subcortical white matter: -33, 14, 45

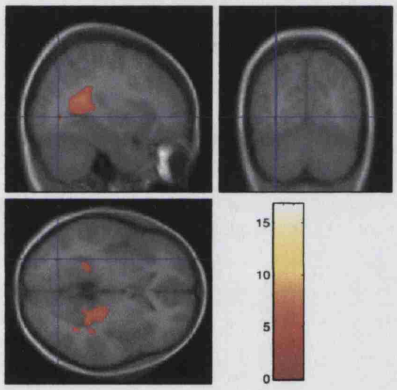


Figure 6.35: Decreased white matter density in left occipital white matter: -32, -72, 0

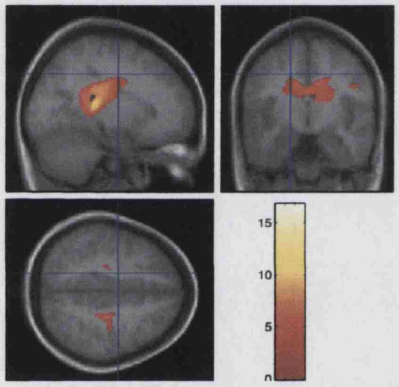


Figure 6.36: Decreased white matter density in left deep frontal white matter: -18, -9, 42

6.4.1.5 Correlations between VBM results and scores on neuropsychological tests of motor and cognitive function for patients with PFT

Correlation analyses were carried out in order to investigate whether there were any associations between regions of grey matter abnormality and performance on the motor and cognitive tests on which patients with PFT had significant difficulties.

(i) Correlations with neuropsychological test scores for patients with PFT as a group

In Chapters 3 and 4, patients with PFT were found to be impaired relative to controls on the following tests:

- **Motor tests:** The Annett pegboard (dominant and non-dominant hand), the Grooved Pegboard (non-dominant hand only), most measures of the posting task, all measures of the bead threading task, all measures of the tapping task and fast and slow learning on the rotary pursuit.
- **Cognitive tests:** The reading comprehension subtest of the WORD and the face sorting task (number of categories completed)

The results of correlation analyses between grey matter density and performance on each of these motor and cognitive tests showed that there were significant correlations for the Annett pegboard (dominant hand) and for the Grooved Pegboard (dominant hand) but not for any of the other tests.

For the Annett pegboard, there was a significant negative correlation between the time taken to complete the task with the dominant hand, and the density of grey matter in lobule V of the cerebellar vermis (see Table 6.5 and Figure 6.37). This indicates that increased grey matter density in vermal lobule V is associated with a decrease in the time taken to complete the Annett pegboard (i.e. improved performance).

Table 6.5: Negative correlation between grey matter density and time taken to move ten pegs with the dominant hand on the Annett Pegboard for patients with PFT

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Cerebellar vermis lobule V	6,-57,-21	5.04	0.009	12mm	6.37

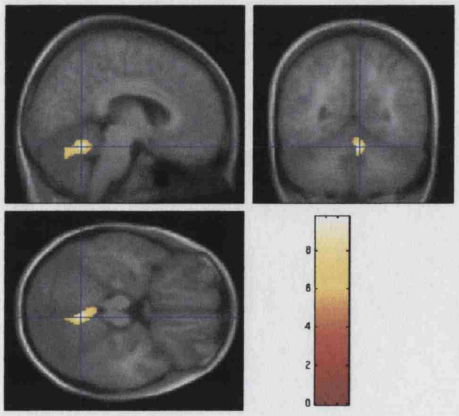


Figure 6.37: Negative correlation between grey matter density in cerebellar vermis lobule V and the time taken to move ten pegs with the dominant hand on the Annett Pegboard task: 6, -57, -21

For the Grooved Pegboard, there was a significant positive correlation between the time taken to complete the task with the dominant hand, and the density of grey matter in the posterior parietal lobe (see Table 6.6 and Figure 6.38). This indicates that an increase in grey matter density in the posterior parietal lobe is associated with an increase in the time taken to complete the Grooved Pegboard.

Table 6.6: Positive correlation between grey matter density and time taken to complete the Grooved Pegboard with the dominant hand for patients with PFT

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Posterior parietal lobe	39, -74, 27	5.10	0.045	12mm	6.38

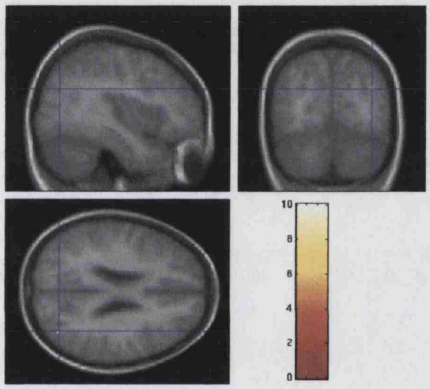


Figure 6.38: Positive correlation between grey matter density in the posterior parietal lobe and the time taken to complete the Grooved Pegboard: 39, -74, 27

(ii) Correlations with neuropsychological test scores for patients with LH pathology

Patients with LH pathology were found to perform significantly better than the other tumour location subgroups on the Annett Pegboard, the posting task, the bead threading task, on mirror tracing initial ability, and on the Benton test of facial recognition. Correlation analyses were therefore carried out between grey matter density and the scores from these tests. The results showed that there were no significant correlations between grey matter density in patients with left hemisphere pathology and performance on any of these neuropsychological tests.

(iii) Correlations with neuropsychological test scores for patients with midline pathology

Patients with midline pathology were found to perform significantly more poorly than the other tumour location subgroups on the Annett pegboard (dominant hand) and more poorly than patients with left hemisphere pathology on the posting task (but at a similar level to patients with right hemisphere pathology on this test). Correlation analyses were therefore carried out between grey matter density and the scores from these tests. Because there were so many trials for the posting task, correlation analyses were only carried out on four of the scores (dominant hand full gap 0 degrees, dominant hand quarter gap 135 degrees, non-dominant hand full gap 45 degrees, non-dominant hand quarter gap 90 degrees) which were chosen to represent the overall level of performance on the posting task. The results showed that there were no significant correlations between grey matter density and performance on any of these neuropsychological tests.

(iv) Correlations with neuropsychological test scores for patients with right hemisphere pathology

Patients with right hemisphere pathology were found to perform significantly more poorly than the other tumour location subgroups on the bead threading task, on mirror tracing initial ability, on the Benton test of facial recognition and more poorly than patients with left hemisphere pathology on the posting task (but at a similar level to patients with midline pathology on this test). Correlation analyses were therefore carried out between grey matter density and the scores from these tests. The results showed that there were no significant correlations between grey matter density in patients with right hemisphere pathology and performance on any of these neuropsychological tests. Given the extensive regions of white matter abnormality that were reported above, correlation analyses were also carried out between white matter density and performance on these tasks. The results showed that there were no significant correlations between white matter density and performance on any of these neuropsychological tests either.

(v) Correlations with neuropsychological test scores for patients with early pathology

Patients with early pathology of the cerebellum (age five and below) performed significantly more poorly than patients with late pathology of the cerebellum (age six and

above) on the Benton test of facial recognition and correlation analyses were therefore carried out between grey matter density and the scores from these tests for both the early and the late pathology subgroups. The results showed that there were no significant correlations between grey matter density and performance on the Benton test of facial recognition for either the early or the late pathology subgroup.

(vi) Correlations with neuropsychological test scores for patients with late pathology

Patients with late pathology of the cerebellum (age six and above) performed significantly more poorly than patients with early pathology of the cerebellum (age five and below) on the WOND and correlation analyses were therefore carried out between grey matter density and the scores from the WOND for both the early and the late pathology subgroups. The results showed that there were no significant correlations between grey matter density and performance on the WOND for either the early or the late pathology subgroup.

6.4.2 Patients with PFT voxel-based morphometry: Diffusion tensor images

There were no regions of increased or decreased fractional anisotropy for the patient group with PFT or for any of the tumour location subgroups compared to controls that reached corrected significance.

6.4.3 Patients with AS voxel-based morphometry: 3d-FLASH data sets

(i) Bilateral increased grey matter in patients with AS compared to their control group

A number of regions of bilateral increased grey matter density in the patient group with AS compared to the control group reached corrected significance. These regions were located in the cerebellum, the superior and middle temporal gyri, the temporal pole, adjacent to the amygdala, regions close to the hippocampus and in the occipital lobe. These regions and their significance levels are shown in Table 6.7 and Figures 6.39-6.48 below:

Table 6.7: Regions of bilateral increased grey matter in patients with AS compared to their control group

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Superior temporal gyrus	+/-60, 4, 0	6.15	0.000	12mm	6.39
Middle temporal gyrus	+/-51, -10, -22	4.74	0.001	12mm	6.40
Temporal pole	+/-36, 22, -33	4.50	0.002	12mm	6.41
Cerebellum	+/-32, -62, -62	4.05	0.006	12mm	6.42
Posterior part of temporal lobe	+/-56, -62, -3	3.46	0.025	12mm	6.43
Adjacent to the amygdala	+/-15, 2, -30	3.32	0.034	12mm	6.44
Grey matter adjacent to cingulate sulcus	+/-14, -40, 42	3.31	0.034	12mm	6.45
Occipital lobe	+/-38, -74, -12	3.17	0.046	12mm	6.46
Adjacent to hippocampus	+/-42, -32, -12	3.15	0.048	12mm	6.47
Superior temporal gyrus	+/-69, -26, 10	3.14	0.049	12mm	6.48

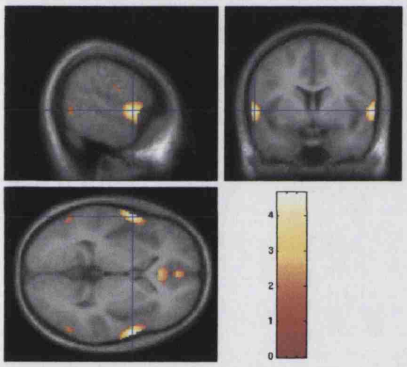


Figure 6.39: Increased grey matter in the superior temporal gyrus: +/-60, 4, 0

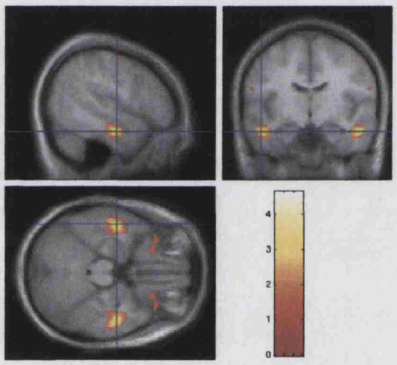


Figure 6.40: Increased grey matter in the middle temporal gyrus: +/-51, -10, -22

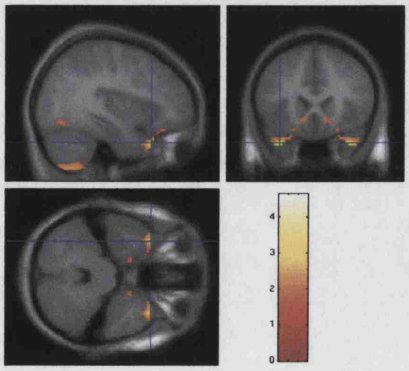


Figure 6.41: Increased grey matter in the temporal pole: +/-36, 22, -33

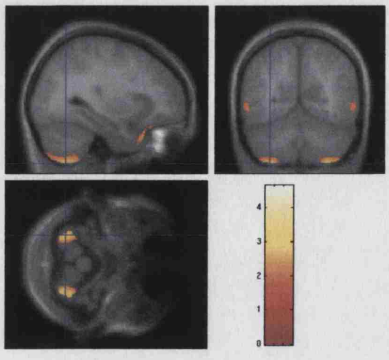


Figure 6.42: Increased grey matter in the posterior cerebellum (lateral regions of lobules VIIb, VIIIa and VIIIb): +/-32, -62, -62

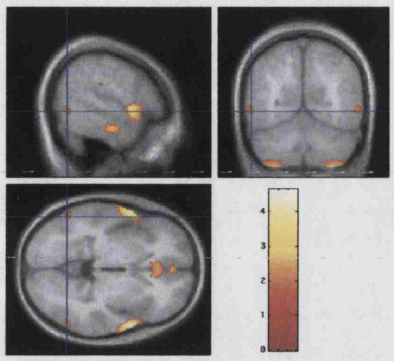


Figure 6.43: Increased grey matter in the posterior part of the temporal lobe: +/-56, -62, -3

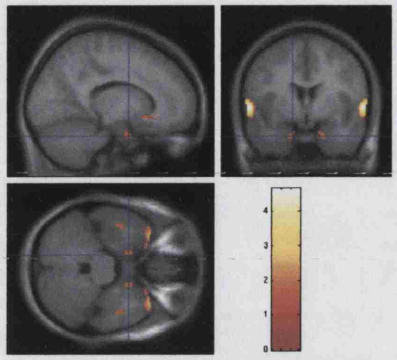


Figure 6.44: Increased grey matter adjacent to the amygdala: 15, 2, -30

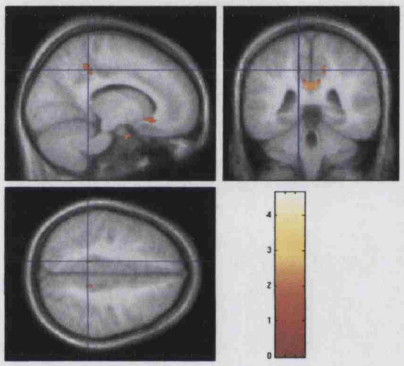


Figure 6.45: Increased grey matter adjacent to the cingulate sulcus: +/-14, -40, 42

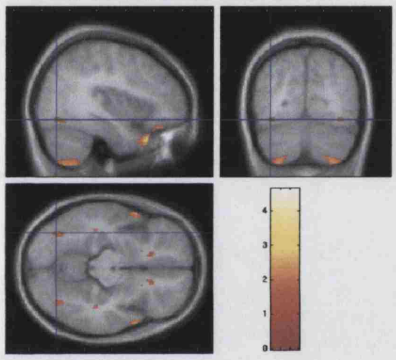


Figure 6.46: Increased grey matter in the occipital lobe: +/-38, -74, -12

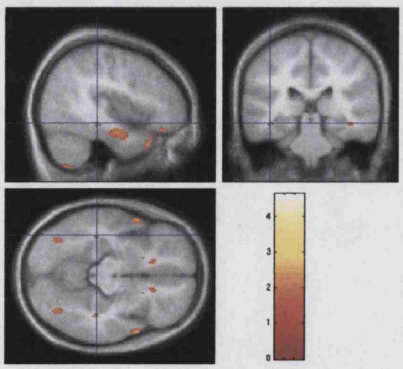


Figure 6.47: Increased grey matter adjacent to the hippocampus: +/-42, -32, -12

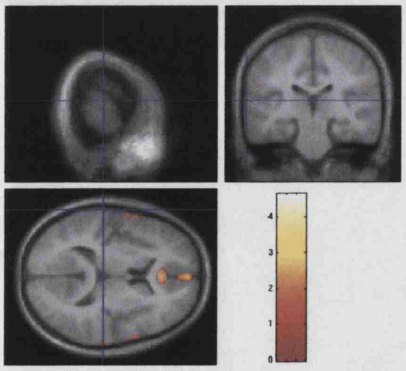


Figure 6.48: Increased grey matter in the superior temporal gyrus: +/-69, -26, 10

(ii) Bilateral decreased grey matter in patients with AS compared to their control group

One region of decreased grey matter density in the patient group with AS compared to the control group reached corrected significance. This was in regions inferior to the calcarine sulcus and is shown in Table 6.8 and Figure 6.49 below.

Table 6.8: Bilateral decreased grey matter in patients with AS compared to their control group

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Inferior to the calcarine sulcus	+/-14, -84, -6	4.20	0.013	12mm	6.49

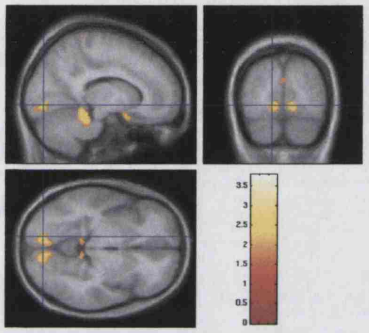


Figure 6.49: Decreased grey matter in regions inferior to the calcarine sulcus: +/-14, -84, -6

6.4.3.1 Bilateral white matter abnormalities in patients with AS compared to their control group

(i) Increased white matter in patients with AS compared to their control group

No regions of increased white matter density in the patient group with AS reached corrected significance.

(ii) Decreased white matter in patients with AS compared to their control group

One region of decreased white matter density in the patient group with AS reached corrected significance. This was in the deep temporal white matter and is shown in Table 6.9 and Figure 6.50 below.

Table 6.9: Regions of bilateral decreased white matter in patients with AS compared to their control group

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Deep temporal white matter	+/-48, -9, -22	4.29	0.009	12mm	6.50

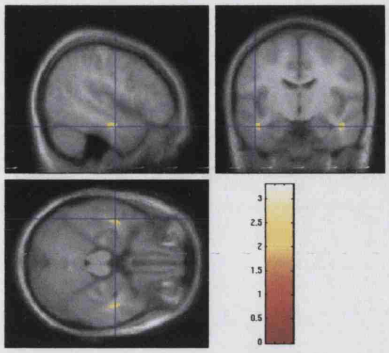


Figure 6.50: Decreased white matter in deep temporal white matter: +/-48, -9, -22

6.4.3.2 Correlations between VBM results and performance on neuropsychological tests of motor and cognitive function for patients with AS

Correlation analyses were carried out in order to investigate whether there were any associations between regions of bilateral grey matter abnormality and performance on the motor and cognitive tests on which patients with AS had significant difficulties.

In Chapters 3 and 4, patients with AS were found to perform significantly more poorly than controls on the following tests:

- **Motor tests:** The Annett Pegboard (dominant hand), most measures of the posting task, all measures of the bead threading task, sequential tapping (dominant and non-dominant hands), fast and slow learning on the rotary pursuit.
- **Cognitive tests:** The word and non-word repetition test (assessing phonological working memory) and the time taken to complete the number cancellation task (assessing an aspect of attention).

The results of correlation analyses between bilateral grey matter density and performance on each of these motor and cognitive tests showed that there were significant correlations for the Annett Pegboard (dominant hand), the posting task, the bead threading task, sequential tapping (dominant and non-dominant hands), word repetition and the time taken to complete the number cancellation task. There were no significant correlations for fast or

slow learning on the rotary pursuit task or for non-word repetition.

(i) Annett Pegboard (dominant hand)

There were significant negative correlations between the time taken to move ten pegs on the Annett Pegboard task, and the density of grey matter in the inferior frontal gyrus, the parahippocampal gyrus, the occipital gyrus, the fusiform gyrus and the middle frontal gyrus bilaterally. These areas of significant correlations are shown in Table 6.10 and Figures 6.51-6.55.

Table 6.10: Negative correlations between grey matter density and the time taken to move ten pegs on the Annett Pegboard task for patients with AS

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Inferior frontal gyrus	+/-40, 39, 8	4.29	0.003	12mm	6.51
Parahippocampal gyrus	+/-21, -22, -26	4.11	0.005	12mm	6.52
Occipital gyrus	+/-24, -92, 24	3.50	0.024	12mm	6.53
Fusiform gyrus	+/-45, -44, -16	3.39	0.032	12mm	6.54
Middle frontal gyrus	+/-52, 16, 42	3.33	0.037	12mm	6.55

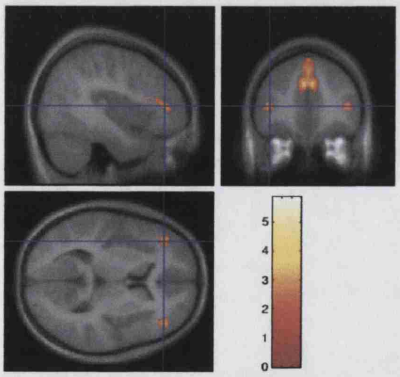


Figure 6.51: Negative correlation between grey matter density in the inferior frontal gyrus and the time taken to move ten pegs on the Annett Pegboard task: +/-40, 39, 8

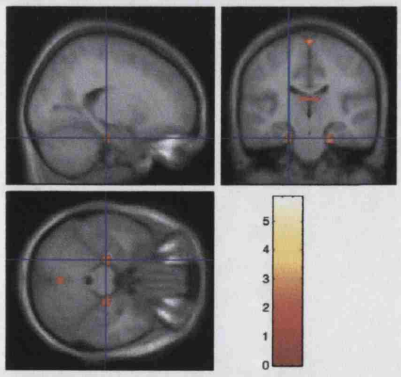


Figure 6.52: Negative correlation between grey matter density in the parahippocampal gyrus and the time taken to move ten pegs on the Annett Pegboard task: +/-21, -22, -26

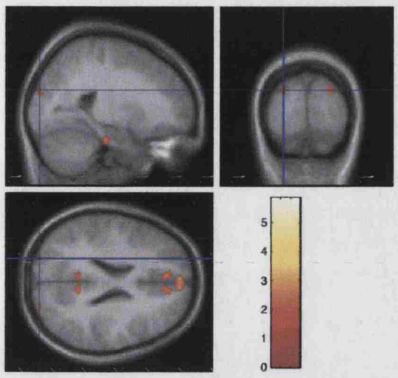


Figure 6.53: Negative correlation between grey matter density in the occipital gyrus and the time taken to move ten pegs on the Annett Pegboard task: +/-24, -92, 24

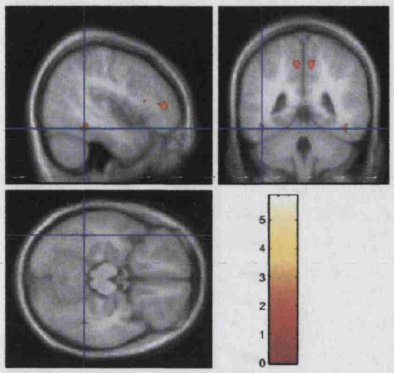


Figure 6.54: Negative correlation between grey matter density in the fusiform gyrus and the time taken to move ten pegs on the Annett Pegboard task: +/-45, -44, -16

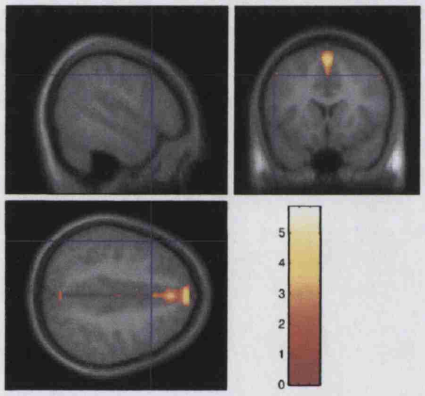


Figure 6.55: Negative correlation between grey matter density in the middle frontal gyrus and the time taken to move ten pegs on the Annett Pegboard task: +/-52, 16, 42

(ii) The posting task

There were numerous regions showing significant negative correlations between grey matter density and performance on the different measures of the posting task. These regions included frontal, occipital and parietal gyri as well as the circular sulcus of the insula. It is unclear why there were so many regions that showed significant correlations with performance on the posting task, but it is conceivable that at least some of these significant findings reflect false positives. The trial for dominant hand full gap 0 degrees will be taken as representative for this task as there were very similar regions of significant correlations for each of the 16 sub-tests of the posting task; and because there were so many

significant regions, only the regions which reached significance at a level of 0.01 are displayed here (See Table 6.11 and Figures 6.56-6.60).

