University of Southampton

An Investigation of Neuropsychological Outcome in Paediatric Heart Surgery Patients

By

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THESIS ABSTRACT

Advances in open-heart surgery have resulted in operations being carried out in early infancy. Numerous studies have been conducted with adults that indicate a variety of neuropsychological deficits after open-heart surgery (e.g. Vingerhoets, Van Nooten, Vermassen, de Soete & Jannes, 1997) which may be associated with the influence of ischaemic-hypoxic injury upon the brain. However, little is known about the effect of cardiac surgery on the cognitive development of children.

This thesis consists of two papers, the first being a literature review which provides a critique of the existing research in the field of infant cardiac surgery, with particular reference to factors that could contribute to postoperative neurological and neuropsychological morbidity. Given the paucity of evidence, the second paper (empirical) documents the findings from a neuropsychological outcome study of paediatric heart surgery patients which was conducted to contribute to current knowledge in this area. The findings of this study are outlined and recommendations are made regarding the direction in which future research should proceed.

Literature Review

Neuropsychological Effects of Paediatric Heart Surgery

Volume I of II

by

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ABSTRACT

Advances in open-heart surgery have resulted in operations being carried out in early infancy. Numerous studies have been conducted with adults that indicate a variety of neuropsychological deficits after open-heart surgery (e.g. Vingerhoets, Van Nooten, Vermassen, de Soete & Jannes, 1997) which may be associated with the influence of ischaemic-hypoxic injury upon the brain. However, little is known about the effect of cardiac surgery on the cognitive development of children.

The aim of this paper is to provide an overview of the current literature in the field of infant cardiac surgery, with particular reference to factors that could contribute to postoperative neurological and neuropsychological morbidity. In order to provide a context within which the effects of congenital heart defects can be discussed, the review begins with a brief description of heart anatomy, diagnosis and treatment. The aetiology of pre, intra and postoperative risks for cerebral injury are then considered and the research evidence regarding anatomical, neurological and neuropsychological outcome after cardiac surgery critically reviewed with the aid of adult and paediatric literature. Finally, the limitations of current research are highlighted and recommendations made regarding the directions in which future research should proceed.

Background

Since the introduction of open heart surgery to correct adult heart problems in the 1950's, clinicians and researchers have been aware of the possible deleterious effects of the surgical procedures involved upon normal brain functioning (Newman & Stygall, 2000). Research findings of the neuropsychological deficits experienced by adults following open-heart surgery have raised concerns regarding the impact of these procedures upon children who require heart surgery for congenital heart defects (Baron, Fennell & Voeller, 1995). As refinements in surgical techniques allow these children to be operated upon at a very early age (often within the first year of life), researchers are beginning to question the implications of this surgery for cognitive development.

Introduction: Cardiac surgery as a source of brain injury

In the 1950's Lillehei (1955) and Kirklin et al (1955) developed open-heart surgery using cardiopulmonary bypass. This involved the redirection of blood away from the heart, allowing the heart to be stopped and opened, whilst maintaining oxygenation and blood flow (perfusion) to the rest of the body. Even in these early days surgeons were alert to the potential risks to the brain, with complications such as coma, delirium and stroke. The obligatory use of some form of externally controlled circulation often resulted in widespread organ dysfunction and was initially associated with significant mortality and morbidity (Taylor, 1993).

Despite major improvements in cardiopulmonary techniques cerebral dysfunction is still an ongoing problem in modern cardiac surgery (Taylor, 1993). Many studies have reported a high frequency of neuropsychological deficits in adults after heart

surgery ranging from 12.5% to 90% (Newman, 1993) with persistent cognitive deficits in up to 30% of adults (Savageau, Stanton, Jenkins & Fraser, 1982; Shaw et al, 1987). The wide variability in incidence rates has been attributed not only to differences in the type of surgical intervention but is also thought to reflect the disparity in the number and type of cognitive tests used, operational definition of deficit and the patient inclusion criteria.

As a consequence of these findings, the research literature has identified three useful diagnostic groups associated with the cerebral damage that is thought to occur as a result of cardiac surgery. The first group refers to all discrete, focal central nervous system lesions ranging on a spectrum from hemiplegia at the severe end and visual field defect at the mild end. The second group is that of global neurological signs such as drowsiness, poor concentration and depressed reflexes (Shaw et al, 1985). The third group refers to patients who have a much more subtle form of damage relating to the postoperative presentation of cognitive deterioration in the absence of new neurological markers (Kirkham, 1998).

Attention has increasingly been focused on the means by which this more discrete cerebral damage can occur and investigations have been conducted to consider not only the neurological, but also the anatomical and neuropsychological implications of heart surgery. Numerous research studies have focused on postoperative effects in adults, however, over the last three decades, work has also been extended to consider the effects of cardiac surgery on paediatric heart patients and the developing brain.