Table 6.11: Negative correlations between grey matter density and time taken to post ten cards on the posting task (dominant hand full gap 0 degrees) for patients with AS

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Orbitofrontal gyrus	+/-32, 66, -14	5.44	0.001	12mm	6.56
Inferior frontal gyrus	+/-48, 45, -21	4.68	0.002	12mm	6.57
Circular sulcus of the insula	+/-40, 30, 9	4.28	0.006	12mm	6.58
Middle occipital gyrus	+/-62, -68, 26	4.23	0.007	12mm	6.59
Superior parietal gyrus	+/-18, -66, 66	4.23	0.007	12mm	6.60

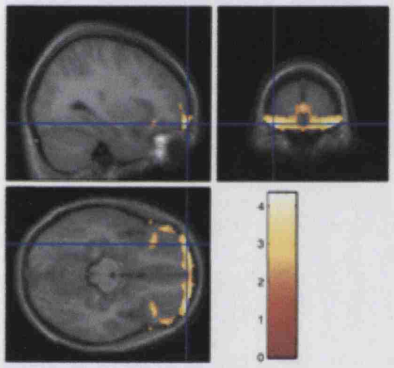


Figure 6.56: Negative correlation between grey matter density in the orbitofrontal gyrus and the time taken to post ten cards on the posting task (dominant hand full gap 0 degrees): +/-32, 66, -14

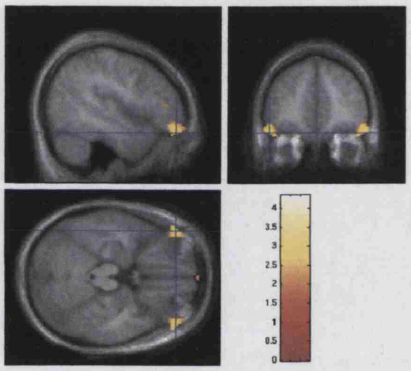


Figure 6.57: Negative correlation between grey matter density in the inferior frontal gyrus and the time taken to post ten cards on the posting task (dominant hand full gap 0 degrees): +/-48, 45, -21

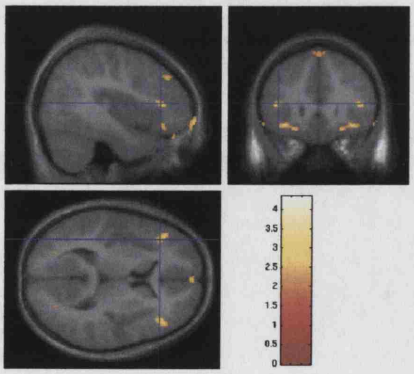


Figure 6.58: Negative correlation between grey matter density in the circular sulcus of the insula and the time taken to post ten cards on the posting task (dominant hand full gap 0 degrees): +/-40, 30, 9

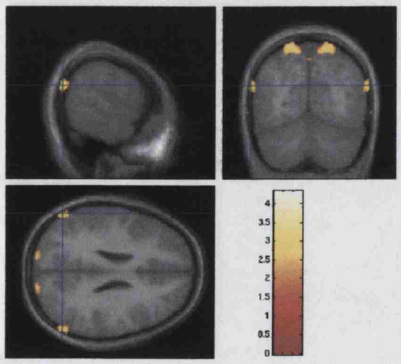


Figure 6.59: Negative correlation between grey matter density in the middle occipital gyrus and the time taken to post ten cards on the posting task (dominant hand full gap 0 degrees): +/-62, -68, 26

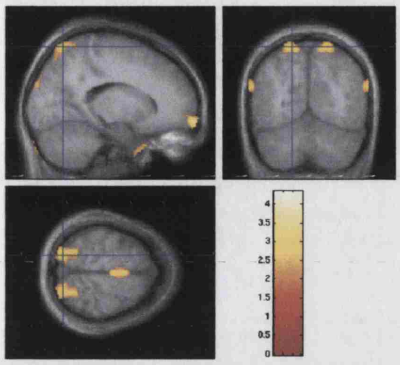


Figure 6.60: Negative correlation between grey matter density in the superior parietal gyrus and the time taken to post ten cards on the posting task (dominant hand full gap 0 degrees): +/-18, -66, 66

(iii) Bead threading

There were extensive regions showing significant negative correlations between grey matter density and performance on the sub-tests of the bead threading task indicating that increases in grey matter density in these regions was associated with a decrease in the time taken to thread 15 beads, and thus an increase in the level of performance on this task. These regions were principally located in lateral regions of occipital and parietal lobes and in the medial temporal lobe. The sub-test for big blue beads will be taken as representative for this task as there were very similar regions of significant correlations for each of the five sub-tests of the bead threading task; and because there were so many significant regions, only the regions which reached significance at a level of 0.01 are displayed here (See Table 6.12 and Figures 6.61-6.63). Once again, it is unclear why there were so many regions that showed significant correlations with performance on the bead threading task, but as was the case for the posting task, it is conceivable that at least some of these significant findings reflect false positives and this requires further investigation as it is unclear what the implication of these results might be.

Table 6.12: Negative correlations between grey matter density and time taken to thread 15 beads on the big blue bead threading task for patients with AS

Task	Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Big blue beads	Middle frontal gyrus	+/-52,14,39	4.57	0.001	12mm	6.61
	Hippocampal/parahippocampal regions	+/-18,-22,-21	4.45	0.001	12mm	6.62
	Inferior parietal gyrus	+/-48,-81,21	4.41	0.001	12mm	6.63

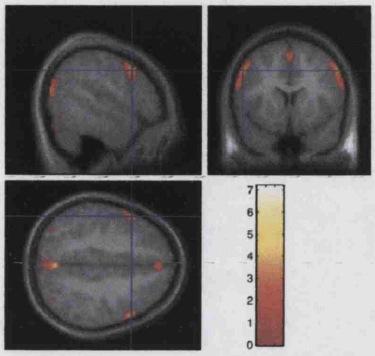


Figure 6.61: Negative correlation between grey matter density in the middle frontal gyrus and the time taken to thread 15 big blue beads: +/-52,14,39

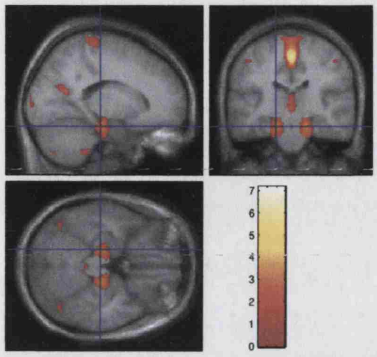


Figure 6.62: Negative correlation between grey matter density in hippocampal/parahippocampal regions and the time taken to thread 15 big blue beads: +/-18,-22,-21

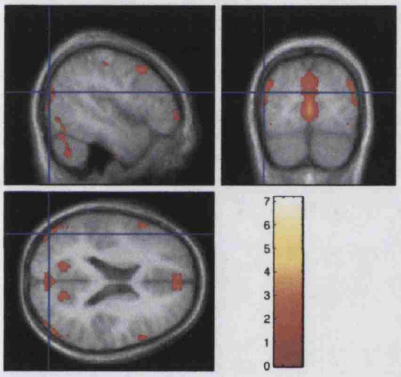


Figure 6.63: Negative correlation between grey matter density in the inferior parietal gyrus and the time taken to thread 15 big blue beads: +/-48, -81, 21

(iv) Sequential tapping

For the sequential tapping, there were significant positive correlations between performance on this task, and the density of grey matter in the cingulate gyrus and the superior temporal gyrus bilaterally. There were also negative correlations between performance on this task, and the density of grey matter in the superior temporal, superior frontal and inferior frontal gyri, and in the orbitofrontal gyrus bilaterally. This indicates that a bilateral increase in grey matter density in both the cingulate gyrus and the superior temporal gyrus is associated with an increase in performance on the sequential tapping, whereas a bilateral increase in grey matter density in the superior temporal, superior frontal and inferior frontal gyri, and in the orbitofrontal gyrus is associated with a decrease in

performance on the sequential tapping. These areas of significant correlations are shown in Table 6.13 and Figures 6.64-6.67 (positive correlations) and in Table 6.14 and Figures 6.68-6.71 (negative correlations).

Table 6.13: Positive correlations between grey matter density and number of taps in 30s on the sequential tapping task for patients with AS

	Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Dominant hand	Cingulate gyrus	+/-16,-60,15	4.51	0.012	12mm	6.64
Nondom. hand	Cingulate gyrus	+/-16,-60,14	4.87	0.030	12mm	6.65
Nondom. hand	Superior temporal gyrus	+/-50,-81,12	4.49	0.039	12mm	6.66
Nondom. hand	Middle temporal gyrus	+/-66,-38,-2	4.14	0.044	12mm	6.67

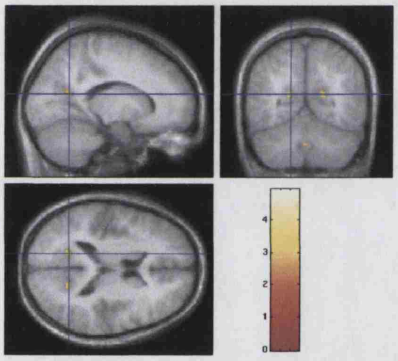


Figure 6.64: Positive correlation between grey matter density in the cingulate gyrus and the number of sequential taps completed with the dominant hand in 30 seconds: +/-16, -60, 15

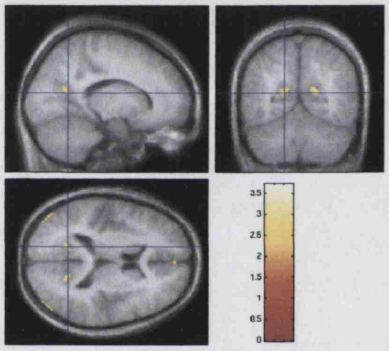


Figure 6.65: Positive correlation between grey matter density in the cingulate gyrus and the number of sequential taps completed with the non-dominant hand in 30 seconds: +/-16, -60, 14

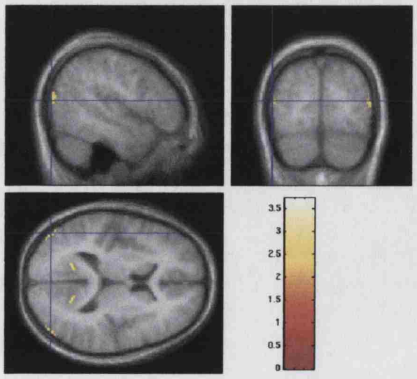


Figure 6.66: Positive correlation between grey matter density in the superior temporal gyrus and the number of sequential taps completed with the non-dominant hand in 30 seconds: +/-50, -81, 12

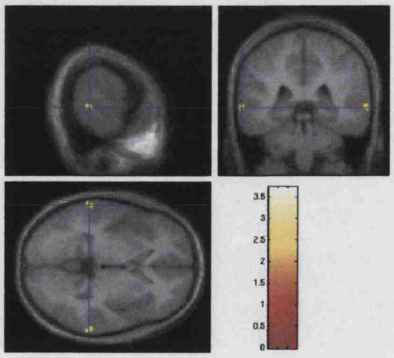


Figure 6.67: Positive correlation between grey matter density in the middle temporal gyrus and the number of sequential taps completed with the non-dominant hand in 30 seconds: +/-66, -38, -2

Table 6.14: Negative correlations between grey matter density and number of taps in 30s on the sequential tapping task for patients with AS

	Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Nondom. hand	Orbitofrontal gyrus	+/-38,26,-24	5.64	0.001	12mm	6.68
Nondom. hand	Superior temporal gyrus	+/-56,3,-8	4.41	0.010	12mm	6.69
Nondom. hand	Superior frontal gyrus	+/-20,66,-2	3.89	0.040	12mm	6.70
Nondom. hand	Inferior frontal gyrus	+/-16,54,32	3.82	0.045	12mm	6.71

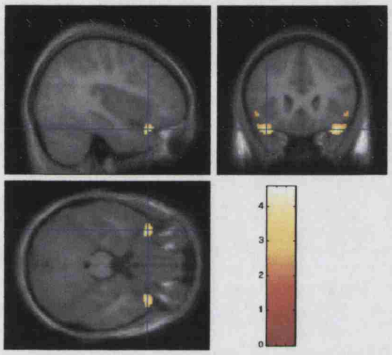


Figure 6.68: Negative correlation between grey matter density in the orbitofrontal gyrus and the number of sequential taps completed with the non-dominant hand in 30 seconds: +/-38, 26, -24

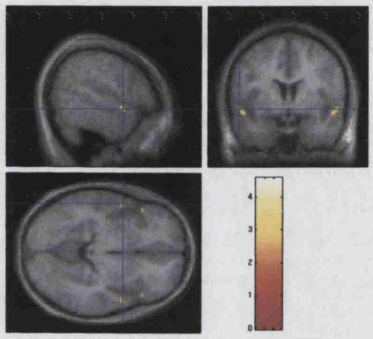


Figure 6.69: Negative correlation between grey matter density in the superior temporal gyrus and the number of sequential taps completed with the non-dominant hand in 30 seconds: +/-56, 3, -8

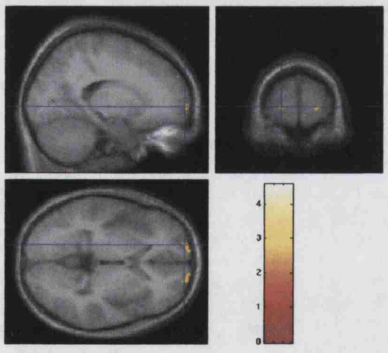


Figure 6.70: Negative correlation between grey matter density in the superior frontal gyrus and the number of sequential taps completed with the non-dominant hand in 30 seconds: +/-20, 66, -2

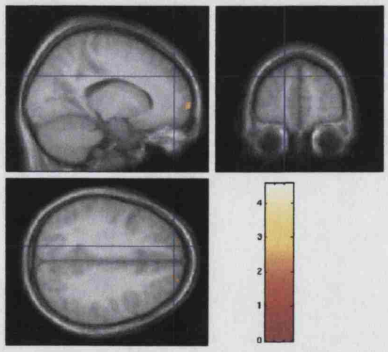


Figure 6.71: Negative correlation between grey matter density in the inferior frontal gyrus and the number of sequential taps completed with the non-dominant hand in 30 seconds: +/-16, 54, 32

(v) Word repetition

There were significant negative correlations between performance on the word repetition tasks and grey matter density in the occipital gyrus, the superior temporal gyrus and the superior frontal gyrus bilaterally. These areas of significant correlations are shown in

Table 6.15 and Figures 6.72-6.74.

Table 6.15: Negative correlations between grey matter density and performance on the word repetition task for patients with AS

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Occipital gyrus	+/-27,-90,-24	4.52	0.022	12mm	6.72
Superior temporal gyrus	+/-50,20,-14	4.02	0.031	12mm	6.73
Superior frontal gyrus	+/-15,48,20	3.95	0.035	12mm	6.74

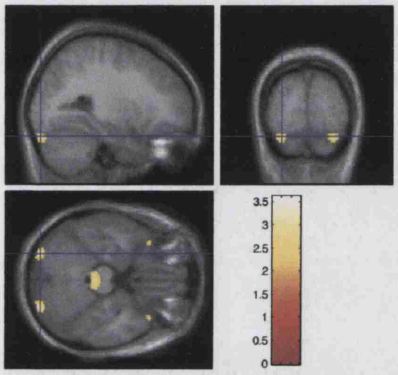


Figure 6.72: Negative correlation between grey matter density in the occipital gyrus and performance on the word repetition test: +/-27, -90, -24

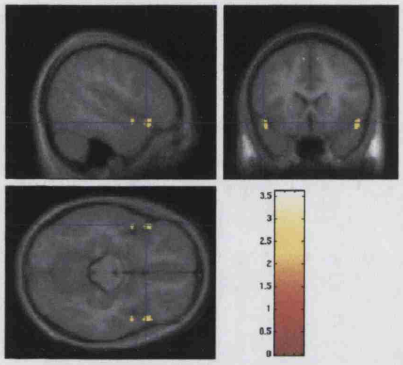


Figure 6.73: Negative correlation between grey matter density in the superior temporal gyrus and performance on the word repetition test: +/-50, 20, -14

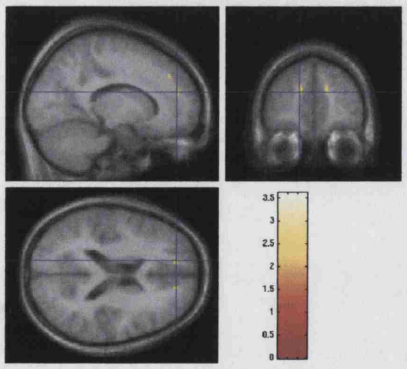


Figure 6.74: Negative correlation between grey matter density in the superior frontal gyrus and performance on the word repetition test: +/-15, 48, 20

(v) Time taken to complete the number cancellation task

There was a significant negative correlation between time taken to complete the number cancellation task and the grey matter density in the inferior frontal gyrus bilaterally. This area of significant correlation is shown in Table 6.16 and Figure 6.75.

Table 6.16: Negative correlation between grey matter density and the time taken to complete the number cancellation task for patients with AS

Location	Co-ordinates	Z score	FDR corrected P	Smoothing	Fig. no.
Inferior frontal gyrus	+/-42, 22, 12	4.36	0.033	12mm	6.75

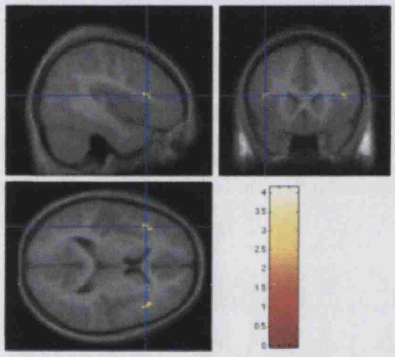


Figure 6.75: Negative correlation between grey matter density in the inferior frontal gyrus and time taken to complete the number cancellation task: +/-42, 33, 12

6.4.4 Patients with AS voxel-based morphometry: Diffusion tensor images

There were no regions of increased or decreased fractional anisotropy for the patient group with AS compared to controls that reached corrected significance. This indicates that there were no white matter tracts in which there were consistent abnormalities in fractional anisotropy for the patient group with AS compared to the control group.

6.5 Discussion

6.5.1 Patients with PFT

a) Voxel-based morphometric analysis of 3D-FLASH data sets for patients with PFT

The results of the VBM analysis of patients with PFT as a group and for each of the tumour location subgroups are summarized in Table 6.17.

Table 6.17: Results of VBM analyses for patients with PFT

Group	Abnormality	Location
All patients with PFT (n=14)	Decreased grey matter	Wall of the 4th ventricle
Midline pathology only subgroup (n=4)	Decreased grey matter	Cerebellum
Midline pathology plus subgroup (n=7)	Decreased grey matter	Cerebellum, thalamus, hypothalamus
RH pathology plus subgroup (n=5)	Decreased grey matter	Cerebellum, thalamus, hypothalamus, globus pallidus
RH pathology only subgroup (n=3)	Decreased grey matter	Cerebellum, thalamus
RH pathology plus subgroup (n=5)	Decreased white matter	Peri-trigonal, right and left parietal, left occipital and right deep frontal white matter
RH pathology only subgroup (n=3)	Decreased white matter	Peri-trigonal, left parietal, left occipital and left deep frontal white matter

As can be seen in this table, there was one region in the wall of the 4th ventricle where there was a consistent decrease in grey matter density for the patients with PFT as a group compared to the controls. However, it is likely that this is due to the presence of scar tissue or oedematous white matter (which has a similar appearance to grey matter on TI images) that can result from the surgical procedures which these patients have undergone in order to remove their posterior fossa tumours.

For the tumour location subgroups, VBM analyses revealed that patients with left hemisphere damage did not have any regions of grey or white matter abnormality compared to controls that reached corrected significance.

Patients with midline pathology had a decrease in grey matter density in a number of cerebellar areas. Although, as expected, these included the midline where the tumour had been removed, there were also regions in the cerebellar hemispheres where there was a decrease in grey matter density. It is likely that these abnormalities are directly associated with the surgery rather than being knock-on effects that resulted from damage to the midline cerebellum. This is because the nature of the anatomical organization of the cerebellum into a series of parallel zones (see Chapter 1) is such that pathology in one cerebellar region would be expected to have knock-on effects on other regions of the cerebellum within the same parallel zone in line with the projections of the Purkinje cells, rather than across zones (the abnormalities in the cerebellar hemispheres are in different zones to the midline pathology in these patients).

For the patients with midline pathology in addition to pathology affecting the cerebellar hemispheres (the midline plus group), there were similar regions of abnormality within the cerebellum to those observed in patients with midline only pathology; however there were a number of additional regions of abnormality outside the cerebellum. These were located in the thalamus and the hypothalamus and are likely to reflect changes in these regions in patients with right hemisphere pathology in particular.

The results of the VBM analyses for the patients with right hemisphere pathology revealed that in addition to abnormalities in the cerebellum, patients with right hemisphere plus pathology also had decreases in the level of grey matter density in the thalamus, the hypothalamus and the globus pallidus and patients with right hemisphere only pathology had decreases in grey matter density in the thalamus. As detailed in Chapter 1, the cerebellum has strong connections with both the thalamus and the hypothalamus. Much of the output of the cerebellum is relayed back to the cortex by means of the thalamus, and the cerebellum has reciprocal connections with the hypothalamus. It is unclear why both of these regions show a decrease in grey matter density in patients with right hemisphere pathology but not in those with left hemisphere pathology. A number of different variables might explain this difference. These include individual differences between patients in, for example, the precise location and extent of surgery, the age at which surgery was carried out, the time between the development of symptoms and the surgery and differences in the surgical approach. In addition, it is possible that these differences may be due to artifacts of the methodology used, as SPM is still a relatively new method for the analysis of MRI data. This discrepancy between patients with right and left cerebellar damage should be investigated further in future studies.

Nevertheless, the present results indicate that pathology of the right cerebellar hemisphere may have a knock-on effect on the projections of this area of the cerebellum which results in a decrease in grey matter in some of the most prominent regions to which the cerebellum projects (the thalamus and the hypothalamus). If a change in the projections of the cerebellum in patients with right hemisphere pathology can explain these changes in grey matter density in associated brain regions, then it would be predicted that changes in white

matter tracts carrying information away from the cerebellum might also be observed. This was in fact the case. VBM analysis of white matter density showed that although there were no significant differences between patients with PFT as a group nor patients with left or midline pathology and the control group, there were significant differences for the patients with right hemisphere pathology. The results showed that there was a significant decrease in white matter density in peri-trigonal, parietal, occipital and deep frontal regions of white matter in patients with right hemisphere pathology. These findings indicate that damage to the right cerebellum resulted in damage to the projections of this region of the cerebellum to other areas of the brain. As a consequence, perhaps the thalamus and hypothalamus did not receive as much input as they would normally and some of their neurons started to die off as they were no longer being used, resulting in a decrease in grey matter density in these areas. This is in line with previous studies that have shown that damage to the cerebellum also results in damage to areas with which the cerebellum is connected (Tecco et al., 1998; Manto et al., 1999; Marien et al. 2000). Furthermore, previous work has shown that functional brain systems involving the cerebellum do not only change in relation to one another within an individual, but have in fact shown correlated patterns of change over evolutionary time throughout the primate order (Whiting and Barton, 2003).

It should be noted that in patients with right hemisphere plus pathology, there was one further brain area that has not yet been discussed which also showed a decrease in grey matter density. This is the globus pallidus. The globus pallidus forms part of the basal ganglia and changes in grey matter density in this area must have been indirect, possibly via the thalamus, as there are no direct connections between the cerebellum and the basal ganglia. However, the basal ganglia are strongly involved in motor function (Jueptner and Krukenberg, 2001; Dreher and Grafman, 2002; Exner et al., 2002; Groenewegen, 2003) and it is therefore possible that a decrease in grey matter density in the globus pallidus is associated with some of the motor difficulties encountered by the patients with PFT, particularly the patients with right hemisphere pathology.

Results from the correlation analyses with neuropsychology scores

Correlation analyses were carried out between the results of VBM analyses and the scores on the tests of motor and cognitive function on which patients with PFT performed significantly more poorly than controls. This was in order to investigate whether their poor performance was associated with subtle differences in grey matter density that could not be seen using conventional MR imaging techniques. The results of these analyses revealed three significant correlations:

(i) Negative correlation between grey matter density in medial regions of vermal lobules IV and V and the time taken to complete the Annett Pegboard with the dominant hand.

This finding indicates that a decrease in grey matter density in vermal lobules IV and V is associated with an increase (and thus poorer performance) in the time taken to complete the Annett pegboard and provides support for previous studies that have implicated lobules in the anterior lobe of the cerebellum as being involved in motor function. In particular, functional imaging studies have found activation in cerebellar lobule V during tasks involving finger movement (Sadato et al., 1996; Blinkenberg et al., 1996) and early work by Holmes (1917) found that lesions of the anterior lobe are associated with ataxia, dysmetria and a lack of control of eye movements.

(ii) Positive correlation between grey matter density in the posterior parietal lobe and the time taken to complete the Grooved Pegboard with the dominant hand.

This finding indicates that an increase in grey matter density in the posterior parietal lobe is associated with an increase (and thus poorer performance) in the time taken to complete the Grooved Pegboard. Previous studies have shown that the posterior parietal lobe is involved in tactile object discrimination (Stoeckel et al., 2004), in reach to grasp movements, particularly in the planning aspect of these movements (Chapman et al. 2002), in spatial selection during a visuomotor task (Shibata and Ioannides, 2001) and in the processing of body part localization (Felician et al., 2004). One possible explanation of the finding that an increase in grey matter density in the posterior parietal lobe was associated with an increase in the time taken to complete the Grooved Pegboard may be that an increase in

grey matter density could be a reflection of an increase in the number of neurons carrying out these various functions and thus an increase in accuracy at the expense of speed.

Unfortunately it is not possible to know whether patients with increased grey matter density in the posterior parietal lobe also had an increase in the level of accuracy during this task; however it would be interesting to look at levels of accuracy in terms of the orientation at which patients try to slot the grooved pegs into the pegboard as it would be predicted that patients with increased grey matter in the posterior parietal lobe, who would be expected to plan movements more accurately, be better at spatial selection and tactile discrimination of the pegs and be more aware of the localization of body parts, would perform the task more accurately than patients with less grey matter in the posterior parietal lobe.

There were no significant correlations with motor or cognitive function for any of the tumour location subgroups (left hemisphere, right hemisphere and midline pathology) nor for the early or late surgery groups. It is likely that this lack of significant results is related to the small number of participants in each of these groups. Furthermore, each patient had slightly different regions and amounts of the cerebellum removed during surgery and there was therefore still much heterogeneity within the subject groups which could account for the lack of consistent findings between different patients and thus the lack of significant results when comparing groups.

b) Voxel-based morphometric analysis of diffusion tensor images for patients with PFT

The results of the VBM analyses for diffusion tensor images for patients with PFT showed that there were no significant differences for patients with PFT as a group, nor for any of the tumour location subgroups, compared to the controls. This lack of significant results was particularly surprising for the right hemisphere pathology subgroup as they had significant regions of decreased white matter (see Section 6.4.1.4) and it would therefore be predicted that they should also have significant regions of decreased fractional anisotropy. However, it may be that larger groups would show the effect or that different individuals had anisotropy abnormalities in different areas of the brain.

6.5.2 Patients with AS

a) Voxel-based morphometric analysis of 3d-FLASH data sets for patients with AS

The results of the VBM analyses for patients with AS are summarized in Table 6.18.

Table 6.18: Results of VBM analyses for patients with AS

Abnormality	Location
Increased grey matter	Cerebellum; middle and superior temporal gyri; regions adjacent to the amygdala, grey matter adjacent to the hippocampus; the temporal pole; the posterior part of the temporal lobe; grey matter adjacent to the cingulate sulcus; occipital lobe
Decreased grey matter	Regions inferior to the calcarine sulcus
Decreased white matter	Deep temporal white matter

As can be seen in this table, there were a number of regions of increased grey matter density for the patients with AS compared to the controls. These results provide support for the study of Salmond et al. (2003) and Abell et al. (1999) who also found increases in grey matter density in the cerebellum and the inferior and middle temporal gyrus in patients with AS compared to controls. The findings for regions of decreased grey and white matter were not in line with the predictions made at the beginning of this chapter. It had been predicted that there would be decreases in grey matter density in the cerebellum, the basal ganglia, the cingulate, frontal and orbitofrontal regions, the inferior frontal gyrus and the superior temporal gyrus; and decreases in white matter density in the cerebellum, pons and in fronto-temporal regions. However, the results showed that the only region of decreased grey matter density in patients with AS was located in regions inferior to the calcarine sulcus and the only area of decreased white matter density was located in deep temporal regions. Nevertheless, it is important to note that there is much heterogeneity in individuals with autism and AS (Salmond et al. 2000). This means that it is likely that there are abnormalities in grey and white matter density in some patients with AS in the regions that Abell et al. (1999) and McAlonan et al. (2002) found; however these abnormalities are not present in all individuals with AS and did therefore not show up in the current investigations.

As discussed in Section 1.4.3.2.1, autism is a neurodevelopmental disorder characterized by a triad of impairments in social interaction and communication and restricted and repetitive

behaviours and interests. Research into the neural correlates of this disorder have identified three main regions of abnormality: the cerebellum, the medial temporal lobes (amygdala and hippocampus) and the frontal lobes. The current results provide some partial support for these neural correlates, although there was no significant abnormality in the frontal lobes. Nevertheless, the findings from this study provide further evidence that autism and AS are multi-region disorders involving abnormalities in grey matter density in a number of different brain areas. The abnormalities adjacent to the amygdala and associated brain regions are likely to explain some of the impairments in social interaction observed in individuals with autism and AS (Abell et al. 1999). However, it is possible that the cerebellar abnormalities also have an effect on social interaction abilities as damage to the cerebellum has recently been associated with the blunting of affect and disinhibited and inappropriate behaviour (part of Schmahmann and Sherman's "cerebellar cognitive affective syndrome"; 1998 – see Section 1.4.3.1.4). The particular lobules of the cerebellum which were found to show an increase in grey matter density in the patients with AS were lobules VIIb, VIIIa and VIIIb. These are all located in the posterior lobe of the cerebellum which has been implicated in cognitive function and it is therefore possible that the developmental cerebellar abnormalities in patients with AS result in difficulties with more cognitive or emotional functions than with the motor functions which are more commonly associated with damage to the cerebellum.

As discussed in Chapter 1, the nature of the cerebellar abnormalities in patients with PFT is very different from that in patients with AS. Patients with PFT had a normal brain prior to the development of the tumour and the subsequent damage that results from surgery is acquired, and generally fairly localized damage. For the patients with AS, they have an abnormal brain right from the beginning of development when the very first connections are being laid down. This means that it is likely that the neural networks in the cerebellum of patients with AS are not the same as those in normal controls and this may result in individuals with AS having difficulties with the functions normally subserved by the areas of the cerebellum that are abnormal.

Results from the correlation analyses with neuropsychology scores

As was the case for the patients with PFT, correlation analyses were also carried out for the patients with AS between levels of grey matter density and performance on the motor and cognitive tests on which they performed significantly differently to the controls. The results showed that there numerous significant correlations for the Annett Pegboard, the bead threading task, the posting task, the sequential tapping task (for both the dominant and non-dominant hands), the word repetition task and time taken on the number cancellation task. These are summarized in Table 6.19 below.

Table 6.19: Significant correlations between neuropsychology test scores and VBM results

Neuropsychology measure	Correlation	Location
Annett Pegboard (time taken to move 10 pegs)	Negative	The inferior frontal gyrus, parahippocampal gyrus, occipital gyrus, fusiform gyrus and middle frontal gyrus
Bead threading (time to thread 15 beads)	Positive	A number of brain regions including the middle frontal gyrus, hippocampal/parahippocampal regions and the inferior parietal gyrus
Posting task (time taken to post 10 cards)	Negative	A number of brain regions, principally in the frontal lobe
Sequential tapping (number of taps in 30 seconds)	Positive	The cingulate gyrus (dominant and non-dominant hand) and the superior and middle temporal gyri (non-dominant hand only)
Sequential tapping (number of taps in 30 seconds)	Negative	The orbitofrontal gyrus, superior temporal gyrus, superior frontal gyrus and inferior frontal gyrus
Word repetition score	Negative	The occipital gyrus, superior temporal gyrus and superior frontal gyrus
Number cancellation (time taken to complete the task)	Negative	The inferior frontal gyrus

For the motor tasks in particular, there were extensive numbers of significant correlations with levels of grey matter density and it is therefore difficult to identify any clear associations between particular regions of brain abnormality and behavioural performance. It is conceivable that at least some (and possibly many) of the significant findings reflect false positives (with false discovery rate (FDR) correction for multiple comparisons, the expected proportion of false positives amongst suprathreshold voxels is 5%). These findings require further investigation as it is unclear what the implication of the results might be. In particular, it will be important to repeat this study with a different group of participants.

b) Voxel-based morphometric analysis of diffusion tensor images for patients with AS

The results of the VBM analyses for diffusion tensor images for patients with AS showed that there were no significant differences compared to the controls. This is in line with the finding that there were very few regions of white matter abnormality in the patients with AS compared to controls.

Taken together, the results from the patients with AS indicate that the principal way in which the brains of individuals with AS differ from those of controls is not in the density or levels of anisotropy of the white matter tracts (the connections of the brain), but in the density of grey matter. The patients with AS have an increased density in grey matter in a number of key areas including the cerebellum, regions adjacent to the amygdala, the middle and superior temporal gyri, the temporal pole, regions adjacent to the cingulate sulcus, regions adjacent to the hippocampus and in the occipital lobe and it is likely that the particular pattern of abnormalities in these different areas determines the nature and extent of the behavioural difficulties encountered by each individual with AS.

6.6 Summary

Voxel-based morphometric analyses were carried out for the patients with PFT and for the patients with AS compared to their control groups in order to identify any subtle regions of abnormality in grey or white matter density which were not apparent on visual inspection of MR images. The results showed that the patients with PFT as a group had a decrease in grey matter density in the wall of the 4^{th} ventricle, that the patients with pathology limited to the midline had a decrease in grey matter density in the cerebellum and that the patients with right hemisphere pathology had a decrease in grey matter density in the cerebellum, the thalamus, the hypothalamus and the globus pallidus. The patients with left hemisphere pathology did not have any significant regions of grey matter abnormality. Furthermore, the only group with PFT to show abnormalities in white matter was the right hemisphere pathology subgroup who had extensive regions of decreased white matter in frontal, parietal, temporal and occipital lobe regions and it is possible that this white matter tract damage is associated with the difficulties encountered on the motor tests by patients with right hemisphere pathology. There were no regions of abnormality in fractional anisotropy in the patients with PFT compared to the controls. Correlation analyses with the scores

from neuropsychological tests showed that there were significant correlations between grey matter density and performance on the Annett pegboard and on the Grooved Pegboard.

For the patients with AS, VBM analyses revealed increases in grey matter density in the cerebellum; middle and superior temporal gyri; regions adjacent to the amygdala and the hippocampus; the temporal lobe; regions adjacent to the cingulate sulcus and in the occipital lobe; decreases in grey matter density in regions inferior to the calcarine sulcus, and decreases in white matter density in the deep temporal white matter. There were no regions of abnormality in fractional anisotropy in the patients with AS compared to the controls. These findings provide further evidence that the behavioural manifestations of AS are associated with abnormalities in a number of different brain regions and possibly brain systems. Furthermore, it is suggested that although abnormalities in the amygdala and associated brain regions are likely to explain some of the impairments in social interaction observed in individuals with autism and AS, it is possible that the cerebellar abnormalities also have an effect on social interaction, given that the cerebellum is known to be involved in the modulation of affect (Schmahmann and Sherman, 1998). The correlation analyses with the scores from neuropsychological tests showed that there were numerous significant correlations between regions of brain abnormality and performance on a number of motor and cognitive tests. The large number of significant results means that it is difficult to associate behavioural difficulties with particular regions of abnormality in the brain, and further investigations are necessary in order to determine what the meaning of these results may be.

CHAPTER 7: GENERAL DISCUSSION

I studied the effects of cerebellar damage on movement and cognition in two patient groups. One group had undergone surgery to remove posterior fossa tumours located in the cerebellum. The other group had Asperger's syndrome, a form of high functioning autism in which abnormalities in the cerebellum have been reported as part of a widespread pattern of brain abnormalities. In order to investigate the motor and cognitive abilities of these two patient groups, a neuropsychological protocol was administered with the aim of uncovering patterns of intact and impaired behavioural functions that may be associated with abnormalities in the cerebellum.

The groups were first characterized using baseline tests of IQ and developmental questionnaires. For the patients with AS and their controls, the Australian Scale for Asperger's Syndrome was also administered in order to identify which characteristics representative of AS were present in the individuals who took part in this study.

Tests of motor function were reported in Chapter 3. The motor tests were selected to assess a range of movements including simple and complex fine motor action, bi-manual co-ordination and motor learning. Tests of cognitive function were reported in Chapter 4. The cognitive tests measured literacy, numeracy, visual matching, copying and drawing, and executive function.

The second half of this thesis aimed to investigate the extent of abnormalities in the cerebellum and in other brain areas in each of the patient groups. The extent of cerebellar lesions in each patient with PFT as determined by conventional MR imaging techniques were presented in Chapter 5. T1 weighted and DTI scans designed to measure structural differences in the brains of each of the patient groups were presented in Chapter 6. Finally, I studied the relationship between brain structure and performance on the behavioural tests.

The results from all of these investigations are summarized and discussed in this chapter, and the implications of this work for future studies are highlighted.

7.1 Patients with PFT

7.1.1 Summary of motor findings for patients with PFT

Patients with PFT had significant problems with motor function. They were impaired on tests of uni-manual fine motor action (the Annett Pegboard and the Grooved Pegboard), on a test of motor control of the hand and arm (the posting task) and on tests of bi-manual motor action that assess co-ordination abilities (bead threading and the tapping task). They were impaired on both slow and fast learning for the rotary pursuit task, but not on mirror tracing, a complex task which tests the learning of mirror-inverted movements.

These findings confirm the well established role of the cerebellum in motor functions first described by Rolando (1809) and Flourens (1824) and more recently extended by functional imaging studies (Fox et al., 1985; Blinkenberg et al. 1996; Nitschke et al., 1996; Sadato et al. 1996; Inoue et al., 1998; Kuhtz-Buschbeck et al. 2003; Rivkin et al. 2003).

Even relatively minor damage to the cerebellum results in motor difficulties. In patients with cerebellar tumours, both the site and extent of surgical removal and the aetiology of the tumour are important factors influencing the resultant motor difficulties. Medulloblastomas that occur in the vermis, for example, will inevitably require chemo or radiotherapy. In the current study, all of the tumours were astrocytomas. None of the patients had had any chemo- or radiotherapy, and their motor difficulties can therefore not be attributed to damage caused by these invasive treatments.

It is likely that the cerebellum is involved in different motor functions to different degrees. One important distinction is that between proximal and distal movements (Bolk, 1906).

Different areas in the cerebral cortex are specialised for different motor tasks. A whole brain PET study which looked at the regions of the motor cortex involved in distal and proximal movements found that movements of the fingers were associated with contralateral activation in the premotor area and in ventral regions of the prefrontal area; and that movements of the arms were associated with activation in similar, but more dorsal

regions (Kawashima et al., 1996).

A study which focussed on the cerebellum in particular was carried out by Mason et al. (1998). They placed injections of muscimol in various regions of monkey cerebella, and studied the effects on forelimb function. The results implicated the anterior interposed nucleus in distal movements of the hand and the posterior interposed nucleus and dentate nucleus in proximal movements of the arm.

Thus, evidence suggests that certain areas of the cerebellum, premotor and superior prefrontal cortex are involved in the fine control of distal muscles; whereas different areas of the cerebellum together with more dorsal regions of the premotor and prefrontal areas, control proximal muscles involved in more gross motor actions.

The involvement of proximal and distal muscles for the motor tests administered in this study is provided in table 7.1 below.

Table 7.1: The physiological demands and involvement of proximal or distal muscles for the motor tests

Motor test	Proximal or distal	Physiological demands
Annett pegboard	Mostly distal, some proximal	Unilateral fine motor control of hands and fingers and smooth control of arm movements. Visuo-motor co-ordination.
Grooved pegboard	Mostly distal, some proximal	Unilateral fine motor control of hands and fingers and smooth control of arm movements. More complex visuo-motor co-ordination than Annett Pegboard.
Posting task	Proximal	Unilateral gross motor control of arm, wrist and hand. Visuo-spatial judgment and visuo-motor co-ordination.
Bead threading	Distal	Bilateral fine motor control of fingers.
Tapping task	Proximal	Uni- and bi-lateral gross motor control of arms and hands.
Rotary pursuit	Proximal	Unilateral gross motor control of arm.
Mirror tracing	Proximal and distal	Unilateral gross motor control of arm and fine motor controls of hand and fingers.

Three of the tests emphasised proximal movements, three distal movements, and one tested both proximal and distal muscles equally.

The current study focused on implicit procedural motor learning rather than explicit episodic motor learning as suggested by previous studies. Muller et al. (2002), for example, using fMRI found activation in the anterior cerebellum during the explicit learning of novel motor sequences; and Eliassen et al. (2001) found activation in the cerebellum in a task requiring the acquisition of explicit knowledge about an eight-element movement sequence. Given this evidence, it would be interesting to look at the performance of patients with PFT on tests of explicit episodic motor learning, as well as implicit motor learning.

In summary, the cerebellum is involved in the control of hand and fingers as well as gross movements of the arm and wrist. The fact that patients with PFT found it difficult to learn new, circular movements of the arm and wrist suggests that the cerebellum is also involved in the learning of novel movements.

7.1.2 Summary of cognitive findings for patients with PFT

Patients with PFT showed remarkably few cognitive problems. They had intact literacy and numeracy skills, attention, verbal and spatial working memory, visual perception, and copying and drawing abilities. The only tests on which they demonstrated difficulties were a rule-based switching task and the coding subtest of the WISC/WAIS, although this may have been due to problems with either motor functions or speed of processing. The weight of evidence strongly argues against a deficit in attention causing the observed deficit.

Previous studies have reported a variety of cognitive difficulties including working memory, auditory, spatial and visual sequential memory, attention, language processing and executive function after cerebellar damage. The fact that such difficulties were not found in the current study could be explained in one of four ways:

a) **Differences in patient populations:** The cognitive problems identified in previous studies may have been due to invasive treatment methods that cause extra-cerebellar

damage. The patients with PFT who participated in this study had tumours of very low malignancy that did not require any chemotherapy or radiotherapy. Although this means that they were a good population to study, it also means that they differed from the patients who took part in previous investigations as this is the first study to focus solely on patients with low-grade pilocytic astrocytomas limited to the cerebellum who did not have any chemo- or radiotherapy. There is evidence to suggest that invasive treatments such as chemotherapy and radiotherapy have adverse effects on cognitive abilities. Spiegler et al. (2004) carried out a study on patients with posterior fossa tumours looking at the effects of cranial irradiation on neurocognitive functioning. They found that cranial irradiation was associated with a decline in a number of cognitive domains including visuo-motor integration, visual memory, verbal fluency and executive functioning. A study by Noad et al. (2004) compared patients with pituitary tumours who had undergone surgery and received radiotherapy with those who had undergone surgery alone. They found that the patients who had undergone radiotherapy in addition to the surgery showed a greater decrease in cognitive function, particularly in executive functioning. Armstrong et al. (2004) reviewed the effects of therapeutic irradiation on the brain. They found that visual attention and visual memory may be particularly vulnerable to this type of intervention. Since chemo- and radiotherapy have adverse effects on cognitive functioning, some of the cognitive difficulties identified in patients with PFT in previous studies may have been caused by the invasive therapy that they received rather than damage to the cerebellum. A further consideration that should be taken into account is that some of the patients with PFT will have had hydrocephalus associated with the surgery to remove their tumours. There is evidence to suggest that hydrocephalus has a negative impact on behavioural functioning (Casey et al., 1997). Given the small sample size in the current study, it was not possible to exclude individuals who had had hydrocephalus and it is therefore possible that the data was confounded by the presence of hydrocephalus in some patients.

b) **Differences in tests chosen:** The particular tests carried out in this study were selected to try to tap the cognitive functions in which the cerebellum has previously

been implicated (see Chapter 4). Since the tests administered in the current study differed from those used in previous studies of patients with PFT, differences between the tests may be the reason for the different results.

c) **Sample size and bias:** Given the small number of previous studies that have been carried out on patients with PFT, and the small numbers of patients included in each of the studies, it is possible that they may not have uncovered a balanced picture of cognitive function. Instead, studies may have been biased by particular characteristics of their patient populations. Both experimental and control groups often have a wide age range and are selected according to different criteria, and discrepancies in factors such as these are likely to introduce bias.

d) **Previous findings could have been incorrectly attributed to the cerebellum:** The cognitive problems identified in previous studies could have been due to knock-on damage to areas outside the cerebellum rather than to the more obvious cerebellar pathology. The cerebellum does not function in isolation. Functions in which the cerebellum participates will necessarily involve other areas of the brain to which it is connected. Because of this systemic organisation of the brain, it is difficult to identify the particular functions in which any individual brain structure may be critically involved. Problems with cognitive functions may have been due to damage to areas outside the cerebellum. This is in line with the possibility that the activation of the cerebellum in functional imaging studies of cognitive functions could simply be due to the fact that the cerebellum is connected to an area of the brain that is strongly involved in a particular cognitive process. For example, in functional imaging studies of working memory, the cerebellum is only one of a number of brain structures to show activation (Fiez et al. 1996; Paulesu et al., 1993; 1995; Desmond et al., 1997; Mathiak et al., 2004). One of the areas which has most consistently been shown to be active during working memory tasks is the prefrontal cortex. The cerebellum has strong connections to the prefrontal cortex and it is therefore not surprising that it would show activation when the prefrontal cortex is activated as there is likely to be much information transfer between these structures. However,

this activation does not necessarily imply that the cerebellum plays an integral role in working memory. Studies of patients with focal lesions in the cerebellum provide the most promising means to determine in which functions the cerebellum plays an integral role. However, it is unlikely that any damage is limited to the cerebellum alone. For this reason, it is possible that previous studies of patients with cerebellar damage may have incorrectly attributed their problems to the areas of the cerebellum that are damaged, rather than to damage to associated brain areas.

Thus, the lack of significant problems with cognitive function in the current study can be attributed to a number of different factors. The possibility remains that in previous studies of patients with PFT, the cognitive problems may have been associated with knock-on damage to other areas of the brain rather than being due to the cerebellar damage per se.

To summarize, this study has identified the motor domains of simple and complex uni-manual and bi-manual fine motor actions and aspects of motor learning as areas that require further investigation using more sensitive tests in order to identify the particular aspects on which the patients with PFT may have difficulty and by implication, for which an intact cerebellum may be necessary. The results for the cognitive tests indicated that an intact cerebellum may not in fact be necessary for the successful execution of a number of cognitive functions, indicating that, contrary to previous research findings, the cerebellum may not play an integral role in cognitive functioning.

Parents reported an inability to modulate affect, which was particularly manifested by a loss of temper-control, as a common post-surgical feature in the patients with PFT. This finding indicates that it is possible that the cerebellum may play a role in the normal control of emotional response but that this control is lost when the cerebellum is damaged. This is in line with Schmahmann and Sherman's cerebellar cognitive-affective syndrome (Schmahmann and Sherman, 1998). It also receives some support from previous work that has implicated the vermis in the modulation of affect (Levisohn et al., 2000; Steinlin et al., 2003), although in this study, patients who did not have any obvious damage to the vermis were also reported to show a loss of control of emotion, suggesting that other areas of the

cerebellum may also be involved in the modulation of affect. Thus, in addition to the motor and cognitive functions that were the focus of this thesis, some preliminary evidence for a role for the cerebellum in the control of emotions has also come to light.

7.1.3 Does age at onset of pathology affect behavioural outcome?

Surgery performed later in childhood (age six and above) may make it difficult to learn new motor skills, and affect numerical abilities, and problem solving abilities (as assessed by the mazes subtest of the WISC/WAIS). Surgery carried out at a younger age (up to age five) may have a negative effect on facial matching ability. It is possible that the difficulties in learning new motor skills in the patients with late pathology are due to the brain being less plastic in older patients (Stiles, 2000). This may also account for the increased difficulties in the manipulation of numbers required in the tests of numerical abilities. For the cognitive functions, the finding that patients with early pathology have difficulties with facial matching is perplexing. On the basis of conserved plasticity in the young brain it would have been predicted that aspects of visuo-spatial processing requiring matching of stimuli would be enhanced rather than restricted. Nevertheless, there is evidence in the literature to suggest that early damage to the cerebellum can result in more severe cognitive problems than late damage (Scott et al. 2001). It may therefore not simply be the case that the high level of plasticity in the developing brain means that cognitive functions can be rescued after early brain damage.

Differences in early versus late damage should be interpreted with caution given the large number of statistical tests that were carried out here, as the probability of obtaining false positive results is high.

7.1.4 Are there effects of time since surgery on behavioural outcome?

There was little evidence to suggest that there was an association between time since surgery and performance on the motor or cognitive tests. This is likely to be because all of the patients with PFT were seen at least two years post-surgery, by which time most of the acute events associated with the surgery would have dissipated. This may also explain some of the differences in the findings in the current study compared to those in previous

studies. Previous investigations (e.g. Riva and Giorgi, 2000) have tended to study patients soon after surgery and it is possible that changes in the brain were still occurring at this time, resulting in different behavioural findings to those that would be found if the patients were studied later, once changes in the brain had dissipated.

7.1.5 Summary of MRI findings for patients with PFT

a) Tumour location

Visual inspection of T1 and T2-weighted MRI scans for the patients with PFT revealed that patients with midline pathology had damage affecting almost all lobules of the vermis (the only lobules which did not appear to be damaged in any of these patients were lobules I, II and IX). Although patients with midline pathology had damage to lobules III, IV and V of the anterior lobe, there was very little pathology of the anterior lobe in patients in the right or left hemisphere pathology groups. The pathology in patients with left hemisphere pathology was principally located in lobules V through to VIIb and that of patients with right hemisphere pathology was principally located in lobules VI through to VIIIa. There was a similar pattern of damaged lobules in patients with left hemisphere and right hemisphere damage and the only clear difference was that two patients with right hemisphere pathology had damage to lobules VIIb, VIIIa, VIIIb and IX in the intermediate zone, whereas these lobules did not appear to damaged in any of the patients with left hemisphere pathology. It is currently not known whether there are differences between the functions of the right and left cerebellum, neither is it known what the effects are of damage to the right versus the left cerebellum.

b) VBM

Voxel-based morphometric analyses showed that there were a number of regions of abnormality of grey and white matter density, indicating structural damage, that were not apparent on visual inspection of MR images. This demonstrates the importance of analyzing MRI scans at a voxel-by-voxel level.

As a group, there were few differences between patients with PFT and their controls, the only significant finding being a decrease in grey matter density in the wall of the 4th

ventricle in the patients with PFT compared to the controls. However, it is likely that this was due to the surgical approach rather than any subtle knock-on effects of the tumour on anatomically connected regions. It had been predicted in the hypotheses that, as a group, patients with PFT would be found to have a decrease in grey matter density in regions to which the cerebellum projects (the thalamus, the red nucleus, the inferior olive, the vestibular nucleus and the hypothalamus). However, the lack of support for this hypothesis could be explained by the variation in the location of the cerebellar damage in each of the patients. It is likely that there was not enough overlap in any knock-on damage to grey or white matter in other brain regions for this to show up in the whole-group analyses.