As the multiple adverse effects of surgery appeared to be magnified in the young, by the 1970's an additional technique involving whole body hypothermia (deep hypothermic circulatory arrest) was introduced (Barratt-Boyes, Simpson & Neutze, 1970; Castadena, Lamberti, Sade, Williams & Nadas, 1974). By combining this method with cardiopulmonary bypass, it was anticipated that blood circulation could be temporarily stopped, whilst still protecting the heart, brain and other organs from the potential damage that can occur when deprived of blood (ischaemic injury). Further refinements in surgery have resulted in the correction of serious cardiac defects earlier and earlier in infancy, to the extent that repair in the neonatal period is now common practice (Mahle & Wernovsky, 2000).

There has, however, been ongoing concern and controversy regarding the potential for cerebral injury during infant heart surgery related to deep hypothermic circulatory arrest and cardiopulmonary bypass. A number of publications have suggested that there is no significant neurological morbidity in children following open-heart surgery (e.g. Brunberg, Reilly & Doty, 1974; Dickinson & Sambrooks, 1979; Haka-Ikse, Blackwood & Steward, 1978; Messmer, Scallberger, Gattiker & Senning, 1976; Stevenson, Stone, Dillard & Morgan, 1974; Wright, Hicks & Newman, 1979). Since these papers, however, contradictory evidence has been provided by techniques such as autopsy (e.g. Bozoky, Bara & Kertesz, 1984) and neuroimaging (e.g. Ashwal, Holshouser, Hinshaw, Schell & Bailey, 1996; Miller, Mamourian, Tesman, Baylen & Myers, 1994), indicating the presence of cerebral damage.

Congenital heart disease is one particular type of heart defect that requires surgical intervention in infancy and is a common paediatric problem. Despite its relatively

high incidence and the longstanding acknowledgement of neurological disorders in a large proportion of these children, either as a consequence of the heart condition or its treatment, there continues to be a paucity of research evidence regarding cognitive complications (Fallon, Haw & Kirkham, in press). The multifactorial aetiology of problems which are present before surgery (preoperative), arise during surgery (intraoperative) or occur after surgery (postoperative) has meant that this area continues to be incompletely understood. Research findings are further complicated by the heterogeneity of congenital heart disorders and presence of preoperative neurological abnormality due to the underlying heart problem (Kirkham, 1998; Majnemer et al, 1996).

The findings from recent literature highlight the possibility of short- and long-term sequelae including cognitive deficits, seizures, involuntary motor activity with poorly co-ordinated and exaggerated movements (choreoathetosis), bilateral motor deficits and hemiparesis (Volpe, 1995). However, although most of these children do not exhibit such obvious cerebral difficulties postoperatively, there is increasing concern regarding the high incidence of subtle long-term cognitive and motor deficits (Kirkham, 1998).

Some research studies have attempted to estimate the magnitude of the problem in children but brain injury incidence figures vary considerably between 1 and 30% depending on the design, methodology and outcome measures adopted (Bellinger et al, 1991; Ferry, 1990; Furlan et al, 1992; McConnell et al, 1990; Mendoza, Wilkerson & Reese, 1991; Miller, Rodichok, Baylen & Meyers, 1991; Newburger et al, 1993; Park & Neches, 1993). Despite the lack of clarity regarding the exact

incidence rate, it is agreed that the neuropsychological deficits that may follow surgical treatment for congenital heart disease can seriously limit positive prognosis.

The aim of this paper is to provide an overview of the current literature in the field of infant cardiac surgery, with particular reference to factors that could contribute to postoperative neurological and neuropsychological morbidity. This review will commence by orientating the reader to the fundamentals of heart anatomy, diagnosis and treatment regimens. The aetiology of pre, intra and postoperative risks for cerebral injury will then be considered and the research evidence regarding anatomical, neurological and neuropsychological outcome after cardiac surgery will be critically reviewed with the aid of adult and paediatric literature. Finally, the limitations of current research will be highlighted and recommendations made regarding the directions in which future research should proceed.

Paediatric heart defects: The extent of the problem

Congenital heart defects occur in 6 to 8 per 1000 liveborn children (Clark, 1992; Perry, Neill, Ferencz, Rubin & Loffredo, 1993). These heart defects result from structural in-utero malformations of which over one third require surgical repair within the first year after birth (Perry et al, 1993). If interim surgical and pharmacological interventions can be used palliatively to allow an infant to grow in strength before more invasive surgical procedures are employed. Due to the relatively high frequency of congenital heart defects, it is these that are of particular interest in this review.

The heart: Anatomy, circulation & congenital abnormalities

The heart is a muscular organ designed to pump blood around the body. It is divided into four separate chambers, with the left and right sides operating separately. On each side there are upper chambers (atria), which receive blood from the veins and lower chambers (ventricles), which return blood back to the body in the arteries. A series of one-way valves allows the blood to circulate through the heart from one chamber to another.

Congenital heart defects relate to anomalies involving valve function, chamber separation or blood vessel structure. Some of these abnormalities result in the heart being unable to maintain a separate oxygenated and deoxygenated blood supply which can lead to reduced blood oxygen saturation (cyanosis) and inadequate oxygen perfusion of the body's tissues. Congenital heart conditions are classified by the presence or absence of cyanosis and are known as cyanotic and acyanotic respectively.