This possibility receives some support from the findings when each of the tumour location subgroups (left hemisphere, right hemisphere and midline) was compared with the controls separately. The most significant finding here was that the patients with right hemisphere pathology had a decrease in grey matter density in the cerebellum, the thalamus, the hypothalamus and the globus pallidus; and extensive regions of decreased white matter in frontal, parietal, temporal and occipital lobe regions. It is unclear at this stage what the functional implication of such differences might be; however the finding that patients with right hemisphere pathology had particular problems with a number of tests of motor function leaves open the possibility that successful completion of motor actions may depend on a number of brain areas outside the cerebellum as well. This is not surprising, given that the thalamus conveys information between the cerebellum and the motor cortex and abnormalities in this area are likely to result in abnormalities in the information transfer between the cerebellum and the motor cortex and, as a consequence, an inability to successfully carry out certain motor actions as normal. However, because the functions of this circuit are not yet well understood, it is difficult to determine at which level in the pathway from the cerebellum to the cerebral cortex the functional deficit may arise.

The results for the patients with left hemisphere pathology showed that they did not have any significant regions of grey or white matter abnormality. It is unclear why patients with right hemisphere pathology should show so many regions of abnormality in grey and white matter density in areas outside the cerebellum while no such abnormalities were found in

patients with left hemisphere pathology. It is possible that this is related to the increased amount of white matter present in the left cerebral hemisphere compared to the right (Pujol et al. 2002; Buchel et al., 2004). That is to say that, because the right cerebellum is connected to the left cerebral hemisphere, it is possible that damage to the right cerebellum has more widespread effects on the rest of the brain, as there is more white matter in the area to which the right cerebellum projects which may be vulnerable. Furthermore, the differences may be related to the fact that the particular lobules damaged in the patients with right and those with left hemisphere pathology were not identical.

The patients with pathology limited to the midline had a decrease in grey matter density in the cerebellum. This is not surprising given that sections of the cerebellum had been removed during surgery. The fact that patients with midline damage were the only subgroup of patients with PFT to show a significant group difference in grey matter density within the cerebellum is likely to be due to the wider variation in tumour location in the patients with damage to the cerebellar hemispheres. Patients with midline damage had fairly localized, overlapping regions of cerebellar damage, whereas patients in the hemisphere subgroups had damage to more widespread regions of the cerebellum including both hemisphere and midline areas. Therefore, there may simply not have been enough overlap in the particular regions of the cerebellum that were damaged in either of the hemisphere subgroups for this to show up in the group analyses. Furthermore, midline lesions produce symptoms earlier, and hemispheric lesions may therefore be more progressed by the time of surgery.

No regions of abnormality in fractional anisotropy were seen in the patients with PFT as a group compared to the controls, nor in any of the tumour location subgroups. However, DTI methods are still in developmental stages and there are still problems that need to be ironed out. Even during the course of the three years that this study was carried out, numerous problems were encountered (for example it was unclear what was the best template to be used for normalization in DTI; and it was not known what threshold should be used as a cut-off for exclusion of blurred images due to motion artefacts).

Despite these problems it was important to include both DTI and VBM investigations in this study as neither of these methods have previously been carried out on patients with PFT and they provide a promising means by which to learn more about these patients. VBM on T1 images provides the most accurate means by which it is currently possible to identify the particular cerebellar lobules that are damaged or missing as a result of surgery to treat posterior fossa tumours. This in turn means that advances can be made in determining to what degree there may be functional localization at a lobular level within the cerebellum, and the degree to which different lobules might be involved in similar functions.

DTI is a promising method still in its infancy. Although there is evidence to show that damage to one area of the brain results in damage to other areas of the brain to which it is connected (Gentry et al. 1988; Sisodiya et al. 1995; Wiese et al. 2004), until now it has been difficult to quantify and accurately assess this knock-on damage. DTI methods will eventually enable the tracking of fibers to trace the effects on individual tracts of damage to one end of these (for example surgery to remove cerebellar tumours will also affect projections from the cerebellum, but it is not currently possible to trace these projections to look at the precise effects). The fact that there were no findings from the DTI studies carried out in this study does not mean that there were no changes in white matter tracts in patients with PFT. Rather, it is likely that this is a reflection of the heterogeneity of the patient group. That is to say that there is likely to have been a wide spread of white matter damage in different regions of the brain (as evidenced by the VBM studies which showed that patients with right hemisphere pathology had widespread regions of decreased white matter, but patients with left hemisphere pathology did not have any regions of significantly decreased white matter density). DTI studies on larger groups of patients with PFT may be more informative, and as the methodology for these studies develops, more accurate results should be attainable.

7.1.6 Evidence from patients with PFT for functional localization in the cerebellum

The uniform structural organisation of the cerebellar cortex suggests that all areas of the cerebellum process neural information in the same way. However, both ablation studies

and functional imaging studies have indicated that the anterior lobe of the cerebellum (lobules I-V) may be specifically involved in movement, and it has been argued that a number of cerebellar areas may be particularly involved in cognitive functions (see Chapter 1). The idea that there may be functional localisation in the cerebellum stems back to the work of Bolk (1906) who proposed that the anterior lobe and the vermis of the posterior lobe control bilaterally co-ordinated movements, whereas the hemispheres control unilateral movements. The possibility of localization of function was investigated in two ways in this thesis.

a) Hemisphere/midline distinctions:

The patients with PFT were split into three groups on the basis of the location of their tumour: right hemisphere, which included patients with any damage to the right cerebellar hemisphere, irrespective of whether there was damage to the vermis; left hemisphere, which included patients with any damage to the left cerebellar hemisphere, irrespective of whether there was damage to the vermis; and midline, which included patients with damage limited to the cerebellar vermis only. The performance of these groups on each of the motor and cognitive tests was then compared in order to determine whether there was any evidence for localization of function within either of the cerebellar hemispheres or the vermis. The results were as follows:

(i) **Left hemisphere:** The patients with damage to the left cerebellar hemisphere performed well on all of the tests of motor function. Given the high level of heterogeneity and the small number of patients, it is unclear whether these findings show that an intact left cerebellar hemisphere may not be essential for all movement abilities, or whether the lack of problems with motor functions are associated with other variables. For the tests of cognitive function, patients with left hemisphere pathology performed significantly more poorly than patients with right cerebellar hemisphere damage on the vocabulary subtest of the WISC/WAIS and there was weak evidence to suggest that they performed more poorly on the comprehension subtest as well. These findings are contrary to expectations given that it is the left cerebral cortex (which is connected to the right cerebellar hemisphere, see Section 1.3.1.2) that is involved in language.

(ii) **Right hemisphere:** The patients with damage to the right cerebellar hemisphere were impaired on a number of motor tests (the posting task, the bead threading and initial ability on the mirror tracing) and on the cognitive test of face matching, indicating that the right cerebellar hemisphere is likely to be involved in a number of motor functions and possibly also in the visuo-perceptual task of face matching.

(iii) **Midline (vermis):** The patients with damage to the midline cerebellum were impaired on a test of fine motor action (the Annett pegboard), but not on tests of cognitive function. This indicates that regions of the vermis may be important for some aspects of fine motor function.

Patients with right hemisphere damage, who performed poorly on a number of motor and cognitive tests, showed abnormalities in a number of regions of grey and white matter density outside the cerebellum and it is therefore possible that some of their difficulties on the motor and cognitive tasks may be associated with damage to areas of the brain which are not limited to within the cerebellum alone. This possibility could be tested by correlation analyses between performance on the neuropsychological tests and the results of the VBM analyses. Such analyses were carried out here, but no significant results were obtained, likely due to the small number of patients (five patients had pathology of the right cerebellar hemisphere). Further investigation is thus needed with larger numbers of patients, in order to investigate the extent to which the difficulties of patients with damage to the right cerebellar hemisphere may be associated with abnormalities in regions of the brain outside the cerebellum.

b) Comparisons at a lobular level

There were some differences in the performance of patients depending on which individual cerebellar lobules were damaged. There was also an association between the number of damaged cerebellar lobules and performance on a number of motor and cognitive tasks (providing support for Lashley's concept of "mass action", see Section 1.1.2). These findings indicate that there may be some localized specialization of function in the cerebellum, but that individual cerebellar lobules may not function in isolation, rather, these may be sub-parts of a highly ordered structure that operates as a coordinated whole.

7.2 Patients with AS

7.2.1 Summary of Australian Scale for Asperger's Syndrome (ASAS) findings for patients with AS

The patients with Asperger's Syndrome showed a variety of characteristics typical of individuals with AS. These included difficulties in the understanding of social conventions (empathy and displays of emotion), problems with communication (unusual eye-contact or tone of voice, pedantry and lack of reciprocal conversation), and unusual fears, phobias, motor mannerisms, sensitivity to pain, as well as a tendency to be obsessed with specific interests. The ratings for the patients were clearly abnormal relative to the controls.

7.2.2 Summary of motor findings for patients with AS

Patients with AS had an interesting pattern of intact and impaired movement abilities. They were impaired on a test of uni-manual fine motor action (the Annett Pegboard, dominant hand) but not on a test of fine motor action that required more intricate movements of the fingers and wrist (the grooved pegboard). They were impaired on most of the trials of a test of motor control of the hand and arm (the posting task) on a test of bi-manual motor action which assess co-ordination abilities (bead threading) and on uni-manual sequential tapping abilities (the tapping task), but not on simple uni-manual tapping or on bi-manual tapping. Patients with AS were not impaired on either of the tests of motor learning, the rotary pursuit and the mirror tracing tasks.

The cerebellum differs in its control of proximal and distal muscles. Patients with AS are impaired on tests involving both of these types of motor control without a bias towards proximal or distal muscles.

Movement abnormalities have not been considered a characteristic of autism or Asperger's Syndrome according to DSM-IV or ICD-10. In order to receive a clinical diagnosis, an individual is not required to show any motor abnormalities. Nevertheless, there is much evidence to suggest that movement abnormalities, particularly in the form of co-ordination problems. Clumsiness is common in this patient population. Asperger (1944) described a number of movement difficulties in his patients, including a lack of fluency in locomotion

and poor fine motor co-ordination skills. Numerous subsequent studies have identified movement abnormalities in the form of awkward or odd posture and poorly co-ordinated motor actions as being common features of autism and AS (Wing, 1981; Burgoyne and Wing, 1983; Ghadziuddin et al. 1992; Gillberg, 1989; Manjiviona and Prior, 1995; Tantam, 1988, 1991; Szatmari et al. 1989b; Hardan et al. 2003). Thus, individuals with AS may have difficulties with fine motor co-ordination and with accurate gross motor actions such as those required for the posting task.

Not all patients with AS have abnormal movements. Parents reported that twelve out of fourteen patients have difficulties with motor actions. Since they are not included as diagnostic criteria in either DSM IV or ICD-10, movement problems are not present in all individuals with AS. As patients with AS may have abnormalities in the cerebellum (see Chapter 6) and show a variety of motor problems, cerebellar abnormalities may be responsible for these motor difficulties. It may even be possible that the patients with AS who do not have movement problems may not have abnormalities in the cerebellum either. This possibility requires further investigation at an individual rather than group level to see whether there is any evidence to suggest a causal relation between cerebellar abnormality and movement problems in patients with AS. Individual analyses using VBM are however subject to a high number of false positives (see for example Salmond et al. 2003) and the results of such studies should therefore be interpreted with caution.

7.2.3 Summary of cognitive findings for patients with AS

Patients with AS had difficulties with verbal working memory, with some aspects of attention, spatial working memory and face matching, but were not impaired on tests of literacy, numeracy, copying and drawing, nor on the executive functions of set maintenance and set-shifting assessed by the face-sorting task.

(i) Verbal and spatial working memory

Working memory has been reported to be intact in autism (Minshew and Goldstein, 2001; Ozonoff and Strayer, 2001). Since the patients with AS studied here were impaired on verbal working memory and had some difficulties with spatial working memory, it is

possible that individuals with AS may have difficulties with some forms of working memory that are not problematic in individuals lower down the autistic spectrum. However, the fact that working memory is not a unitary function but that it is made up of several subcomponents means that different results are likely to be obtained depending on which component is assessed in a given study. Aspects of working memory are known to involve the frontal lobes; however functional imaging studies have recently implicated the cerebellum as being involved in working memory as well. A study by Morris et al. (1999) found that patients with AS had more substantial difficulties with spatial working memory than patients who had had regions of the frontal lobe excised. This finding is likely to be associated with the fact that patients with AS have abnormalities not only in the frontal lobes, but also in additional regions of the brain which may play a role in working memory.

(ii) **Attention**

Patients with AS had difficulties with one test of attention, the number cancellation task, which they took significantly longer to complete than did controls. Attention is not a unitary function, and as well as there being different types of attention, it is also likely that there are different ways in which attention can be used. One explanation for the problems encountered by the patients with AS on the number cancellation task may be that patients with AS have difficulty simultaneously processing multiple sensory inputs resulting in them being slower to attend to stimuli. They may not have problems with the actual process of attending to stimuli per se, but they may be slower than controls at focusing on a stimulus when there are other inputs simultaneously vying for their attention.

Attention is known to involve the frontal lobes and evidence suggests that the frontal lobes are abnormal in autism (Zilbovicius et al. 1995; Bailey et al. 1998; Carper and Courchesne 2000). However, no abnormalities in grey or white matter density, i.e. no structural damage, was found in the frontal lobes in this study (see Chapter 6). The problems with attention when faced with competing stimuli simultaneously which were observed in the present study may therefore be due to abnormalities in regions outside of the frontal lobes. A possible candidate may be the cerebellum. Functional imaging studies of normal subjects have shown activation in the cerebellum during attention tasks (Allen et al., 1997; Rees et

al., 1997; Le et al., 1998), and a recent fMRI study of patients with autism and controls showed that individuals with autism demonstrated significantly less activation in the cerebellar lobules thought to be involved in attention than did controls (Allen and Courchesne, 2003).

If the abnormalities in attention observed in individuals with AS are found to be associated with abnormalities in the cerebellum in these patients, then this would provide support for the possibility that the cerebellum may play a role in attention. Functional imaging studies are required to determine exactly which brain regions are involved in which aspects of attention. In addition, structural imaging studies are required in order to determine which of these brain regions are abnormal in patients with AS. Then, by looking at the performance of these patients on a variety of tasks which tap different aspects of attention, it should be possible to identify which areas of the brain are involved in which aspects of attention.

The possibility does remain that the problems with attention encountered by individuals with AS may be associated with damage to regions of the frontal lobe known to underlie attention processes, even though these regions of damage were not identified in the current study due to the group analysis methods. It is possible that certain individuals had damage to slightly different regions of the frontal lobes, but because there was limited overlap between these areas, they did not show up in the analyses. In order to overcome this problem, analysis of the MR data at an individual level is required, and this may be a good avenue to pursue in future investigations, as long as results are interpreted with caution given the large number of false positives generated by such methods.

(iii) **Visual perceptual face matching**

Patients with AS may be impaired on matching face-on photographs under different lighting conditions. There was a strong prediction that they would be impaired on this task because patients with autism have difficulties with the recognition of faces (Deruelle et al. 2004; Kracke, 1994; Szatmari et al., 1990). Problems on this task may be due to patients with AS focussing on local rather than global features of stimuli so that they process

particular local parts of information rather than integrating individual pieces of information into a coherent whole in order to establish meaning or context (Frith, 1989).

7.2.5 Summary of MRI findings for patients with AS

Patients with AS had increases in grey matter density in the cerebellum; middle and superior temporal gyri; regions adjacent to the amygdala and the hippocampus; the temporal lobe; regions adjacent to the cingulate sulcus and in the occipital lobe. They had decreases in grey matter density in regions inferior to the calcarine sulcus, and decreases in white matter density in the deep temporal white matter. There were no regions of abnormality in fractional anisotropy in the patients with AS compared to the controls.

The behavioural manifestations of AS are likely to be associated with abnormalities in a number of different brain regions or brain systems. The correlation analyses with the scores from neuropsychological tests showed that there were numerous significant correlations between regions of brain abnormality and performance on the bead threading task, the posting task, the sequential tapping and the word repetition task. Although the large number of significant results means that it is difficult to associate particular behavioural difficulties with particular regions of abnormality in the brain, these results do suggest that there may be significant associations between regions of brain abnormality in patients with AS and their performance on certain neuropsychological tests.

7.2.6 Evidence for cerebellar structure-function relations from patients with AS

(i) **The role of the cerebellum in working memory and attention:** Patients with AS were impaired on measures of working memory and attention which are known to be subserved by the frontal lobes. Analysis of the MRI scans did not reveal abnormalities in the frontal lobes of these patients. It is therefore possible that abnormalities in the connections between the cerebellum and the frontal lobes (or possibly in the cerebellum itself) may be associated with the difficulties in working memory and attention encountered by these patients. This possibility receives support from functional imaging studies which have found activation in the cerebellum during tasks tapping both working memory

(Paulesu et al.; 1993; 1995; Fiez et al., 1996; Desmond et al., 1997; Mathiak et al., 2004) and attention (Allen et al., 1997; Rees et al., 1997; Le et al., 1998).

(ii) **The cerebellum and social interaction:** One of the three principal characteristics of autism and AS is an impairment in social interaction. The cerebellum has been argued to be involved in the modulation of affect (Schmahmann and Sherman, 1998). Abnormalities in the cerebellum may result in abnormalities in the normal control or even understanding of emotions in patients with AS, which would likely result in an inability to engage in normal social interaction due to problems with the interpretation of emotions of both self and others. This possibility is in line with the failure to acquire a theory of mind explanation of autism (e.g. Baron-Cohen et al. 1985), although it is less severe, suggesting only that patients with AS may have difficulties in the interpretation and display of emotions, rather than in understanding the mind or thoughts of another person. Although the theory of mind explanation of autism has traditionally implicated abnormalities in the prefrontal cortex as the causative factor, it is also possible that abnormalities in the cerebellum may play a role. It may even be the case that the precise location of the abnormality is not all that important, but that damage to any structure within this connected brain system can have a negative impact on the acquisition of a theory of mind.

The extent of abnormalities of the cerebellum in individuals with AS remains unclear. The present study found an increase in grey matter density in lobules VIIb, VIIIa and VIIIb. However, given that AS involves abnormalities in the early connections of the brain, it is likely that there are also abnormalities in the neural networks both within the cerebellum and in the connections of the cerebellum to other brain areas. The current findings should thus be interpreted with caution. However, they have provided direction for future studies, which should aim to investigate further the possibility that some of the problems with social interaction, working memory and attention in individuals with AS may be associated with abnormalities in the cerebellum or in the connections of the cerebellum to other brain areas known to be involved in these functions. Section 7.5 gives further details on suggestions for future studies.

7.3 Neurodevelopmental versus acquired pathology of the cerebellum

A distinction should be drawn between brains affected by neurodevelopmental abnormalities and brains affected by acquired pathology (see Section 1.1.4). Those affected by neurodevelopmental abnormalities are thought to have been affected from the beginning of embryological development so that there are abnormalities in the connections and neural networks. Brains affected by acquired pathology, on the other hand, are thought to have had normal, intact, neural connectivity before the insult, and until the onset of the acquired pathology, they also had normal potential. The results of this thesis have shown that there are differences in the patterns of performance between patients with AS who have neurodevelopmental abnormalities and patients with PFT who have acquired pathology of the cerebellum. Although patients with AS have abnormalities in a number of brain areas in addition to the cerebellum, it was suggested in Chapter 4 that the differences in performance between patients with PFT and patients with AS may be associated with differences in the way that the two patient groups approach tasks. Patients with AS may not approach tasks in the conventional way (e.g. focusing on local rather than global features of a stimulus), due to abnormalities in the neural networks of the brain, whereas patients with PFT may approach tasks in the normal way, but may encounter difficulties with the normal completion of the tasks due to damage to the regions of the cerebellum that normally subserve a particular function, or to the connections between the cerebellum and other brain regions that subserve that function.

7.4 Limitations of the current study

(i) Patients with PFT:

a) **Small sample size:** There were insufficient patients for detailed comparisons between patients with damage to different regions of the cerebellum. A large cohort of patients with damage to variety of different lobules is needed in order that there can be a systematic investigation of localization of function. In addition, a large cohort would enable further investigations of the effects of age at surgery on behavioural outcome.

b) **Limited investigations at an individual level:** There were no investigations of motor and cognitive function or of changes in grey or white matter

density in individual patients, these investigations were all carried out at a group-level. However, as reported in Chapter 5, each patient with PFT had pathology of a different region and a different amount of the cerebellum. It would have been interesting to look at the associated effects of pathology of different regions of the cerebellum on different regions of the rest of the brain. In this way it may have been possible to determine whether individual patients who had difficulties with reading comprehension or the executive ability of set-shifting also had abnormalities in areas of the brain such as the frontal lobes which are known to subserve those functions, but which would not have shown up in group VBM analyses because the particular areas of abnormality did not overlap enough between the different patients.

c) **Measures of emotion:** There was no objective measure of emotion and modulation of affect. Parental reports indicated that a lack of control of emotions, particularly manifested in the form of temper-tantrums, was common after surgery for PFT. It would be interesting to document the emotional problems that may be associated with cerebellar damage. Possible standardized scales that could be used include the PAD Emotional Scales (Mehrabian, 1998), which look at the positive-negative affective quality of emotional states, at mental alertness and at the level of control versus lack of control. The Risk of Eruptive Violence Scale (REV – Mehrabian, 1997) is a measure used to identify angry and potentially violent individuals and as such could be used as a way in which to document the problems with anger control observed in the patients with PFT. Thus, in addition to parental questionnaires, standardized scales should be used in order to gain a more comprehensive picture of the emotional problems that may be associated with cerebellar damage.

(ii) Patients with AS:

a) **Heterogeneity of group** - AS is such a heterogeneous condition that it would be useful to look at an individual level as well as at a group level. AS

involves abnormalities in the earliest connections of the brain that result in a wide range of brain abnormalities. Patients may have difficulties with certain behaviours because of a particular pattern of brain abnormalities. However, other patients who don't have abnormalities in those same areas may not have the same behavioural difficulties. Therefore, although group studies are useful in order to gain an understanding of what the syndrome involves, case studies would be more useful for investigations of structure-function relations in the brain. A study on patients with autism and AS by Salmond et al. (2003) involved VBM analyses of single cases. They found that half of the individuals had abnormalities in the amygdala. In such an investigation, comparisons between the behaviours of patients with abnormalities in the amygdala and those without are likely to shed light on what functions the amygdala is involved in.

b) **Small sample size** – Given the level of heterogeneity in AS, it is important to include as many patients as possible in any investigation. The present study was limited in that only 14 patients with AS could be included and it is therefore possible that an accurate representation of individuals with AS may not have been gained.

7.5 Future investigations

This study has identified a number of areas that require further investigation and the most interesting avenues for future studies are outlined below:

7.5.1 Functions of the cerebellum

a) **Memory and attention in patients with PFT:** I found no impairment in working memory or in one aspect of attention in patients with PFT. However, the fact that previous patient studies and functional imaging studies have both implicated the cerebellum as being involved in these functions suggests that further investigation is required. The cerebellum sends projections to areas of the dorsal prefrontal cortex that are known to be involved in memory and attention and there is thus a neural substrate in place that may support a cerebellar role in these cognitive

functions. Both memory and attention are complex abilities that are made up of several subcomponents, each of which may have a different neural substrate and hence a different pathway of connections. The tests used in the current study only looked at one aspect of memory and of attention. Future studies should administer more complex tests in order to separate different aspects of memory or attention and in turn to determine whether there are any aspects of these abilities on which patients with PFT exhibit difficulties.

b) **Effects of cerebellar abnormality on behaviour in Asperger's Syndrome:** The current study flagged certain simple and complex uni- and bi-manual motor functions, verbal working memory, aspects of attention, spatial working memory and visual perceptual face matching as being problematic in patients with AS. In order to investigate whether any of these difficulties are related to the abnormalities in the cerebellum found in these patients, functional imaging studies should be carried out on patients for whom voxel-based morphometric (VBM) analyses have already been carried out so that the regions of abnormality in the cerebellum have already been identified. In this way it will be possible to determine what the functional implications of the abnormal cerebellum may be and by association, shed light on the functions normally subserved by the cerebellum.

7.5.2 Functional organization of the cerebellum

A comparison between the performance of patients with damage to different cerebellar lobules such as that carried out in Chapter 5 provides a promising means to investigate functional localisation in the cerebellum. However, much larger sample sizes are required in order that statistical analyses can be carried out. In addition, because the functional organization of the cerebellum is as yet unconfirmed, comparisons should also be made between patients with damage to different longitudinal zones of the cerebellum (the middle, intermediate and lateral zones – see Figure 1.5) in order to determine whether some cerebellar functions may rely on a zonal rather than lobular organisation.

7.5.3 Investigating compensation mechanisms in the developing brain

As detailed in Section 1.1, it is believed that after pathology of the brain during development, compensation mechanisms come into play that attempt to rescue functions subserved by the damaged region. By carrying out functional imaging studies on patients with resected posterior fossa tumours, it should be possible to investigate whether additional brain areas are active in patients with PFT compared to healthy controls during tasks normally subserved by the cerebellum (for example simple finger-tapping) and thus to determine the extent to which compensation mechanisms may drive other brain areas to take over the functions normally subserved by the cerebellum.

7.6 Conclusion: linking cerebellar structure and function

The investigation of motor and cognitive function in patients with PFT and patients with AS has revealed that the cerebellum plays an important role in motor actions and is also involved in the modulation of affect. Contrary to previous evidence, however, the results suggested that the cerebellum does not in fact play an integral role in cognitive functions.

Different cerebellar lobules seem to be involved in different behavioural functions. Further work is needed in order to characterize the pattern of functional organization of the cerebellum.

The results of the MR investigations for the patients with PFT provided preliminary evidence that damage to certain areas of the cerebellum (in particular the right cerebellar hemisphere) may result in decreases in grey and white matter densities in other brain areas within cerebellar systems (the thalamus, hypothalamus and globus pallidus). In addition to providing evidence that the cerebellum, thalamus, hypothalamus and globus pallidus form parts of common functional systems, these findings suggest that pathology of one brain area is unlikely to affect that area alone, but is likely to have knock-on effects on other regions within the same functional brain system.

The results of the MR investigations for the patients with AS showed that there were abnormalities in grey and white matter densities in a number of different brain regions, one

of which was the cerebellum. These findings provide further evidence that the behavioural manifestations of AS are associated with abnormalities in a number of different brain structures and possibly functional brain systems and leave open the possibility that some of the behavioural difficulties encountered by patients with AS may be associated with abnormalities in the cerebellum.

REFERENCES

Abell, F., Krams, M., Ashburner, J., Passingham, R., Friston, K., Frackowiak, R., Happe, F., Frith, C. and Frith, U. (1999). The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. *Neuroreport.* 10, 1647-51

Ackermann, H., Graber, S., Hertrich, I. and Daum, I. (1997). Categorical speech perception in cerebellar disorders. *Brain and Language* 60, 323-331

Ackermann, H., Wildgruber, D., Daum, I. and Grodd, W. (1998). Does the cerebellum contribute to cognitive aspects of speech production? A functional magnetic resonance imaging (fMRI) study in humans. *Neuroscience Letters* 247, 187-190

Akshoomoff, N.A. and Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behavioural Neuroscience* 106, 731-8.

Allen, G.I., Buxton, R.B., Wong, E.C. and Courchesne, E. (1997). Attentional activation of the cerebellum independent of motor involvement. *Science* 275, 1940-3

Allen, G.I. and Courchesne, E. (2003). Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism. *American Journal of Psychiatry* 160, 262-273

Allen, G.I. and Tsukahara, N. (1974). Cerebrocerebellar communication systems. *Physiological Review* 54, 957-1006.

Andreasen, N.C., O'Leary, D.S., Arndt, S., Cizadlo, T., Hurtig, R., Rezai, K., Watkins, G.L., Ponto, L.L. and Hichwa, R.D. (1995). Short-term and long-term verbal memory: a positron emission tomography study. *Proceedings of the National Academy of Sciences, U.S.A.* 92, 5111-5

Andreasen, N.C., O'Leary, D.S., Flaum, M., Nopoulos, P., Watkins, G.L., Boles Ponto, L.L. and Hichwa, R.D. (1997). Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. *Lancet* 349, 1730-1734

Angevine, J.B., Mancall, E.L. and Yakovlev, P.I. (1961). "The Human Cerebellum: An atlas of gross topography in serial sections". Little, Brown and Company, Boston

Annett, M. (1970). The growth of manual preference and speed. *British Journal of Psychology* 61, 545-558

Armstrong, C.L., Gyato, K., Awadalla, A.W., Lustig, R. and Tochner, Z.A. (2003). A critical review of the clinical effects of therapeutic irradiation damage to the brain: the roots of controversy. *Neuropsychological Review* 14, 65-86

Ashburner, J. and Friston, K.J. (2000). Voxel-based morphometry--the methods. *Neuroimage* 11, 805-821

Asperger, H. (1944). Die "autistischen Psychopathen" im Kindesalter. *Arch fur Psychiatrie und Nervenkrankheiten* 117, 76-136

Aylward, E.H., Minshew, N.J., Goldstein, G., Honeycutt, N.A., Augustine, A.M., Yates, K.O., Barta, P.E. and Pearlson, G.D. (1999). MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology* 53, 2145-50
Azzone, G.F. (2003). The dual biological identity of human beings and the naturalization of morality. *Historical Philosophy of Life Sciences* 25, 211-241

Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M and Lantos P. (1998). A clinicopathological study of autism. *Brain* 121, 889-905

Baker, J., Gibson, A., Glickstein, M. and Stein, J. (1976). Visual cells in the pontine nuclei of the cat. *Journal of Physiology* 255, 415-433

Barker, C., Pistrang, N. and Elliott, R. (2002). *Research methods in clinical psychology.* John Wiley and Sons, Ltd, England.

Baron-Cohen, S., Leslie, A.M. and Frith, U. (1985). Does the autistic child have a "theory of mind"? *Cognition* 21, 37-46

Baron-Cohen, S., Ring, H., Moriarty, J., Schmitz, B., Costa, D. and Ell, P. (1994). Recognition of mental state terms. Clinical findings in children with autism and a functional neuroimaging study of normal adults. *British Journal of Psychiatry* 165, 640-649

Barth, P.G. (1993). Pontocerebellar hypoplasias. An overview of a group of inherited neurodegenerative disorders with fetal onset. *Brain development* 15, 411-422

Bauman, M.L. and Kemper, T.L. (1985). Histoanatomic observation of the brain in early infantile autism. *Neurology* 35, 866-874

Bauman, M.L. and Kemper, T.L. (1986). Developmental cerebellar abnormalities: A consistent finding in early infantile autism. *Neurology* 36 [Suppl.1], 190

Bauman, M.L. and Kemper, T.L. (1990). Limbic and cerebellar abnormalities are also present in an autistic child of normal intelligence. *Neurology* 36 [Suppl.1], 359

Bauman, M.L. and Kemper, T.L. (1994). Neuroanatomic observations of the brain in autism. In: *The neurobiology of autism*, p.119-145. Baltimore: John Hopkins UP.

Bechara, A., Damasio, A.R., Damasio, H. and Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50, 7-15

Beery, K.E. (1967). *Developmental Test of Visual-Motor Integration. Administration and Scoring manual.* Chicago: Follett Publishing Company.

Beery, K.E. (1982). *Revised Administration, Scoring, and Teaching Manual for the Developmental Test of Visual-Motor Integration.* Cleveland: Modern Curriculum Press

Beery, K.E. (1989). *The Visual-Motor Integration Test. Administration, Scoring and Teaching Manual.* Cleveland: Modern Curriculum Press.

Beery, K.E. (1997). *The Visual-Motor Integration Test (4th Ed.). Administration, Scoring and Teaching Manual.* Austin, TX: Pro-Ed.

Belton, E., Salmond, C.H., Watkins, K.E., Vargha-Khadem, F. and Gadian, D.G. (2003). Bilateral brain abnormalities associated with dominantly inherited verbal and orofacial dyspraxia. *Human brain mapping* 18, 194-200

Bengtsson, S.L., Ehrsson, H.H., Forssberg, H. and Ullen, F. (2004). Dissociating brain regions controlling the temporal and ordinal structure of learned movement sequences. *European Journal of Neuroscience* 19, 2591-2602

Benton, A.L. and Van Allen, M.W. (1968). Impairment in facial recognition in patients with cerebral disease. *Cortex* 4, 344-358.

Benton, A.L., Varney, N.R. and Hamsher, K. D. (1978). Visuospatial judgment: A clinical test. *Archives of Neurology* 35, 364-367

Benton, A.L., Hamsher, K. de S., Varney, N.R. and Spreen, O. (1983). *Contributions to neuropsychological assessment: A clinical manual.* New York: Oxford University Press.

Benton, A.L., Sivan, A.B., Hamsher, K. de S., Varney, N.R. and Spreen, O. (1994). *Contributions to Neuropsychological Assessment. A Clinical Manual (2nd ed.).* New York: Oxford University Press.

Bennetto, L., Pennington, B.F. and Rogers, S.J. (1996). Intact and impaired memory functions in autism. *Child Development* 67, 1816-1835

Berman, K.F., Ostrem, J.L., Randolph, C., Gold, J., Goldberg, T.E., Coppola, R., Carson, R.E., Herscovitch, P. and Weinberger, D.R. (1995). Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: a positron emission tomography study. *Neuropsychologia* 33, 1027-1046

Berquin, P.C., Giedd, J.N., Jacobsen, L.K., Hamburger, S.D., Krain, A.L., Rapoport, J.L. and Castellanos, F.X. (1998). Cerebellum in attention-deficit hyperactivity disorder - A morphometric MRI study. *Neurology* 50, 1087-1093

Berthier, M.L., Starkstein, S.E. and Leiguarda, R. (1990). Developmental cortical anomalies in Asperger's syndrome: neuroradiological findings in two patients. *Journal of Neuropsychiatry and Clinical Neuroscience* 2, 197-201

Bertolino, A., Frye, M., Callicott, J.H., Mattay, V.S., Rakow, R., Shelton-Repella, J., Post, R. and Weinberger, D.R. (2003). Neuronal pathology in the hippocampal area of patients with bipolar disorder: a study with proton magnetic resonance spectroscopic imaging. *Biological Psychiatry* 53, 906-913

Bishop, D.V.M. (1993). Annotation: Autism, executive functions and theory of mind: a neuropsychological perspective. *Journal of Child Psychology and Psychiatry* 34, 279-293.

Blinkenberg, M., Bonde, C., Holm, S., Svarer, C., Andersen, J., Paulson, O.B. and Law, I. (1996). Rate dependence of regional cerebral activation during performance of a repetitive motor task: a PET study. *Journal of Cerebral Blood Flow Metabolism* 16, 794-803

Blumberg, H.P., Stern, E., Martinez, D., Ricketts, S., de Asis, J., White, T., Epstein, J., McBride, P.A., Eidelberg, D., Kocsis, J.H. and Silbersweig, D.A. (2000). Increased anterior cingulate and

caudate activity in bipolar mania. *Biological Psychiatry* 48, 1045-1052

Bolk, L. (1906). *Das Cerebellum der Säugetiere.* Jena G. Fisher

Bolton, P.F., Macdonald, H., Pickles, A., Rios, P., Goode, S., Crowson, M., Bailey, A. and Rutter, M. (1994). A case-control family history study of autism. *Journal of Child Psychology and Psychiatry* 35, 877-900

Boltshauser, E. (2004). Cerebellum-small brain but large confusion: a review of selected cerebellar malformations and disruptions. *American Journal of Medical Genetics* 126A, 376-385

Botez-Marquard, T., Bard, C., Leveille, J. and Botez, M.I. (2001). A severe frontal-parietal lobe syndrome following cerebellar damage. *European Journal of Neurology* 8, 347-353

Boucher, J. (1981). Immediate free recall in early childhood autism: another point of behavioural similarity with the amnesic syndrome. *British Journal of Psychology* 72, 211-215

Boucher, J. (2003). Language development in autism. *International Journal of Pediatric Otorhinolaryngology* 67, S159-163

Boucher, J. and Lewis, V. (1989). Memory impairments and communication in relatively able autistic children. *Journal of Child Psychology and Psychiatry* 30, 99-122

Boucher, J. and Warrington, E.K. (1976). Memory deficits in early infantile autism: some similarities to the amnesic syndrome. *British Journal of Psychology* 67, 73-87

Bowler, D.M. (1992). "Theory of mind" in Asperger's syndrome. *Journal of Child Psychology and Psychiatry* 33, 877-893

Bowler, D.M., Matthews, N.J. and Gardiner, J.M. (1997). Asperger's syndrome and memory: similarity to autism but not amnesia. *Neuropsychologia* 35, 65-70

Bradley, L. and Bryant, P.E. (1983). Categorising sounds and learning to read: a causal connection. *Nature* 301, 419–421

Braitenberg, V., Heck, D. and Sultan, F. (1997). The detection and generation of sequences as a key to cerebellar function: experiments and theory. *Behavioural and Brain Sciences* 20, 229-45

Brambilla, P., Harenski, K., Nicoletti, M., Sassi, R.B., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S. and Soares, J.C. (2003). MRI investigation of temporal lobe structures in bipolar patients. *Journal of Psychiatry Research* 37, 287-295

Brodal, P. (1968a). The corticopontine projection in the cat. Demonstration of a somatotopically organized projection from the primary sensorimotor cortex. *Experimental Brain Research* 5, 210-234

Brodal, P. (1968b). The corticopontine projection in the cat. Demonstration of a somatotopically organized projection from the second somatosensory cortex. *Archives of Italian Biology* 106, 310-312

Brodal, A. (1971). Anatomical organization of vestibular nuclei. *Arkh. Anat. Gistol. Embriol.* 60, 5-22

Brodal, P. (1982). Further observations on the cerebellar projections from the pontine nuclei and the nucleus reticularis tegmenti pontis in the rhesus monkey. *Journal of Comparative Neurology* 204, 44-55

Brodal, P. (1987). Organisation of cerebropontocerebellar connections as studied with anteriograde and retrograde transport of HRP-WGA in the cat. In King, J.S., (Ed.). *New Concepts in Cerebellar Neurobiology* p.151-182 New York, Liss Publisher

Brooks, V.B. and Thach, W.T. (1981) Cerebellar control of posture and movement. In: Brooks, V.B. (Ed.): *Handbook of Physiology, Sec 1, The nervous system, Vol 2, Motor control* p.877-946. Bethesda, MD: American Physiological Society.

Brown, W.E., Eliez, S., Menon, V., Rumsey, J.M., White, C.D. and Reiss, A.L. (2001). Preliminary evidence of widespread morphological variations of the brain in dyslexia. *Neurology* 27, 781-783

Bruininks, R.H. (1978). *Bruininks-Oseretsky Test of Motor Proficiency: Manual.* American Guidance Serv. Inc. USA

Buchel, C., Raedler, T., Sommer, M., Sach, M., Weiller, C. and Koch, M.A. (2004). White matter asymmetry in the human brain: a diffusion tensor MRI study. *Cerebral Cortex* 14, 945-951

Buckner, R.L., Petersen, S.E., Ojemann, J.G., Miezin, F.M., Squire, L.R. and Raichle, M.E. (1995). Functional anatomical studies of explicit and implicit memory retrieval tasks. *Journal of Neuroscience* 15, 12-29

Burgoyne, E. and Wing, L. (1983). Identical triplets with Asperger's syndrome. *Journal of Psychiatry* 143, 261-265

Burne, R.A., Mihailoff, G.A. and Woodward, D.J. (1978). Visual corticopontine input to the paraflocculus: a combined autoradiographic and horseradish peroxidase study. *Brain Research* 143, 139-146

Bushnell, I.W.R., Sai, F. and Mullin, J.T. (1989). Neonatal recognition of the mother face. *British Journal of Developmental Psychology* 7, 3-15.

Carpenter, M.B. (1976). *Human Neuroanatomy.* Baltimore: Williams and Wilkins Co.

Carper, R.A. and Courchesne, E. (2000). Inverse correlation between frontal lobe and cerebellum sizes in children with autism. *Brain* 123, 836-844

Casey, A.T., Kimmings, E.J., Kleinlugtebeld, A.D., Taylor, W.A., Harkness, W.F. and Hayward, R.D. (1997). The long-term outlook for hydrocephalus in childhood. A ten-year cohort study of 155 patients. *Paediatric Neurosurgery* 27, 63-70

Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Vauss, Y.C., Snell, J.W., Lange, N., Kaysen, D., Krain, A.L., Ritchie, G.F., Rajapakse, J.C. and Rapoport, J.L. (1996). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Archives of General Psychiatry* 53, 607-616

Castro-Sierra, E., Chico-Ponce De Leon, F., Gordillo-Dominguez, L.F. and Raya-Gutierrez, R. (2003). Surgery of tumors of the cerebellum and prefrontal cortex, and sensory memory and motor planning disturbances in children. *Children's Nervous System* 19, 736-743

Chapman, H., Gavrilescu, M., Wang, H., Kean, M., Egan, G. and Castiello, U. (2002). Posteior parietal cortex control of reach-to-grasp movements in humans. *European Journal of Neuroscience* 15, 2037-2042

Corsi, P.M. (1972). *Human memory and the medial temporal region of the brain.* Thesis at McGill University, Montreal

Courchesne, E., Press, G.A. and Yeung-Courchesne, R. (1993). Parietal lobe abnormalities detected with MR in patients with infantile autism. *American Journal of Roentgenology* 160, 387-93.

Courchesne, E., Karns, C.M., Davis, H.R., Ziccardi, R., Carper, R.A., Tigue, Z.D., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A.J., Pizzo, S., Schreibman, L., Haas, R.H., Akshoomoff, N.A. and Courchesne, R.Y. (2001). Unusual brain growth patterns in early life in patients with autistic disorder - An MRI study. *Neurology* 57, 245-254

Curtis, C.E. and D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences* 7, 415-423

Dasen, P. (1978). Strong and weak universals: sensori-motor intelligence and concrete operations. In Warren, N. (Ed.). *Studies in cross-cultural psychology.* Academic Press, London

Dawson, G. and Zanolli, K. (2003). Early intervention and brain plasticity in autism. *Novartis Foundation Symposium* 251, 266-274

Debaere, F., Wenderoth, N., Sunaert, S., Van Hecke, P. and Swinnen, S.P. (2004). Cerebellar and premotor function in bimanual coordination: parametric neural responses to spatiotemporal complexity and cycling frequency. *Neuroimage* 21, 1416-1427

DelBello, M.P., Strakowski, S.M., Zimmerman, M.E., Hawkins, J.M. and Sax, K.W. (1999). MRI analysis of the cerebellum in bipolar disorder: A pilot study. *Neuropsychopharmacology* 21, 63-68

Deruelle, C., Rondan, C., Gepner, B. and Tardif, C. (2004). Spatial frequency and face processing in children with autism and Asperger syndrome. *Journal of Autism and Developmental Disorders* 34, 199-210

Desmond, J.E., Gabrieli, J.D., Wagner, A.D., Ginier, B.L. and Glover, G.H. (1997). Lobular patterns of cerebellar activationi n verbal working-memory and finger-tapping tasks as revealed by functional MRI. *Journal of Neuroscience* 17, 9675-9685

Desmond, J.E., Gabrieli, J.D. and Glover, G.H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. *Neuroimage* 7, 368-376

Dobbinson, S., Perkins, M.R. and Boucher, J. (1998). Structural patterns in conversations with a woman who has autism. *Journal of Communication Disorders* 31, 113-133

Dreher, J.C. and Grafman, J. (2002). The roles of the cerebellum and basal ganglia in timing and error prediction. *European Journal of Neuroscience* 16, 1609-1619

Eccles, J.C. (1977). *The understanding of the brain.* New York: McGraw-Hill.

Eckert, M.A., Leonard, C.M., Richards, T.L., Aylward, E.H., Thomson, J. and Berninger, V.W. (2003). Anatomical correlates of dyslexia: frontal and cerebellar findings. *Brain* 126, 482-494

Eden, G.F., Van Meter, J.W., Rumsey, J.M. and Zeffiro, T.A. (1996). The visual deficit theory of developmental dyslexia. *NeuroImage* 4, S108–S117

Eliassen, J.C., Souza, T. and Sanes, J.N. (2001). Human brain activation accompanying explicitly directed movement sequence learning. *Experimental Brain Research* 141, 269-280

Ellerman, J.M., Flament, D., Kim, S-G., Fu O-G, Merkle, H., Ebner, T.J. and Urgurbil, K. (1994). Spatial patterns of functional activation of the cerebellum investigated using high field (4T) MRI. *NMR Biomed.* 7, 63-68

Elman, J.L., Bates, E.A., Johnson, M.H., Karmiloff-Smith, A., Parisi, D. and Plunkett, K. (1996). *Rethinking Innateness: A connectionist perspective on development.* MIT press, Cambridge, Massachusetts

Exner, C., Koschack, J. and Irle, E. (2002). The differential role of premotor frontal cortex and basal ganglia in motor sequence learning: evidence from focal basal ganglia lesions. *Learning and memory* 9, 376-386

Fabbro F., Moretti, R. and Bava, A. (2000). Language impairments in patients with cerebellar lesions. *Journal of Neurolinguistics* 13, 173-188.

Farrant, A., Blades, M. and Boucher, J. (1998). Source monitoring by children with autism. *Journal of Autism and Developmental Disorders* 28, 43-50

Fatemi, S.H., Halt, A.R., Stary, J.M., Kanodia, R., Schulz, S.C. and Realmuto, G.R. (2002). Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biological Psychiatry* 15, 805-10

Felician, O., Romaiguere, P., Anton, J.L., Nazarian, B., Roth, M., Poncet, M. and Roll, J.P. (2004). The role of human left superior parietal lobule in body part localization. *Annals of Neurology* 55, 749-751

Fellows, S.J., Ernst, J., Schwarz, M., Topper, R. and Noth, J. (2001). Precision grip deficits in cerebellar disorders in man. *Clinical Neurophysiology* 112, 1793-1802

Fiez, J.A., Raife, E.A., Balota, D.A., Schwarz, J.P., Raichle, M.E. and Petersen, S.E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. *Journal of Neuroscience* 16, 808-822

Finch, A.J., Nicolson, R.I. and Fawcett, A.J. (2002). Evidence for a neuroanatomical difference within the olivo-cerebellar pathway of adults with dyslexia. *Cortex* 38, 529-39

Flourens, M.J.P. (1824). *"Recherches Expérimentales sur les Propriétés et les Fonctions du*

Système Nerveux dans les Animaux Vertébrés," 1st ed. Crevot, Paris

Fox, P.T., Raichle, M.E. and Thach, W.T. (1985). Functional mapping of the human cerebellum with positron emission tomography. *Proceedings of the National Academy of Science U.S.A.* 82, 7462-7466

Frith, U. (1989). *Autism: Explaining the Enigma.* Oxford: Basil Blackwell

Frith, U. (2003). *Autism: Explaining the enigma.* (2nd ed.) Oxford: Blackwells.

Frith, C.D., Friston, K., Liddle, P.F. and Frackowiak, R.S.J. (1991). Willed action and the prefrtonal cortex in man: a study with PET. *Proceedings of the Royal Society of London, Series B* 244, 241-246

Frostig, M., Lefever, D.W. and Whittlesey, J.R.B. (1966). *Administration and Scoring Manual for the Frostig Developmental Test of Visual Perception. Palo Alto, CA: Consulting Psychologists Press.*

Gans, A. (1924). Beitrag zue Kenntnis des Aufbaus des Nucleus Dentatus aus zwei Teilen namentlich auf Grund von Untersuchungen mit der Eisenreaktion. Ztschr. f. d. ges. *Neurol. Psychiatry* 93, 750-755

Garnet, M.S. and Attwood, A.J. (1997). The Australian Scale for Asperger's Syndrome. In Attwood, A.J. (Ed.) *Asperger's Syndrome: A Guide for Parents and Professionals.* Taylor & Francis Group

Garth, J., Anderson, V. and Wrennall, J. (1997). Executive functions following moderate to severe frontal lobe injury: impact of injury and age at injury. *Pediatric Rehabilitation* 1, 99-108

Gasparini, M., Di Piero, V., Ciccarelli, O., Cacioppo, M.M., Pantano, P. and Lenzi, G.L. (1999). Linguistic impairment after right cerebellar stroke: a case report. *European Journal of Neurology* 6, 353-6

Gathercole, S.E. and Baddeley, A.D. (1989). Evaluation of the role of phonological STM in the development of vocabulary in children: A longitudinal study. *Journal of Memory and Language* 28, 200-213

Gentry, L.R., Godersky, J.C. and Thompson, B. (1988). MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. *American Journal of Roentgenology* 150, 663-672

George, A.P., Kuehn, S.M., Vassilyadi, M., Richards, P.M., Parlow, S.E., Keene, D.L. and Ventureyra, E.C. (2003). Cognitive sequelae in children with posterior fossa tumors. *Pediatric Neurology* 28, 42-47

Geurts, H.M., Verte, S., Oosterlaan, J., Roeyers, H. and Sergeant, J.A. (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *Journal of Child Psychology and Psychiatry* 45, 836-854

Ghaziuddin, M., Tsai, L. and Ghaziuddin, N. (1992). Brief report: A reappraisal of clumsiness as a diagnostic feature of Asperger's syndrome. *Journal of Autism and Developmental Disorders* 22, 651-656

Ghaziuddin, M., Butler, E., Tsai, L. and Ghaziuddin, N. (1994). Is clumsiness a marker for Asperger syndrome? *Journal of Intellectual Disability Research* 38, 519-527

Gibson, A., Baker, J., Mower, G. and Glickstein, M. (1978). Corticopontine cells in area 18 of the cat. *Journal of Neurophysiology* 41, 484-495

Gibson, A.R., Robinson, F.R., Alam, J. and Houk, J.C. (1987). Somatotopic alignment between climbing fiber input and nuclear output of the cat intermediate cerebellum. *Journal of Comparative Neurology* 260, 362-377

Gillberg, C. (1989). Asperger's syndrome in 23 Swedish children. *Developmental Medicine and Child Neurology* 31, 520-531

Gillberg, C. (1991). Clinical and Neurobiological aspects of Asperger's Syndrome in six family studies. In Frith, U. (Ed.) *Autism and Asperger's Syndrome.* Cambridge: Cambridge University Press 122-146

Glickstein, M. (1994). Cerebellar agenesis. *Brain* 117, 1209-12

Glickstein, M. (1998). Cerebellum and the sensory guidance of movement. *Novartis Foundation Symposium* 218, 252-266

Glickstein, M., King, R.A. and Stein, J.F. (1971). The visual input to neurones in N. pontis. *Journal of Physiology* 218, 79P

Glickstein, M., Stein, J. and King, R.A. (1972). Visual input to the pontine nuclei. *Science* 178, 1110-1111

Glickstein, M., May, J.G. 3rd and Mercier, B.E. (1985). Corticopontine projection in the macaque: the distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. *Journal of Comparative Neurology* 15, 343-359

Glickstein, M., Gerrits, N., Kralj-Hans, I., Mercier, B., Stein, J. and Voogd, J. (1994). Visual pontocerebellar projections in the macaque. *Journal of Comparative Neurology* 349, 51-72

Glickstein, M., Buchbinder, S and May, J.L. (1998). Visual control of the arm, the wrist and the fingers: pathways through the brain. *Neuropsychologia* 36, 981-1001.

Gray, H. (1918). *Anatomy of the human body.* Lea and Febiger, Philadelphia.

Gray, H., Bannister, L.H., Berry, M.M. and Williams, P.L. (2000). *Gray's anatomy* (38th Edition). Churchill Livinstone.

Green, D., Baird, G., Barnett, A.L., Henderson, L., Huber, J. and Henderson, S.E. (2002). The severity and nature of motor impairment in Asperger's syndrome: a comparison with specific developmental disorder of motor function. *Journal of Child Psychology and Psychiatry* 43, 655-668

Groenewegen, H.J. (2003). The basal ganglia and motor control. *Neural Plasticity* 10, 107-120

Happe, F. (1994). *Autism: An introduction to psychological theory.* London, UCL Press

Happe, F. (1999). Autism: Cognitive deficit or cognitive style? *Trends in Cognitive Sciences* 3, 216-222

Hardan, A.Y., Minshew, N.J. and Keshavan, M.S. (2000). Corpus callosum size in autism. *Neurology* 55, 1033-1036

Hardan, A.Y., Minshew, N.J., Harenski, K. and Keshavan, M.S. (2001). Posterior fossa magnetic resonance imaging in autism. *Journal of the American Academy of Child and Adolescent Psychiatry* 40, 666-72

Hardan, A.Y., Kilpatrick, M., Keshavan, M.S. and Minshew, N.J. (2003). Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. *Journal of Child Neurology* 18, 317-324

Haznedar, M.M., Buchsbaum, M.S., Wei, T.C., Hof, P.R., Cartwright, C., Bienstock, C.A. and Hollander, E. (2000). Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. *American Journal of Psychiatry* 157, 1994-2001

Heath, R.G. (1977). Modulation of emotion with a brain pacemaker. Treatment for intractable psychiatric illness. *Journal of Nervous Mental Disorders* 165, 300-317

Hebb, D. (1949). *The organization of behaviour: A neuropsychological theory.* Lawrence Erlbaum Associates, Mahwah, New Jersey.

Henderson, S.E. and Sugden, D. (1992). *The Movement Assessment Battery for Children.* London: The Psychological Corporation.

Hetherington, R., Dennis, M. and Spiegler, B. (2000). Perception and estimation of time in long-term survivors of childhood posterior fossa tumors. *Journal of the International Neuropsychological Society* 6, 682-92

Hill, D.E., Yeo, R.A., Campbell, R.A., Hart, B., Vigil, J. and Brooks, W. (2003). Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology* 17, 496-506

Hill, E.L. and Frith, U. (2003). Understanding autism: insights from mind and brain. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 358, 281-289

Hoddevik, G.H. (1977). The pontine projection to the flocculonodular lobe and the paraflocculus studied by means of retrograde axonal transport of horseradish peroxidase in the rabbit. *Experimental Brain Research* 30, 511-526

Hodges, J.R. (1994). *Cognitive assessment for clinicians.* Oxford: Oxford University Press

Holmes, G. (1917). The symptoms of acute cerebellar injuries due to gunshot wounds. *Brain* 40, 461-535

Holttum, J.R., Minshew, N.J., Sanders, R.S. and Phillips, N.E. (1992). Magnetic resonance imaging of the posterior fossa in autism. *Biological Psychiatry* 32, 1091-101

Howard, M.A., Cowell, P.E., Boucher, J., Broks, P., Mayes, A., Farrant, A. and Roberts, N. (2000). Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. *Neuroreport* 11, 2931-2935

Hughes, C., Russell, J. and Robbins, T.W. (1994). Evidence for executive dysfunction in autism. *Neuropsychologia* 32, 477-492

Immisch, I., Quintern, J. and Straube, A. (2003). Unilateral cerebellar lesions influence arm movements bilaterally. *Neuroreport* 14, 837-840
Inoue, K., Kawashima, R., Satoh, K., Kinomura, S., Goto, R., Koyama, M., Sugiura, M., Ito, M. and Fukuda, H. (1998). *Journal of Neurophysiology* 79, 117-125

Isaacs, E.B. and Vargha-Khadem, F. (1989). Differential cause of development of spatial and verbal memory span: a normative study. *British Journal of Developmental Psychology* 7, 377-380

Ivry, R.B., Keele, S.W. and Diener, H.C. (1988). Dissociation of the lateral and medial cerebellum in movement timing and movement execution. *Experimental Brain Research* 73, 167-180

Jansen, J. and Brodal, A. (1940). Experimental studies on the intrinsic fibers of the cerebellum II the cortico-nuclear projection. *Journal of Comparative Neurology* 73, 267-321.

Jansen, J. and Brodal, A. (1958). Das Kleinhirn. In "*Handbuch der mikroskopischen anatomie des menschen, Vol.4*" (v. Mollendorff, Ed.) p.674-916. Berlin: Springer

Jenkins, I.H., Frackowiak, R.S. (1993). Functional studies of the human cerebellum with positron emission tomography. *Revue Neurologique* (Paris) 149, 647-653

Jolliffe, T. and Baron-Cohen, S. (1997). Are people with autism and Asperger syndrome faster than normals on the embedded figure test? *Journal of Child Psychology and Psychiatry* 38, 527-534

Jordan, R. and Powell, S. (1995). *Understanding and teaching children with autism.* Wiley publishers

Jueptner, M., Ottinger, S., Fellows, S.J., Adamschewski, J., Flerich, L., Muller, S.P., Diener, H.C., Thilmann, A.F. and Weiller, C. (1997). The relevance of sensory input for the cerebellar control of movements. *Neuroimage* 5, 41-8

Jueptner, M. and Weiller, C. (1998). A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. *Brain* 121, 1437-49

Jueptner, M. and Krukenberg, M. (2001). Motor system: cortex, basal ganglia, and cerebellum. *Neuroimaging Clinics of North America* 11, 203-219

Kalil, K. (1979). Projections of the cerebellar and dorsal column nuclei upon the inferior olive in the rhesus monkey: an autoradiographic study. *Journal of Comparative Neurology* 188, 43-62

Kandel, E.R., Schwartz, J.H. and Jessel, T.M. (2000). *Principles of Neural Science, 4th edn.* London: McGraw-Hill.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child* 2, 217-250

Kawashima, R., Itoh, H., Ono, S., Satoh, K., Furumoto, S., Gotoh, R., Koyama, M., Yoshioka, S., Takahashi, T., Takahashi, K., Yanagisawa, T. and Fukuda, H. (1996). Changes in regional cerebral blood flow during self-paced arm and finger movements. A PET study. *Brain Research* 716, 141-148.

Kawato, M. and Gomi, H. (1992). A computational model of four regions of the cerebellum based on feedback-error learning. *Biological Cybernetics* 68, 95-103

Kerbeshian, J. and Burd, l. (1986). Asperger's syndrome and Tourette syndrome: the case of the pinball wizard. *British Journal of Psychiatry* 148, 731-736

Kleiman, M.D., Neff, S. and Rosman, N.P. (1992). The brain in infantile autism: are posterior fossa structures abnormal? *Neurology* 42, 753-60

Klin, A., Volkmar, F.R., Sparrow, S.S., Cicchetti, D.V. and Rourke, B.P. (1995). Validity and neuropsychological characterization of Asperger's syndrome: Convergence with Non-verbal learning disabilities syndrome. *Journal of Child Psychology and Psychiatry* 36, 1127-1139

Kracke, I. (1994). Developmental prosopagnosia in Asperger's Syndrome: presentation and discussion of an individual case. *Developmental Medicine and Child Neurology* 36, 873-886

Kuhlenbeck, H. (1975). *The central nervous system of vertebrates Volume 4.* Basel: S. Karger.

Kuhtz-Buschbeck, J.P., Mahnkopf, C., Holzknecht, C., Siebner, H., Ulmer, S. and Jansen, O. (2003). Effector-independent representations of simple and complex imagined finger movements: a combined fMRI and TMS study. *European Journal of Neuroscience* 18, 3375-3387

Laforce, R. Jr and Doyon, J. (2002). Differential role for the striatum and cerebellum in response to novel movements using a motor learning paradigm. *Neuropsychologia* 40, 512-517

Lainhart, J.E., Piven, J., Wzorek, M., Landa, R., Santangelo, S., Coon, H., and Folstein, S. (1997) Macrocephaly in children and adults with autism. *Journal of the American Academy of Child and Adolescent Psychiatry* 36:282-290.

Larsell, O. (1947). The development of the cerebellum in man in relation to its comparative anatomy. *Journal of Comparative Neurology* 87, 85-129

Lashley, K.S. (1924). Studies of cerebral function in learning. VI. The theory that synaptic resistance is reduced by the passage of the nerve impulse. Psychological Review 31, 369-375. In J. Orbach, *The Neuropsychological Theories of Lashley and Hebb* (1998) MD: University Press of America

Lashley, K. S. (1929). *Brain Mechanisms and Intelligence.* Chicago: University of Chicago Press. Reprinted in Dover (Ed.) 1963, with Introduction by D. O. Hebb

Le, T.H., Pardo, J.V. and Hu, X. (1998). 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. *Journal of Neurophysiology* 79, 1535-1548

Le Bihan, D., Mangin, J.F., Poupon, C., Clark, C.A., Pappata, S., Molko, N. and Chabriat, H. (2001). Diffusion tensor imaging: concepts and applications. *Journal of Magnetic Resonance Imaging* 13, 534-546

Leestma, J.E. and Torres, J.V. (2000). Unappreciated agenesis of cerebellum in an adult: case report of a 38-year-old man. *American Journal of Forensic Medical Pathology* 21, 155-161

Leiner, H.C., Leiner, A.L. and Dow, R.S. (1986). Does the cerebellum contribute to mental skills? *Behavioural Neuroscience* 100, 443-454

Leiner, H.C., Leiner, A.L. and Dow, R.S. (1993). Cognitive and language functions of the human cerebellum. *Trends in Neuroscience* 16, 444-7

Leiner, H.C. and Leiner, A.L. (1997). How fibers subserve computing capabilities: similarities between brains and machines. *International Review of Neurobiology* 41, 535-553

Levin, H.S., Song, J., Scheibel, R.S., Fletcher, J.M., Harward, H., Lilly, M. and Goldstein,F. (1997). Concept formation and problem-solving following closed head injury in children. *Journal of the International Neuropsychological Society* 3, 598-607

Levin,H.S., Song, J., Ewing-Cobbs, L. and Roberson, G. (2001). Porteus Maze performance following traumatic brain injury in children. *Neuropsychology* 15, 557-567

Levisohn, L., Cronin-Golomb, A. and Schmahmann, J.D. (2000). Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain* 123, 1041-50

Levitt, J.J., McCarley, R.W., Nestor, P.G., Petrescu, C., Donnino, R., Hirayasu, Y., Kikinis, R., Jolesz, F.A. and Shenton, M.E. (1999). Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: Clinical and cognitive correlates. *American Journal of Psychiatry* 156, 1105-1107

Levy, R. and Goldman-Rakic, P.S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental brain research* 133, 23-32

Loveland, K.A., Tunali-Kotoski, B., Chen, Y.R., Ortegon, J., Pearson, D.A., Brelsford, K.A. and Gibbs, M.C. (1997). Emotion recognition in autism: verbal and nonverbal information. *Developmental Psychopathology* 9, 579-593

Luria, A. (1975). *The working brain.* Penguin Press

Lyoo, I.K., Noam, G.G., Lee, C.K., Lee, H.K., Kennedy, B.P. and Renshaw, P.F. (1996). The corpus callosum and lateral ventricles in children with attention-deficit hyperactivity disorder: a brain magnetic resonance imaging study. *Biological Psychiatry* 40, 1060-1063

Mackenna, B.R. and Callander, R. (1990). *Ilustrated Physiology.* Churchill Livingstone.

Manjiviona, J. and Prior, M. (1995). Comparison of Asperger's syndrome and high functioning autistic children on a test of motor impairment. *Journal of Autism and Developmental Disorders* 25, 23-41

Manni, E and Petrosini, L. (2004). A century of cerebellar somatotopy: a debated representation. *Nature Reviews Neuroscience* 5, 241-249

Manto, M., Setta, F., Jacquy, J. and Godaux, E. (1999). Cerebellar decompensation following a stroke in contralateral posterior parietal cortex. *Journal of the Neurological Sciences* 167, 117-120

Marien, P., Engelborghs, S., Pickut, B.A. and De Deyn, P.P. (2000) Aphasia following cerebellar damage: fact or fallacy? *Journal of Neurolinguistics* 13, 145-171

Marr, D. (1969). A theory of cerebellar cortex. *Journal of Physiology* 202, 437-70

Martin, A., Haxby, J.V., Lalonde, F.M., Wiggs, C.L. and Ungerleider, L.G. (1995). Discrete cortical regions associated with knowledge of color and knowledge of action. *Science* 270, 102-105

Mason, C.R., Miller, L.E., Baker, J.F. and Houk, J.C. (1998). Organisation of reaching and grasping movements in the primate cerebellar nuclei as revealed by focal muscimol inactivations. *Journal of Neurophysiology* 79, 537-554

Mataro, M., Garcia-Sanchez, C., Junque, C., Estevez-Gonzalez, A. and Pujol, J. (1997). Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. *Archives of Neurology* 54, 963-968

Mathiak, K., Hertrich, I., Grodd, W. and Ackermann, H. (2002). Cerebellum and speech perception: a functional magnetic resonance imaging study. *Journal of Cognitive Neuroscience* 14, 902-912

Mathiak, K., Hertrich, I., Grodd, W. and Ackermann, H. (2004). Discrimination of temporal information at the cerebellum: functional magnetic resonance imaging of nonverbal auditory memory. *Neuroimage* 21, 154-162

Matthews, J.N., Altman, D.G., Campbell, M.J. and Royston, P. (1990). Analysis of serial measurements in medical research. *British Medical Journal* 300, 230-235

McAlonan, G.M., Daly, E., Kumari, V., Critchley, H.D., van Amelsvoort, T., Suckling, J., Simmons, A., Sigmundsson, T., Greenwood, K., Russell, A., Schmitz, N., Happe, F., Howlin, P. and Murphy, D.G. (2002). Brain anatomy and sensorimotor gating in Asperger's syndrome. *Brain* 125, 1594-606

McCrory, E., Frith, U., Brunswick, N. and Price, C. (2000). Abnormal functional activation during a simple word repetition task: A PET study of adult dyslexics. *Journal of Cognitive Neuroscience* 12, 753-762

Mehrabian, A. (1997). Relations among personality scales of aggression, violence, and empathy. Validational evidence bearing on the Risk of Eruptive Violence Scale. *Aggressive Behaviour* 23, 433-445

Mehrabian, A. (1998). Manual for a comprehensive system of measures of emotional states: The PAD Model.

Meltzoff, A.N. and Moore, M.K. (1977). Imitation of facial and manual gestures by human neonates. *Science* 198, 74-78

Mesulam, M.-M. (1985). *Principles of Behavioural Neurology*. Philadelphia: F.A. Davis

Meyer, B.U., Roricht, S. and Machetanz, J. (1994). Reduction of corticospinal excitability by magnetic stimulation over the cerebellum in patients with large defects of one cerebellar hemisphere. *Electroencephalography and clinical Neurophysiology* 93, 372-379

Miall, R.C., Weir, D.J., Wolpert, D.M. and Stein, J.F. (1993). Is the Cerebellum a Smith Predictor? *Journal of Motor Behaviour* 25, 203-216

Miall, R.C., Imamizu, H. and Miyauchi, S. (2000). Activation of the cerebellum in co-ordinated eye and hand tracking movements: an fMRI study. *Experimental Brain Research* 135, 22-33

Miall, R.C., Reckess, G.Z. and Imamizu, H. (2001). The cerebellum coordinates eye and hand tracking movements. *Nature Neuroscience* 4, 638-644

Middleton, F.A. and Strick, P.L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* 266, 458-461

Middleton, F.A. and Strick, P.L. (1997). Cerebellar output channels. *International Review of Neurobiology* 41, 61-82

Middleton, F.A. and Strick, P.L. (2001). Cerebellar projections to the prefrontal cortex of the primate. *Journal of Neuroscience* 21, 700-712

Miller, J.N. and Ozonoff, S. (2000). The external validity of Asperger disorder: lack of evidence from the domain of neuropsychology. *Journal of Abnormal Psychology* 109, 227-238

Milner, B. (1963). Effects of different brain lesions on card sorting. *Archives of Neurology* 9, 90-100

Milner, A.D., Perrett, D.I., Johnston, R.S., Benson, P.J., Jordan, T.R., Heeley, D.W., Bettucci, D., Mortara, F., Mutani, R., Terazzi, E. and Davidson, D.L.W. (1991). Perception and action in 'visual form agnosia'. *Brain* 114, 405-28

Minshew, N.J., Goldstein, G., Dombrowski, S.M., Panchalingam, K. and Pettegrew, J.W. (1993). A preliminary 31P MRS study of autism: evidence for undersynthesis and increased degradation of brain membranes. *Biological Psychiatry* 33, 762-773

Minshew, N.J. and Goldstein, G. (2001). The pattern of intact and impaired memory functions in autism. *Journal of Child Psychology and Psychiatry* 42, 1095-1101

Miyahara, M., Tsujii, M., Hori, M., Nakanishi, K., Kageyama, H. and Sugiyama, T. (1997). Brief report: motor incoordination in children with Asperger syndrome and learning disabilities. *Journal of Autism and Developmental Disorders* 27, 595-603

Morris, R.G., Rowe, A., Fox, N., Feigenbaum, J.D., Miotto, E.C. and Howlin, P. (1999). Spatial working memory in Asperger's syndrome and in patients with focal frontal and temporal lobe lesions. *Brain and Cognition* 41, 9-26

Mottron, L., Burack, J.A., Stauder, J.E. and Robaey, P. (1999). Perceptual processing among high-functioning persons with autism. *Journal of Child Psychology and Psychiatry* 40, 203-211

Mottron, L., Burack, J.A., Iarocci, G., Belleville, S. and Enns, J.T. (2003). Locally oriented perception with intact global processing among adolescents with high-functioning autism: evidence from multiple paradigms. *Journal of Child Psychology and Psychiatry* 44, 904-913

Mower, G., Gibson, A., Robinson, F., Stein, J. and Glickstein, M. (1980). Visual pontocerebellar projections in the cat. *Journal of Neurophysiology* 43, 355-366

Mugnaini, E. and Oertel, W.H. (1985). GABAergic neurons and terminals in the rat CNS as revealed by GABA-immuno- histochemistry. In: Bjorklund, A., Hökfelt, T (Eds.): *GABA and Neuropeptides in the CNS: The Handboodk of Chemical Neuroanatomy* Part 1, vol. 4. Elsevier, Amserdam, pp. 541-543

Muller, R.A., Kleinhans, N., Pierce, K., Kemmotsu, N. and Courchesne, E. (2002). Functional MRI of motor sequence acquisition: effects of learning stage and performance. *Cognitive Brain Research* 14, 277-293

Muratori, F., Cesari, A. and Casella, C. (2001). Autism and cerebellum - An unusual finding with MRI *Panminerva Medica* 43, 311-315

Murphy, D.G., Critchley, H.D., Schmitz, N., McAlonan, G., Van Amelsvoort, T., Robertson, D., Daly, E., Rowe, A., Russell, A., Simmons, A., Murphy, K.C. and Howlin, P. (2002). Asperger Syndrome: a proton magnetic resonance spectroscopy study of brain. *Archives of General Psychiatry* 59, 885-891

Nawrot, M. and Rizzo, M. (1995). Motion perception deficits from midline cerebellar lesions in human. *Vision Research* 35, 723-732

Nawrot, M. and Rizzo, M. (1998). Chronic motion perception deficits from midline cerebellar lesions in human. *Vision Research* 38, 2219-2224

Nicolson, R.I. and Fawcett, A.J. (1993). Children with dyslexia automatize temporal skills more slowly. *Annals of the New York Academy of Science* 682, 390-392

Nicolson, R.I., Fawcett, A.J. and Dean, P. (2001). Developmental dyslexia: the cerebellar deficit hypothesis. *Trends in Neuroscience* 24, 508-511

Nieminen-von Wendt, T., Salonen, O., Vanhala, R., Kulomaki, T., von Wendt, L. and Autti, T. (2002). A quantitative controlled MRI study of the brain in 28 persons with Asperger Syndrome. *International Journal of Cicumpolar Health* 61, Suppl. 2, 22-35

Nitschke, M.F., Kleinschmidt, A., Wessel, K. and Frahm, J. (1996). Somatotopic motor representation in the human anterior cerebellum - A high-resolution functional MRI study. *Brain* 119, 1023-1029

Nitschke, M.F., Stavrou, G., Melchert, U.H., Erdmann, C., Petersen, D., Wessel, K. and Heide, W. (2003). Modulation of cerebellar activation by predictive and non-predictive sequential finger movements. *Cerebellum* 2, 233-240

Noad, R., Narayanan, K.R., Howlett, T., Lincoln, N.B. and Page, R.C. (2004). Evaluation of the effect of radiotherapy for pituitary tumours on cognitive function and quality of life. *Clinical Oncology* 16, 233-237

Nyberg, L., Petersson, K.M., Nilsson, L.G., Sandblom, J., Aberg, C. and Ingvar, M. (2001). Reactivation of motor brain areas during explicit memory for actions. *Neuroimage* 14, 521-528

Ohnishi, T., Matsuda, H., Hashimoto, T., Kunihiro, T., Nishikawa, M., Uema, T. and Sasaki, M. (2000). Abnormal regional cerebral blood flow in childhood autism. *Brain* 123, 1838-1844

Oktem, F., Diren, B, Karaagaoglu, E. and Anlar, B. (2001). Functional magnetic resonance imaging in children with Asperger's Syndrome. *Journal of Child Neurology* 16, 253-256

Ozonoff, S., Pennington, B.F. and Rogers, S.J. (1991). Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *Journal of Child Psychology and Psychiatry* 32, 1081-1105

Ozonoff, S. and Strayer, D.L. (2001). Further evidence of intact working memory in autism. *Journal of Autism and Developmental Disorders* 31, 257-263

Ozonoff, S., Cook, I., Coon, H., Dawson, G., Joseph, R.M., Klin, A., McMahon, W.M., Minshew, N., Munson, J.A., Pennington, B.F., Rogers, S.J., Spence, M.A., Tager-Flusberg, H., Volkmar, F.R. and Wrathall, D. (2004). Performance on Cambridge Neuropsychological Test Automated Battery subtests sensitive to frontal lobe function in people with autistic disorder: evidence from the Collaborative Programs of Excellence in Autism network. *Journal of Autism and Developmental Disorders* 34, 139-150

Packer, R. (2002). *Medulloblastoma.* www.childhoodbraintumour.org/02revision Medullo.htm

Pakkenberg, B. (1993). Total nerve cell number in neocortex in chronic schizophrenics and controls estimated using optical disectors. *Biological Psychiatry* 34, 768-772

Paller, K.A., Ranganath, C., Gonsalves, B., LaBar, K.S., Parrish, T.B., Gitelman, D.R., Mesulam, M.M. and Reber, P.J. (2003). Neural correlates of person recognition. *Learning and Memory* 10, 253-260

Paulesu, E., Frith, C.D. and Frackowiak, R.S. (1993). The neural correlates of the verbal component of working memory. *Nature* 362, 342-345

Paulesu, E., Connelly, A., Frith, C.D., Friston, K.J., Heather, J., Myers, R., Gadian, D.G. and Frackowiak, R.S. (1995). Functional MR imaging correlations with positron emission tomography. Initial experience using a cognitive activation paradigm on verbal working memory. *Neuroimaging Clin. N. America* 5, 207-225

Penhune, V.B., Zattore, R.J. and Evans, A.C. (1998). Cerebellar contributions to motor timing: a PET study of auditory and visual rhythm reproduction. *Journal of Cognitive Neuroscience* 10, 752-765

Petersen, S.E., Fox, P.T., Posner, MI., Mintum, M.A. and Raichle, M.E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331, 585-589

Petersen, S.E., Fox, P.T., Posner, MI., Mintum, M.A. and Raichle, M.E. (1989). Positrong emission tomographic studies of the processing of single words. *Journal of Cognitive Neuroscience* 1, 153-170

Petersen, S.E. and Fiez, J.A. (1993). The processing of single words studied with positron emission tomography. *Annual Review of Neuroscience* 16, 509-30

Piaget, J. (1954). *The construction of reality in the child.* NewYork, Basic Books

Piaget, J. (1966). *The origins of intelligence in children.* Routledge and Kegan Paul, UK

Piaget, J. (1971). *Biology and Knowledge.* Edinburgh University Press

Pickering, S.J., Gathercole, S.E. and Peaker, S.M. (1998). Verbal and visuospatial short-term memory in children: evidence for common and distinct mechanisms. *Memory and Cognition* 26, 1117-1130

Piven, J., Saliba, K., Bailey, J. and Arndt, S. (1997). An MRI study of autism: the cerebellum revisited. *Neurology* 49, 546-51

Piven, J., Bailey, J., Ranson, B.J. and Arndt, S. (1998). No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. *Journal of Autism and developmental Disorders* 28, 105-110

Price, C.J., Wise, R.J.S., Warburton, E.A., Moore, C.J., Howard, D., Patternson, K., Frackowiak, R.S.J. and Friston, K.J. (1996). Hearing and saying: The functional neuroanatomy of auditory word processing. *Brain* 119, 919-931

Pujol, J., Lopez-Sala, A., Deus, J., Cardoner, N., Sebastian-Galles, N., Conesa, G. and Capdevila, A. (2002). The lateral asymmetry of the human brain studied by volumetric magnetic resonance imaging. *Neuroimage* 17, 670-679

Rae, C., Harasty, J.A., Dzendrowskyj, T.E., Talcott, J.B., Simpson, J.M., Blamiro, A.M., Dixon, R.M., Lee, M.A., Thompson, C.H., Styles, P., Richardson, A.J. and Stein, J.F. (2002). Cerebellar morphology in developmental dyslexia. *Neuropsychologia* 40, 1285-1292

Raichle, M.E., Fiez, J.A., Videen, T.O., MacLeod, A.M., Pardo, J.V., Fox, P.T. and Petersen, S.E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex* 4, 8-26

Rakic, P. (1991). Experimental manipulation of cerebral cortical areas in primates. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 331, 291-294

Ramnani, N. and Miall, C. (2001). Expanding cerebellar horizons. *Trends in Cognitive Sciences* 5, 135-136

Ramus, F., Pidgeon, E. and Frith, U. (2003). The relationship between motor control and phonology in dyslexic children. *Journal of Child Psychology and Psychiatry* 44, 712-722

Raymond, G.V., Bauman, M.L. and Kemper, T.L. (1996). Hippocampus in autism: a Golgi analysis. *Acta Neuropathologica* 91, 117-119

Rees, G., Frackowiak, R. and Frith, C. (1997). Two modulatory effects of attention that mediate object categorization in human cortex. *Science* 275, 835-838

Rinehart, N.J., Bradshaw, J.L, Moss, S.A., Brereton, A.V. and Tonge, B.J (2001). A deficit in shifting attention present in high functioning autism but not Asperger's disorder. *Autism* 5, 67-80

Rinehart, N.J., Bradshaw, J.L, Tonge, B.J., Brereton, A.V. and Bellgrove, M.A. (2002). A neurobehavioural examination of individuals with high-functioning autism and Asperger's disorder using a fronto-striatal model of dysfunction. *Behavioural and Cognitive Neuroscience reviews* 1, 164-177

Ritvo ER, Freeman BJ, Scheibel AB, Duong T, Robinson H, Guthrie D and Ritvo A. (1986). Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC autopsy research report. *American Journal of Psychiatry* 143, 862-866

Riva, D. and Giorgi, C. (2000). The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 123, 1051-61

Rivkin, M.J., Vajapeyam, S., Hutton, C., Weiler, M.L., Hall, E.K., Wolraich, D.A., Yoo, S.S., Mulkern, R.V., Forbes, P.W., Wolff, P.H. and Waber, D.P. (2003). A functional magnetic resonance imaging study of paced finger tapping in children. *Paediatric Neurology* 28, 89-95

Roberts, R.C., Conley, R., Kung, L., Peretti, F.J. and Chute, D.J. (1996). Reduced striatal spine size in schizophrenia: a postmortem ultrastructural study. *Neuroreport* 7, 1214-1218

Robinson, F.R., Cohen, J.L., May, J., Sestokas, A.K. and Glickstein, M. (1984). Cerebellar targets of visual pontine cells in the cat. *Journal of Comparative Neurology* 223, 471-482

Rolando, L. (1809). *"Saggio sopra la vera struttura del cerbell dell'uome e degli animali e sopra le funzoini del sistema nervosa."* Stampeia da S.S.R.M. Privilegiata, Sassari (quoted in Dow and Moruzzi, 1958)

Rosina, A. and Provini, L. (1984). Pontocerebellar system linking the two hemispheres by intracerebellar branching. *Brain Research* 296, 365-369

Rowe, J., Toni, I., Josephs, O., Frackowiak, R.S.J. and Passingham, R.E. (2000). Separate fronto-parietal systems for selection versus maintenance within working memory. *Science* 288, 1656-1660

Rowe, J. and Passingham, R.E. (2001). Working memory for location and time: activity in prefrontal area 46 relates to selection rather than to maintenance in memory. *Neuroimage* 14, 77-86

Ruigrok, T.J. and Voogd, J. (1990). Cerebellar nucleo-olivary projections in the rat: an anterograde tracing study with Phaseolus vulgaris-leucoagglutinin (PHA-L). *Journal of Comparative Neurology* 298, 315-333

Ruigrok, T.J. and Voogd, J. (2000). Organization of projections from the inferior olive to the cerebellar nuclei in the rat. *Journal of Comparative Neurology* 426, 209-228

Russell, J., Jarrold, C. and Henry, L. (1996). Working memory in children with autism and with moderate learning difficulties. *Journal of Child Psychology and Psychiatry* 37, 673-686.

Rust, J. (1996). *Wechsler Objective Numerical Dimensions.* The Psychological Corporation: London

Rust, J., Golombok, S. and Trickey, G. (1993). *Wechsler Objective Reading Dimensions.* The Psychological Corporation: London

Sadato, N., Campbell, G., Ibanez, V., Deiber, M. and Hallett, M. (1996). Complexity affects regional cerebral blood flow change during sequential finger movements. *Journal of Neuroscience* 16, 2691-2700

Sadato, N., Ibanez, V., Deiber, M.P., Campbell, G., Leonardo, M. and Hallett, M. (1996). Frequency-dependent changes of regional cerebral blood flow during finger movements. *Journal of cerebral blood flow metabolism* 16, 23-33

Saitoh, O., Courchesne, E., Egaas, B., Lincoln, A.J. and Schreibman, L. (1995). Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. *Neurology* 45, 317-324

Sallet, P.C., Elkis, H., Alves, T.M., Oliveira, J.R., Sassi, E., Campi de Castro, C., Busatto, G.F. and Gattaz, W.F. (2003). Reduced cortical folding in schizophrenia: an MRI morphometric study. *American Journal of Psychiatry* 160, 1606-1613

Salmond, C.H., Ashburner, J., Vargha-Khadem, F., Gadian, D.G. and Friston, K.J. (2000). Detecting bilateral abnormalities with voxel-based morphometry. *Human Brain Mapping* 11, 223-232

Salmond, C.H., de Haan, M., Friston, K.J., Gadian, D.G. and Vargha-Khadem, F. (2003). Investigating individual differences in brain abnormalities in autism. *Philosophical Transactions of the Royal Society of London B (Biological Sciences)* 358, 405-13

Sanes, J.N., Dimitrov, B. and Hallett, M. (1990). Motor learning in patients with cerebellar dysfunction. *Brain* 113, 103-120

Sarnat, H.B. (1992). *Cerebral dysgenesis: Embryology and clinical expression.* New York, Oxford: Oxford University Press.

Schmahmann, J.D. (1991). An emerging concept: The cerebellar contribution to higher function. *Archives of Neurology* 48, 1178-1187

Schmahmann, J.D. and Sherman, J.C. (1998). The cerebellar cognitive affective syndrome. *Brain* 121, 561-579

Schmahmann, J.D., Doyon, J., Toga, A.W., Petrides, M. and Evans, A.C. (2000). *MRI Atlas of the Human Cerebellum.* Academic Press

Schmahmann, J.D. (2000). Cerebellum and Brainstem. In: Toga, A. and Mazziotta, J. (Eds.) *Brain Mapping. The Systems.* San Diego, Academic Press. P.207-259

Schweighofer, N., Arbib, M.A. and Kawato, M. (1998). Role of the cerebellum in reaching movements in humans. I. Distributed inverse dynamics control. *European Journal of Neuroscience* 10, 86-94

Scott, R.B., Stoodley, C.J., Anslow, P., Paul, C., Stein, J.F., Sugden, E.M. and Mitchell, C.D. (2001). Lateralized cognitive deficits in children following cerebellar lesions. *Developmental Medicine and Child Neurology* 43, 685-91

Selemon, L.D., Rajkowska, G. and Goldman-Rakic, P.S. (1998). Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional, stereologic counting method. *Journal of Comparative Neurology* 392, 402-412

Semrud-Clikeman, M., Filipek, P.A., Biederman, J., Steingard, R., Kennedy, D., Renshaw, P. and Bekken, K. (1994). Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. *Journal of the American Academy of Child and Adolescent Psychiatry* 33, 875-881

Sener, R.N. and Jenkins, J.R. (1993). Subtotal agenesis of the cerebellum in an adult. MRI demonstration. *Neuroradiology* 35, 286-7

Shah, A. and Frith, U. (1983). An islet of ability in autism: a research note. *Journal of Child Psychology and Psychiatry* 24, 613-620.

Shallice, T. (1988). *From neuropsychology to mental structure.* Cambridge, Cambridge University Press

Shankweiler, D., Crain, S., Katz, L., Fowler, A.E., Liberman, A.M., Brady, S.A., Thornton, R., Lindquist, E., Dreyer, L., Fletcher, J.M., Stuebing, K.K., Shaywitz, S.E. and Shaywitz, B.A. (1995). Cognitive profiles of reading-disabled children: Comparison of language skills in phonology, morphology, and syntax. *Psychological Science* 6, 149-156.

Shibata, T. and Ioannides, A.A. (2001). Contribution of the human superior parietal lobule to spatial selection process: an MEG study. *Brain Research* 897, 164-168

Shimony, J.S., McKinstry, R.C., Akbudak, E., Aronovitz, J.A., Snyder, A.Z., Lori, N.F., Cull, T.S. and Conturo, T.E. (1999). Quantitative diffusion-tensor anisotropy brain MR imaging: normative human data and anatomic analysis. *Radiology* 212, 770-784

Shu, B.C., Lung, F.W., Tien, A.Y. and Chen, B.C. (2001). Executive function deficits in non-retarded autistic children. *Autism* 5, 165-174

Silveri, M.C., Leggio, M.G. and Molinari, M. (1994). The cerebellum contributes to linguistic production: a case of agrammatic speech. *Neurology* 44, 2047-2050

Silveri, M.C., Di-Betta, A.M., Filippini, V., Leggio, M.G. and Molinari, M. (1998). Verbal short-term store-rehearsal system and the cerebellum. Evidence from a patient with a right cerebellar lesion. *Brain* 121, 2175-2187

Sigman, M. and Capps, L. (1997). *Children with Autism: A developmental perspective.* Cambridge, MA: Harvard University Press

Sisodiya, S.M., Free, S.L., Stevens, J.M., Fish, D.R. and Shorvon, S.D. (1995). Widespread cerebral structural changes in patients with cortical dysgenesis and epilepsy. *Brain* 118, 1039-50

Skoyles, J.R. (2002). Is autism due to cerebral-cerebellum disconnection? *Medical Hypotheses* 58, 332-6

Snider, R.S. (1952). Interrelations of cerebellum and brainstem. *Res Publ.-Assoc. Nerv. Res. Ment. Dis.* 30, 267-281

Sparks, B.F., Friedman, S.D., Shaw, D.W., Aylward, E.H., Echelard, D., Artru, A.A., Maravilla, K.R., Giedd, J.N., Munson, J., Dawson, G. and Dager, S.R. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology* 59, 184-92

Stanovich, K.E. (1988). The right and wrong places to look for the cognitive locus of reading disability. *Annals of Dyslexia* 38, 154–177

Stein, J.F. and Glickstein, M. (1992). Role of the cerebellum in visual guidance of movement. *Physiological Review* 72, 967-1017

Stein, J. and Walsh, V. (1997). To see but not to read; the magnocellular theory of dyslexia. *Trends in Neuroscience* 20, 147–152

Steinlin, M., Imfeld, S., Zulauf, P., Boltshauser, E., Lovblad, K.O., Ridolfi Luthy, A., Perrig, W. and Kaufmann, F. (2003). Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. *Brain* 126, 1998-2008

Stiles, J. (2000). Neural plasticity and cognitive development. *Developmental Neuropsychology* 18, 237-272

Stilling, B. (1864). *Untersuchungen über den Bau des kleinen Gehirns des Menschen.* Kassel.

Stoeckel, M.C., Weder, B., Binkofski, F., Choi, H.J., Amunts, K., Pieperhoff, P., Shah, N.J. and Seitz, R.J. (2004). Left and right superior parietal lobule in tactile object discrimination. *European Journal of Neuroscience* 19, 1067-1072

Stott, D.H., Moyes, F.A. and Henderson, S.E. (1984). *The test of motor impairment.* The psychological corporation

Straube, A., Scheuerer, W. and Eggert, T. (1997). Unilateral cerebellar lesions affect initiation of ipsilateral smooth pursuit eye movements in humans. *Annals of Neurology* 42, 891-898

Stuss, D.T., Levine, B., Alexander, M.P., Hong, J., Palumbo, C., Hamer, L., Murphy, K.J. and Izukawa, D. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia* 38, 388-402

Szatmari, P., Bartolucci, G. and Bremner, R. (1989b). Asperger's syndrome and autism: comparison of early history and outcome. *Developmental Medicine and Child Neurology* 31, 709-720

Szatmari, P., Tuff, L., Finlayson, M.A.J. and Bartolucci, G. (1990). Asperger's syndrome and autism: Neurocognitive aspects. *Journal of the American Academy of Child and Adolescent Psychiatry* 29, 130-136

Tager-Flusberg, H. (1996). Brief report: current theory and research on language and communication in autism. *Journal of Autism and Developmental Disorders* 26, 169-172

Tallal, P., Miller, S. and Fitch, R.H. (1993). Neurobiological basis of speech-a case for the pre-eminence of temporal processing. *Annals of the New York Acadamy of Science* 682, 27–47

Tantam, D. (1988). Lifelong eccentricity and social isolation II Asperger's syndrome and autism: Or schizoid personality disorder. *British Journal of Psychiatry* 153, 783-791

Tantam, D. (1991). Asperger's syndrome in adulthood. In U. Frith (Ed.), *Autism and Asperger's syndrome.* Cambridge: Cambridge University Press

Tecco, J.M., Wuilmart, P., Lasseaux, L., Widler, D., Damhaut, P., Goldman, S. and Gilles, C. (1998). Cerebello-thalamo-cerebral diaschisis: a case report. *Journal of Neuroimaging* 8, 115-116

Thach, W.T., Goodkin, H.P. and Keating, J.G. (1992). The cerebellum and the adaptive coordination of movement. *Annual Review of Neuroscience* 15, 403-42

Thickbroom, G.W., Byrnes, M.L. and Mastaglia, F.L. (2003). Dual representation of the hand in the cerebellum: activation with voluntary and passive finger movement. *Neuroimage* 18, 670-674

Timmann, D., Watts, S. and Hore, J. (2000). Causes of left-right ball inaccuracy in overarm throws made by cerebellar patients. *Experimental Brain Research* 130, 441-452

Timmann, D., Dimitrova, A., Hein-Kropp, C., Wilhelm, H. and Dorfler, A. (2003). Cerebellar agenesis: clinical, neuropsychological and MR findings. *Neurocase* 9, 402-413

Trevarthen, C., Aitken, K., Papoudi, D. and Robarts, J. (1998). *Children with autism: Diagnosis and interventions to meet their needs* (2nd edition). Jessica Kingsley Publishers, London.

Tsatsanis, K.D., Rourke, B.P., Klin, A., Volkmar, F.R., Cicchetti, D. and Schultz, R.T. (2003). Reduced thalamic volume in high-functioning individuals with autism. *Biological Psychiatry* 15, 121-9

Upton, D. and Corcoran, R. (1995). The role of the right temporal lobe in card sorting: a case study. *Cortex* 31, 405-409

Van Kan, P.L., Houk, J.C. and Gibson, A.R. (1993). Output organization of intermediate cerebellum of the monkey. *Journal of Neurophysiology* 69, 57-73

Vargha-Khadem, F., Isaacs, E. and Muter, V. (1994). A review of cognitive outcome after unilateral lesions sustained during childhood. *Journal of Child Neurology* 9 Suppl. 2, 67-73

Vargha-Khadem, F. and Mishkin, M. (1997). Speech and Language outcome after hemispherectomy in childhood. In *Paediatric Epilepsy Syndromes and Their Surgical Treatment*, I. Tuxhorn, H. Holthausen and H.E. Boenigk (Eds.). John Libbey & Company Ltd. Medical Books, p. 774-784;

Vargha-Khadem, F., Carr, L.J., Isaacs, E., Brett, E., Adams, C. and Mishkin, M. (1997). Onset of speech after left hemispherectomy in a nine-year-old boy. *Brain* 120, 159-182

Vargha-Khadem F., Isaacs E., Watkins K. and Mishkin M. (2000). Ontogenetic specialization of hemispheric function. In *Intractable Focal Epilepsy: Medical and Surgical Treatment*, J.M. Oxbury, C.E. Polkey, and M. Duchowney (Eds.). Harcourt Publishers, London, p 405-418

Vargha-Khadem, F., Salmond, C.H., Watkins, K.E., Friston, K.J., Gadian, D.G. and Mishkin, M. (2003). Developmental amnesia: effect of age at injury. *Proceedings of the National Academy of Science USA* 100, 10055-10060

Voogd, J. (2003). The human cerebellum. *Journal of Chemical Neuroanatomy* 26, 243-252

Voogd, J. and Glickstein, M. (1998). The anatomy of the cerebellum. *Trends in Neuroscience* 21, 370-375

Wechsler, D. (1986). *Wechsler Adult Intelligence Scale – Revised UK Edition.* Sidcup, Kent: The Psychological Corporation

Wechsler, D. (1992). *Wechsler Intelligence Scale for Children – Third UK Edition.* Sidcup, Kent: The Psychological Corporation

Weimer, A.K., Schatz, A.M., Lincoln, A., Ballantyne, A.O. and Trauner, D.A. (2001). "Motor" impairment in Asperger syndrome: evidence for a deficit in proprioception. *Journal of Developmental Behaviour and Pediatrics* 22, 92-101

Weintraub, S. and Mesulam, M.-M. (1985). Mental state assessment of young and elderly adults in behavioural neurology. In: *Principles of Behavioural Neurology.* Mesulam, M.-M. (Ed.). Philadelphia: F.A. Davis

Wek, S.R. and Husak, W.S. (1989). Distributed and massed practice effects on motor performance and learning of autistic children. *Perception and motor skills* 68, 107-113

Whiting, B.A. and Barton, R.A. (2003). The evolution of the cortico-cerebellar complex in primates: anatomical connections predict patterns of correlated evolution. *Journal of Human Evolution* 44, 3-10

Wiese, H., Stude, P., Nebel, K. Osenberg, D., Volzke, V., Ischebeck, W., Stolke, D., Diener, H.C. and Keidel, M. (2004). Impaired movement-related potentials in acute frontal traumatic brain injury. *Clinical Neurophysiology* 115, 289-298

Wing, L. (1976). Diagnosis, clinical description and prognosis. In L. Wing (Ed.), *Early childhood autism: Clinical, educational and social aspects* (2nd ed., p. 15-64). Oxford: Pergamon

Wing, L. (1981). Asperger's syndrome: A clinical account. *Psychological Medicine* 11, 115-129

Wing, L. (1988). The continuum of autistic characteristics. In E. Schopler and G. Mesibov (Eds.), *Diagnosis and assessment in autism,* p.91-110. New York: Plenum

Wing, L. (1996). *The autistic spectrum: A guide for parents and professionals.* London: Constable

Wing, L. and Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. *Journal of Autism and Developmental Disorders* 9, 11-29

World Health Organisation (1992). *The ICD-10 Classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines.* Geneva: WHO

Xiang, H., Lin, C., Ma, X., Zhang, Z., Bower, J.M., Weng, X. and Gao, J.H. (2003). Involvement of the cerebellum in semantic discrimination: an fMRI study. *Human Brain Mapping* 18, 208-214

Zilbovicius, M., Garreau, B., Samson, Y., Remy, P., Barthelemy, C., Syrota, A. and Lelord, G. (1995). Delayed maturation of the frontal cortex in childhood autism. *American Journal of Psychiatry* 152, 248-252

Zilbovicius, M., Boddaert, N., Belin, P., Poline, J.B., Remy, P., Mangin, J.F., Thivard, L., Barthelemy, C. and Samson, Y. (2000). Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography. *American Journal of Psychiatry* 157, 1988-93

Appendix A: DSM-IV criteria for autism

(i) A total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)

(A) Qualitative impairment in social interaction, as manifested by at least two of the following:

1. Marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
2. Failure to develop peer relationships appropriate to developmental level
3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
4. Lack of social or emotional reciprocity (note: in the description, it gives the following as examples: not actively participating in simple social play or games, preferring solitary activities, or involving others in activities only as tools or "mechanical" aids)

(B) Qualitative impairments in communication as manifested by at least one of the following:

1. Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
2. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
3. Stereotyped and repetitive use of language or idiosyncratic language
4. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(C) Restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least two of the following:

1. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2. Apparently inflexible adherence to specific, nonfunctional routines or rituals
3. Stereotyped and repetitive motor mannerisms (e.g hand or finger flapping or twisting, or complex whole-body movements)
4. Persistent preoccupation with parts of objects

(ii) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

(A) Social interaction
(B) Language as used in social communication
(C) Symbolic or imaginative play

(iii) The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

Appendix B: ICD-10 diagnostic criteria for autism issued by the World Health Organisation (WHO) in 1992.

At least 8 of the following items must be fulfilled:

a. Qualitative impairments in reciprocal social interaction, as manifested by at least three of the following five:

1. Failure adequately to use eye-to-eye gaze, facial expression, body posture and gesture to regulate social interaction.
2. Failure to develop peer relationships.
3. Rarely seeking and using other people for comfort and affection at times of stress or distress and/or offering comfort and affection to others when they are showing distress or unhappiness.
4. Lack of shared enjoyment in terms of vicarious pleasure in other peoples' happiness and/or spontaneous seeking to share their own enjoyment through joint involvement with others.
5. Lack of socio-emotional reciprocity.

b. Qualitative impairments in communication:

1. Lack of social usage of whatever language skills are present.
2. Impairment in make-believe and social imitative play.
3. Poor synchrony and lack of reciprocity in conversational interchange.
4. Poor flexibility in language expression and a relative lack of creativity and fantasy in thought processes.
5. Lack of emotional response to other peoples' verbal and non-verbal overtures.
6. Impaired use of variations in cadence or emphasis to reflect communicative modulation.
7. Lack of accompanying gesture to provide emphasis or aid meaning in spoken communication.

c. Restricted, repetitive and stereotyped patterns of behaviour, interests and activities, as manifested by ate least two of the following six:

1. Encompassing preoccupation with stereotyped and restricted patterns of interest.
2. Specific attachments to unusual objects.
3. Apparently compulsive adherence to specific, non-functional routines or rituals.
4. Stereotyped and repetitive motor mannerisms.
5. Preoccupations with part-objects or non-functional elements of play material.
6. Distress over changes in small, non-functional details of the environment.

d. Developmental abnormalities must have been present in the first three years for the diagnosis to be made.

Appendix C: DSM-IV criteria for Asperger's Syndrome

A. Qualitative impairment in social interaction, as manifested by at least two of the following:

1. Marked impairment in the use of multiple nonverbal behaviors such as eye-to- eye gaze, facial expression, body postures, and gestures to regulate social interaction
2. Failure to develop peer relationships appropriate to developmental level
3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
4. Lack of social or emotional reciprocity

B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

1. Encompassing preoccupation with one or more stereotyped and restricted
2. Patterns of interest that is abnormal either in intensity or focus
3. Apparently inflexible adherence to specific, nonfunctional routines or rituals
4. Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or
5. Twisting, or complex whole-body movements)
6. Persistent preoccupation with parts of objects

C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).

E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

Appendix D: ICD-10 diagnostic criteria for Asperger's Syndrome issued by the World Health Organisation (WHO) in 1992.

A. A lack of any clinically significant general delay in language or cognitive development. Diagnosis requires that single words should have developed by two years of age and that communicative phrases be used by three years of age or earlier. Self-help skills, adaptive behaviour and curiosity about the environment during the first three years should be at a level consistent with normal intellectual development. Motor milestones may be somewhat delayed and motor clumsiness is usual (although not a necessary feature).

B. Qualitative impairment in reciprocal social interaction (criteria as for autism, see Appendix B).

C. Restricted, repetitive, and stereotyped patterns of behaviour, interests and activities. (Criteria as for autism, see Appendix B).

Appendix E: Parental questionnaire for patients with PFT

Development questionnaire

Name:	**Sex:**
Date of Birth:	**Age:**

1. School and Education

- At what age did your child start school? .....
- Have you always been pleased with their progress at school? Yes ☐ No ☐

If no, please tell us about your concerns: .....

.....

- Does your child enjoy going to school? Yes ☐ No ☐
- Has your child ever been seriously bullied? Yes ☐ No ☐
- Has your child ever had detention at school? Never ☐ Sometimes ☐ Often ☐
- Has your child ever been excluded from school? Expelled ☐ Suspended ☐ Never ☐
- Does your child get into fights with other children? Never ☐ Sometimes ☐ Often ☐
- Is your child polite and well-behaved at home? Never ☐ Sometimes ☐ Most of the time ☐
- Is your child particularly rude (e.g. verbally aggressive) towards you? Never ☐ Sometimes ☐ Often ☐
- Has your child ever been physically violent towards another person? Yes ☐ No ☐
- Are you worried that your child is particularly quiet (withdrawn)? Yes ☐ No ☐
- Do you think your child has problems with: Memory Yes ☐ No ☐
  Language Yes ☐ No ☐
- Is your child in a mainstream or a special school? .....
- Examinations passed .....
- Currently studying for any examinations? .....
- What would they like to do after finishing school? .....

2. Development

(i) Early development

- How much did your baby weigh when they were born? .....
- Was your baby born at the right time? Yes □ No □

  If no, were they early or late? ..... How many weeks early/late? .....
- How was your baby born? Natural delivery □ planned c-section □ emergency c –section □
- Did your baby require any special care after birth? Extra oxygen Yes □ No □

  Special care baby unit Yes □ No □
- Did your baby sleep well? Yes □ Most of the time □ Sometimes □ Never □
- Were there any problems with your baby's health in the first two years? (e.g. sickly, coughs, cholic, fever...) .....

(ii) Developmental milestones

- At what age did your child first:

Smile/give eye contact?	
Sit?	
Crawl?	
Walk?	
Say first words?	
Say first sentences?	
Become toilet trained?	

(iii) Specific interests

- Does your child have any specific interests or pre-occupations? Yes □ No □

If yes, details: .....

3. Motor abilities

- At what age did your child start to write? .....
- What hand does your child use to write with? Left □ Right □ Both □

	Before surgery	After surgery
• Have there been any problems with writing?	.....	.....
• Is his/her writing legible?	.....	.....
• How does he/she hold a pencil?	.....	.....
• At what age did he/she learn to ride a bike?	.....	.....
• Has your child ever toe-walked?	.....	.....
• Has your child ever shown hand-flapping?	.....	.....
• Has your child ever shown twirling?	.....	.....

Difficulties: Has your child ever had any difficulties with:

	Before surgery	After surgery
• Swallowing	.....	.....
• Chewing	.....	.....
• Taking solid foods	.....	.....
• Biting	.....	.....
• Drinking through straw	.....	.....
• Blowing (e.g. candles)	.....	.....
• Cutting with scissors	.....	.....
• Buttons	.....	.....
• Shoe laces	.....	.....
• Climbing	.....	.....
• Catching a ball	.....	.....
• Kicking a ball	.....	.....
• Hopping on one leg	.....	.....
• Running into furniture	.....	.....
• Spilling things	.....	.....
• Clumsiness	.....	.....
• Organizing belongings	.....	.....

4. Medical

- How old was your child when the tumour was discovered? .....
- What were the symptoms? .....

.....

- How old was your child when the surgery was carried out? .....
- Before surgery, did he/she ever have a seizure (fit)? Yes □ No □
- After surgery, did he/she ever have a seizure (fit)? Yes □ No □
- Did he/she lose their language after surgery? Yes □ No □

If yes, how long for? .....

Are there any remaining problems with language? .....

- Did you notice any changes in mood after surgery? .....
- Did you notice any changes in personality after surgery? .....
- Did you notice any changes in movement abilities after surgery? .....

.....

- Did you notice any other changes after surgery? .....

.....

5. Health

- Does your child need glasses? Yes □ No □
- Do you think that your child has any difficulty with hearing? Yes □ No □
- Has your child had a lot of ear infections? Yes □ No □
- Does your child sleep well? Never □ Sometimes □ Most of the time □
- In the last year, about how many days has your child had off school because of illness? .....
- Does your child have headaches? Daily □ Weekly □ Monthly □ Not often □
- Has your child ever fainted? Yes □ No □ If yes, how many times? .....
- Has your child ever had a seizure (fit)? Yes □ No □ If yes, how many times? .....

6. Family

- Brothers and sisters: Please describe all your children starting with the oldest:

First Name	Boy or girl?	Date of birth	Any problems/abnormal development?

- Parental professions

.....

- Family history of psychiatric disorders or neurological problems? (e.g. epilepsy) Yes □ No□

Details: .....

- Family history of learning difficulties? (either specific e.g. dyslexia, or general?) Yes □ No □

Details: .....

- Family history of speech/language/motor difficulties? Yes □ No □

Details: .....

- Ethnic origin: Caucasian Black Asian Other

Appendix F: Parental questionnaire for patients with AS and all control participants

Development questionnaire

Name:	**Sex:**
Date of Birth:	**Age:**

1. School and Education

- At what age did your child start school? .....
- Have you always been pleased with their progress at school? Yes ☐ No ☐

If no, please tell us about your concerns: .....

.....

- Does your child enjoy going to school? Yes ☐ No ☐
- Has your child ever been seriously bullied? Yes ☐ No ☐
- Has your child ever had detention at school? Never ☐ Sometimes ☐ Often ☐
- Has your child ever been excluded from school? Expelled ☐ Suspended ☐ Never ☐
- Does your child get into fights with other children? Never ☐ Sometimes ☐ Often ☐
- Is your child polite and well-behaved at home? Never ☐ Sometimes ☐ Most of the time ☐
- Is your child particularly rude (e.g. verbally aggressive) towards you? Never ☐ Sometimes ☐ Often ☐
- Has your child ever been physically violent towards another person? Yes ☐ No ☐
- Are you worried that your child is particularly quiet (withdrawn)? Yes ☐ No ☐
- Do you think your child has problems with: Memory Yes ☐ No ☐
  Language Yes ☐ No ☐
- Is your child in a mainstream or a special school? .....
- Examinations passed .....
- Currently studying for any examinations? .....
- What would they like to do after finishing school? .....

2. Development

(iv) Early development

- How much did your baby weigh when they were born? .....
- Was your baby born at the right time? Yes □ No □

  If no, were they early or late? ..... How many weeks early/late? .....
- How was your baby born? Natural delivery □ planned c-section □ emergency c –section □
- Did your baby require any special care after birth? Extra oxygen Yes □ No □

  Special care baby unit Yes □ No □
- Did your baby sleep well? Yes □ Most of the time □ Sometimes □ Never □
- Were there any problems with your baby's health in the first two years? (e.g. sickly, coughs, cholic, fever...) .....

(v) Developmental milestones

- At what age did your child first:

Smile/give eye contact?	
Sit?	
Crawl?	
Walk?	
Say first words?	
Say first sentences?	
Become toilet trained?	

(vi) Specific interests

- Does your child have any specific interests or pre-occupations? Yes □ No □

If yes, details: .....

3. Motor abilities

- At what age did your child start to write? .....
- What hand does your child use to write with? Left □ Right □ Both □
- Have there been any problems with writing? .....
- Is his/her writing legible? .....
- How does he/she hold a pencil? .....
- At what age did he/she learn to ride a bike? .....
- Has your child ever toe-walked? .....
- Has your child ever shown hand-flapping? .....
- Has your child ever shown twirling? .....

Difficulties: Has your child ever had any difficulties with:

Swallowing .....

Chewing .....

Taking solid foods .....

Biting .....

Drinking through straw .....

Blowing (e.g. candles) .....

Cutting with scissors .....

Buttons .....

Shoe laces .....

Climbing .....

Catching a ball .....

Kicking a ball .....

Hopping on one leg .....

Running into furniture .....

Spilling things .....

Clumsiness .....

Organizing belongings .....

4. Health

- Does your child need glasses? Yes □ No □
- Do you think that your child has any difficulty with hearing? Yes □ No □
- Has your child had a lot of ear infections? Yes □ No □
- Does your child sleep well? Never □ Sometimes □ Most of the time □
- In the last year, about how many days has your child had off school because of illness? .....
- Does your child have headaches? Daily □ Weekly □ Monthly □ Not often □
- Has your child ever fainted? Yes □ No □ If yes, how many times? .....
- Has your child ever had a seizure (fit)? Yes □ No □ If yes, how many times? .....

5. Family

- Brothers and sisters: Please describe all your children starting with the oldest:

First Name	Boy or girl?	Date of birth	Any problems/abnormal development?

- Parental professions .....
- Family history of psychiatric disorders or neurological problems? (e.g. epilepsy) Yes □ No□

Details: .....

- Family history of learning difficulties? (either specific e.g. dyslexia, or general?) Yes □ No □

Details: .....

- Family history of speech/language/motor difficulties? Yes □ No □

Details: .....

- Ethnic origin: Caucasian Black Asian Other

Appendix G: Australian Scale for Asperger's Syndrome

Australian Scale for Asperger's Syndrome

M.S. Garnett and A.J. Attwood (1997)

A. SOCIAL AND EMOTIONAL ABILITIES

	Rarely						Frequently
1. Does the child lack an understanding of how to play with other children? For example, unaware of the unwritten rules of social play?	0	1	2	3	4	5	6
2. When free to play with other children, such as school lunchtime, does the child avoid social contact with them? For example, finds a secluded place or goes to the library.	0	1	2	3	4	5	6
3. Does the child appear unaware of social conventions or codes of conduct and make inappropriate actions and comments? For example, making a personal comment to someone but the child seems unaware of how the comment could offend.	0	1	2	3	4	5	6
4. Does the child lack empathy, ie. the intuitive understanding of another person's feelings? For example, not realising an apology would help the other person feel better.	0	1	2	3	4	5	6
5. Does the child seem to expect other people to know their thoughts, experiences and opinions? For example, not realising you could not know about something because you were not with the child at the time.	0	1	2	3	4	5	6

6. Does the child need an excessive amount of reassurance, especially if things are changed or go wrong?	0	1	2	3	4	5	6
7. Does the child lack subtlety in their expression of emotion? For example, the child shows distress or affection out of proportion to the situation.	0	1	2	3	4	5	6
8. Does the child lack precision in their expression of emotion? For example, not understanding the levels of emotional expression appropriate for different people.	0	1	2	3	4	5	6
9. Is the child not interested in participating in competitive sports, games and activities. 0 means the child enjoys competitive sports.	0	1	2	3	4	5	6
10. Is the child indifferent to peer pressure? 0 means the child follows crazes. For example, does not follow the latest craze in toys or clothes.	0	1	2	3	4	5	6

B. COMMUNICATION SKILLS

	Rarely						Frequently
11. Does the child take a literal interpretation of comments? For example, is confused by phrases such as "pull your socks up," "looks can kill" or "hop on the scales."	0	1	2	3	4	5	6
12. Does the child have an unusual tone of voice? For example, the child seems to have a "foreign" accent or monotone that lacks emphasis on key words.	0	1	2	3	4	5	6
13. When taking to the child does he or she appear uninterested in your side of the conversation? For example, not asking about or commenting on your thoughts or opinions on the topic.	0	1	2	3	4	5	6

14. When in a conversation, does the child tend to use less eye contact than you would expect?	0	1	2	3	4	5	6
15. Is the child's speech over-precise or pedantic? For example, talks in a formal way or like a walking dictionary.	0	1	2	3	4	5	6
16. Does the child have problems repairing a conversation? For example, when the child is confused, he or she does not ask for clarification but simply switches to a familiar topic, or takes ages to think of a reply.	0	1	2	3	4	5	6

C. COGNITIVE SKILLS

	Rarely						Frequently
17. Does the child read books primarily for information, not seeming to be interested in fictional works? For example, being an avid reader of encyclopaedias and science books but not keen on adventure stories.	0	1	2	3	4	5	6
18. Does the child have an exceptional long-term memory for events and facts? For example, remembering the neighbour's car registration of several years ago, or clearly recalling scenes that happened many years ago.	0	1	2	3	4	5	6
19. Does the child lack social imaginative play? For example, other children are not included in the child's imaginary games or the child is confused by the pretend games of other children.	0	1	2	3	4	5	6

D. SPECIFIC INTERESTS

	Rarely						Frequently
20. Is the child fascinated by a particular topic and avidly collects information or statistics on that interest? For example, the child becomes a walking encyclopaedia of knowledge on vehicles, maps or league tables.	0	1	2	3	4	5	6
21. Does the child become unduly upset by changes in routine or expectation? For example, is distressed by going to school by a different route.	0	1	2	3	4	5	6

22. Does the child develop elaborate routines or rituals that must be completed? For example, lining up toys before going to bed.	0	1	2	3	4	5	6

E. MOVEMENT SKILLS

	Rarely						Frequently
23. Does the child have poor motor coordination? For example, is not skilled at catching a ball.	0	1	2	3	4	5	6
24. Does the child have an odd gait when running?	0	1	2	3	4	5	6

F. OTHER CHARACTERISTICS

For this section, tick whether the child has shown any of the following characteristics:

(a) Unusual fear or distress due to:

ordinary sound, e.g. electrical appliances _____

light touch on skin or scalp _____

wearing particular items of clothing _____

unexpected noises _____

seeing certain objects _____

noisy, crowded places, e.g. supermarkets _____

(b) A tendency to flap or rock when excited or distressed _____

(c) A lack of sensitivity to low levels of pain _____

(d) Late in acquiring speech _____

(e) Unusual facial grimaces or tics _____

Appendix H: Description of the subtests that make up the WISC-III and the WAIS-III

WISC-III

Verbal scale subtests

- **Information:** A series of orally presented questions to measure the subject's knowledge of common events, objects, places and people.
- **Similarities:** A series of orally presented word pairs, for which the subject is required to explain the similarity between the objects or the concepts they represent.
- **Arithmetic:** A series of arithmetic problems that the subject is required to solve mentally and respond to orally
- **Vocabulary:** A series of words presented orally which the subject is required to define.
- **Comprehension:** A series of orally presented questions that require the subject to solve everyday problems or to show understanding of social rules and concepts.
- **Digit span (supplementary subtest):** A series of orally presented number sequences that the subject is required to repeat verbatim for Digits Forward, and in reverse order for Digits Backward.

Performance scale subtests

- **Picture completion:** A set of pictures of common objects and scenes that all have an important part missing which the subject is required to identify.
- **Coding:** A series of simple shapes or numbers each paired with a symbol are provided as a key. The subject is required to draw the symbol in its corresponding shape or under its corresponding number according to the key within a time limit.
- **Picture arrangement:** A series of pictures describing a story, presented in the wrong order, which the subject is required to rearrange into a logical story sequence.
- **Block design:** A set of three-dimensional blocks that the subject is required to use to reproduce two-dimensional abstract patterns
- **Object assembly:** A set of jigsaw puzzles of common objects that the subject is required to assemble to form a meaningful whole
- **Symbol search (supplementary subtest):** A series of paired groups of symbols, each pair consisting of a target group and a search group: the subject is required to decide whether any of the symbols in the target group are also present in the search group within a time limit.
- **Mazes (supplementary subtest):** A series of increasingly complex line drawings of mazes for which the subject is required to start in the centre and find their way out.

WAIS-III

The description of the WISC-III subtests applies for the WAIS-III with the exception of the following:

- **Digit Symbol-Coding:** As for Coding on the WISC-III
- **Matrix reasoning:** A series of incomplete gridded patterns that the subject is required to complete by pointing to or saying the number of the correct response from five possible choices.
- **Object assembly:** This is a supplementary subtest on the WAIS-III

Appendix I: Consent form for parents

GREAT ORMOND Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Consent Form for PARENTS OR GUARDIANS of Children Participating in Research Studies

Title: Motor and cognitive functions in children with neuro-developmental versus acquired pathology of the cerebellum

NOTES FOR PARENTS OR GUARDIANS

1. Your child has been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.
2. Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.
3. If you decide, now or at any other stage, that you do not wish your child to participate in the research project, that is entirely your right, and if your child is a patient it will not in any way prejudice and present or future treatment.
4. You will be given an information sheet which describes the research project. This information sheet is for you to keep and refer to. ***Please read it carefully.***
5. If you have any complaints about the way in which this research project has been or is being conducted please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

CONSENT

I/We _____, being the parent(s)/guardian(s) of _____ agree that the Research Project named above has been explained to me to my/our satisfaction, and I/We give permission for our child to take part in this study. I/We have read both the notes written above and the Information Sheet provided, and understand what the research study involves.

SIGNED (Parent(s)/Guardian(s))	PRINTED	DATE
.....	.....	.....
SIGNED (Researcher)	PRINTED	DATE
.....	.....	.....

Appendix J: Consent form for participants

GREAT ORMOND Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Assent Form for CHILDREN Participating in Research Studies

Title: Motor and cognitive functions in children with neuro-developmental versus acquired pathology of the cerebellum

NOTES FOR CHILDREN

1. You have been asked to take part in some research. The person organising that study must explain the project to you before you agree to take part.
2. Please ask the researcher any questions you like about this project, before you decide whether to join in.
3. If you decide, now or at any other time, that you do not wish to be involved in the research project, just tell us and we will stop the research. If you are a patient your treatment will carry on as it would normally.
4. You will be given an information sheet which describes the research. This information is for you to keep and refer to. ***Please read it carefully.***
5. If you have any complaints about the research project, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

ASSENT

I _____ agree that the Research Project named above has been explained to me to my satisfaction, and I agree to take part in this study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

SIGNED	PRINTED	DATE
.....	.....	.....
SIGNED (Researcher)	PRINTED	DATE
.....	.....	.....

Appendix K: Information sheet

The role of the cerebellum in cognitive and motor function during childhood.

Information for Parents

We invite you to consider allowing your child to take part in a research study that we think may be important. The information that follows will give you some details about the study. It is important that you understand this information as it says what will happen if you agree to let your child take part, and what, if any, the risks might be. Try to make sure that you understand what will happen to your child if you decide to allow them to take part. Whether or not you do give permission for your child to take part is entirely your choice. Please feel free to ask any questions you may have about the research and we will try our best to answer them for you.

The aim of the study

The aim of the study is to develop a greater understanding about the part of the brain called the cerebellum. The cerebellum is located at the back of the brain, tucked in behind the brain stem, and is thought to be involved in movement and some aspects of learning. We would like to learn more about the role of the cerebellum in the development of thinking, learning and motor functions in children.

Why is the study being carried out?

It is important to understand how cognitive and motor functions related to the cerebellum may develop in children with and without cerebellar abnormalities. Very little is currently known about the precise functions of the cerebellum, and the current study is particularly important because approximately half of all brain tumours occurring in childhood affect the cerebellum, and some other syndromes, such as Autism, are also believed to involve changes in the cerebellum. At present, we know relatively little about how these children function. In this study, we will develop tests of brain function that can be used to screen children for various cognitive and motor difficulties associated with cerebellar abnormalities.

Who is involved in the study?

A number of people are involved in the research. The project will be co-ordinated and administered by Bryony Whiting, a PhD student working under the supervision of Professor Faraneh Vargha-Khadem, Head of the Developmental Cognitive Neuroscience

Unit, and Professor Annette Karmiloff-Smith, Head of the Neurocognitive Development Unit, both of the Institute of Child Health in London.

What will the study involve?
The study will involve two one-day visits to us as the Institute of Child Health in London. On the first visit, you will be asked to help us to fill in some questionnaires about your child's development and their abilities. Your child will then be asked to participate in some games to look at movement abilities and some paper and pencil tests of thinking. The paper and pencil tests are similar to those administered at school and together with the movement tests, these should take about three hours to complete.

On the second visit, your child will be asked to participate in some more games to look at thinking, learning and memory. As in the first visit, these tests should not take longer than about three hours altogether. In addition, your child will have an MRI scan to look at the structure of their brain. The brain scan is a particularly important part of this investigation, as it will help us to sort out the relationship between cognitive and motor function and brain structure. The brain scan should take no longer than 45 minutes.

You will have the opportunity to ask more questions about all the tests when you come to see us. You will also be given feedback about some of the results at a later date.

Are there any risks or discomfort?
When you are in the scanner, a thumping noise created by the movements inside the magnet will be heard. Headphones will be provided which will greatly reduce this noise, and can also be used for playing music. Also, you may become uncomfortable because of having to lie in a confined space and will be asked not to move your head. If you do not like the feeling of being confined for too long, or do not like the noise, you can ring a bell and the staff will come and take you out of the machine immediately.

What are the potential benefits?
If we find out more about the cognitive and motor functions of the cerebellum, we may be able to intervene to help children with cerebellar abnormalities reach their full potential.

What other treatments are available?
This is not primarily a treatment study.

Who will have access to the case / research records?
Access to the case / research records will be available to all doctors and psychologists involved with the study and to a representative of the Ethics Committee if requested. Your child's results from the assessments and procedures will be entered onto a computer database, but a code will be used instead of their name.

What are the arrangements for compensation?
This project has been approved by an independent research ethics committee who believe that it is of minimal risk to your child. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in the study.

The research is covered by a no-fault compensation scheme that may apply in the event of any significant harm resulting to your child from involvement in the study. Under this scheme it would be necessary for you to prove fault. You also have the right to claim damages in a court of law. This would require you to prove fault on the part of the Hospital / Institute and/or any manufacturer involved.

Does my child have to take part in the study?
If you decide now, or at a later stage, that you do not wish your child to participate in this research project, that is entirely your right and will not in any way prejudice any present or future treatment.

Who do I speak to if problems arise?
If you have any complaints about the way in which this research project has been, or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via the Research & Development Office, Institute of Child Health, 30 Guildford Street, London, WC1N 1EH, or, if urgent, by phone on 020 7905 2620, and the Committee administration will put you in touch with him.

You will always be able to contact someone to discuss any concerns you may have.

If you have any questions about the research, please contact:

Bryony Whiting
Research Psychologist
Developmental Cognitive Neuroscience Unit
Institute of Child Health
The Wolfson Centre
Mecklenburgh Square
London, WC1N 2AP tel: 020 7905 2921

Email: b.whiting@ich.ucl.ac.uk

If you have a question about your child's health, please contact your GP.

Appendix L: Missing data

(i) Behavioural data:

The only patient who did not complete the full protocol of behavioural tests was patient PFT 14 who withdrew from the study because of exam pressure and did therefore not complete the following tasks: The posting task
The rotary pursuit task
The face-sorting task

In addition, four AS controls did not complete and return the Australian Scale for Asperger's Syndrome (ASAS) questionnaire.

(ii) MR data:

MRI scans for the following four participants were not included in the analyses:

Patient PFT7 – This patient was not scanned because she had a brain reservoir (Rickham's Reservoir) in situ and it was unclear whether or not this was MR compatible

Patient AS1 – This patient had orthodontic braces which meant the MRI scans had to be discarded

Patient AS9 – This patient had orthodontic braces which meant the MRI scans had to be discarded

One AS control subject – Could not be scanned because of problems with the scanner during his visit

Appendix M: Abbreviations

ADHD	Attention deficit hyperactivity disorder
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AS	Asperger's Syndrome
CSF	Cerebrospinal fluid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition (produced by the American Psychiatric Association, Washington D.C., 1994)
DTI	Diffusion tensor imaging
EPI	Echo planar imaging
FA	Fractional anisotropy
3-d FLASH	Three-dimensional Fast Low Action Shot
GABA	Gamma-aminobutyric acid
ICD-10	International Classification of Diseases, 10th revision (issued by the World Health Organisation in 1992)
ICN	Interposed cerebellar nucleus (emboliform and globose nuclei)
IQ	Intelligence quotient
LCN	Lateral cerebellar nucleus (dentate nucleus)
LH	left hemisphere (of the cerebellum)
Log_n	Natural logarithmic base
MCN	Middle cerebellar nucleus (fastigial nucleus)
MNI	Montreal Neurological Institute
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NAA	N-acetylaspartate
PET	Positron emission tomography
PFC	Prefrontal cortex
PFT	Posterior fossa tumours
PIQ	Performance intelligence quotient
RH	Right hemisphere (of the cerebellum)
SD	Standard deviation
SE	Standard error
SPM	Statistical parametric mapping
V	Vermis (midline cerebellum)
VBM	Voxel-based morphometry
VIQ	Verbal intelligence quotient
WAIS-III	Weischler adult intelligence scale (third revision)
WHO	World Health Organisation
WISC-III	Weischler intelligence scale for children (third revision)
WOND	Weischler objective numerical dimensions
WORD	Weischler objective reading dimensions