Cyanosis usually occurs when deoxygenated blood mixes with oxygenated blood and can occur in the atrial chambers, ventricular chambers or the blood vessels. It is, however, also possible for oxygenated blood to be pumped from the left to the right side of the heart instead of to the body. The degree to which oxygen saturation is lowered can have marked consequences upon the individual's ability to function normally and can lead to death or significant morbidity as a consequence of ischaemic-hypoxic cerebral injury. In addition, some defects can increase the heart's workload which may enlarge the heart or increase blood pressure (Baron et al, 1995). Although a comprehensive overview of the different types of congenital heart defect

is beyond the scope of this review, a summary is provided elsewhere for the reader who requires more information (Appendix 1).

Cardiac surgery techniques

The introduction of the cardiopulmonary bypass technique enabled the repair of congenital heart defects by supporting the circulation whilst stopping and opening the heart. During this procedure, large bore catheters (cannulas) are placed in the right side of the heart, allowing deoxygenated blood to be sent to the cardiopulmonary bypass circuit. This consists of a mechanical pump to regulate cardiac output, an oxygenator (membrane or bubble oxygenators) to supply necessary gases and remove gaseous by-products, a heat exchanger to regulate temperature and arterial filters to remove particles from the blood. Re-oxygenated blood is then returned to the body via another cannula.

In adult open-heart surgery, operations are conducted at normal temperature (normothermia) or mild hypothermia, as the flow of blood does not need to be significantly reduced. In paediatric heart surgery deep hypothermia with complete arrest of blood to all parts of the body (total circulatory arrest) is often employed in cases where the surgery is technically complex and a bloodless operating field is required. Under these circumstances all blood is drained from the body and the heart is stopped. Repair must be completed within 60 minutes or severe damage may occur to the central nervous system.

Deep hypothermic cardiopulmonary bypass with low blood flow or total circulatory arrest has been associated with improved survival and reduced morbidity in

paediatric patients (Mahle & Wernovsky, 2000) as it is thought to reduce the risk of ischaemia or tissue damage when the blood supply is interrupted (Griepp. Ergin, Lansman, Gall & Pogo, 1991). However, the duration of hypothermia appears to be an area of particular research interest as it has been suggested that even in cases where deep hypothermia lasts less than 60 minutes, significant neurological impairment may occur (Baron et al, 1995).

Although there is an abundance of literature regarding the detrimental effects of cardiopulmonary bypass upon the central nervous system of adults, studies on paediatric heart surgery patients are much more limited. It is difficult, however, to generalise adult findings to children for two main reasons. Firstly, the surgical techniques employed in adult and paediatric cardiac surgery differ markedly. Secondly, it is not possible to parallel the effects that surgery may have on the developed adult brain with that of a child's brain, which is still undergoing developmental changes, and for which increased plasticity may offer some form of protection from neurological insult. In order to gain an understanding of the ways in which these surgical procedures could affect the paediatric brain it is important to first understand the aetiology of cerebral injury.

Aetiology of cerebral injury following cardiac surgery

Current research literature suggests that there are many variables that could potentially influence neuropsychological outcome following open-heart surgery in children with congenital heart defects. This includes preoperative, intraoperative and post-operative factors, each of which will now be discussed.

i) Preoperative factors

Children with congenital heart disease can have a variety of difficulties associated with their diagnosis. The classification of the heart problem (cyanotic or acyanotic) and variations in the type of structural anomaly, as well as the complexity and severity of the deficit can significantly influence the degree to which a child is at risk of brain injury (e.g. Haka-Ikse et al, 1978; Jonas, 2000). Neurological abnormalities suggestive of ischaemia-hypoxia are thought to often be apparent before cardiac surgery. This has been reflected in lower than normal preoperative cerebral oxygen saturation in children with congenital heart disease, although this was strongly related to the type of anatomic diagnosis (Kurth et al, 2001).

The findings from pathology and neuroimaging studies indicate a higher than normal incidence of anatomic abnormalities in children with congenital heart disease as well as a significantly higher incidence of congenital or developmental brain abnormalities than in the general population. These anomalies include specific genetic syndromes (e.g. trisomy 21 and microdeletion of 22q11.2) and are associated with poor developmental and cognitive outcomes. Common neurological abnormalities include reduced brain size (microcephaly), abnormal muscle tone and poor mouth (oromotor) co-ordination.

One of the main problems related to the cyanotic heart disorders is the risk of chronic hypoxic damage to the brain prior to surgical correction. Research findings suggest that the IQ of these children is closely related to the age at which surgical repair occurred (O'Dougherty, Wright, Loewenson & Torres, 1985), although these findings are not undisputed. In addition, the right to left flow of blood which occurs

in many of the cyanotic conditions, means that blood containing clots and bacteria is not filtered through the lungs before passing into the body, increasing the risk of stroke.

The acyanotic congenital anomalies although associated with different physiological problems, may also have an effect upon normal development. One particular problem is that of failure to thrive due to the increased effort required to breathe, higher work load on the heart and difficulty in consuming higher levels of calories to maintain a normal weight. Failure to thrive is also associated with developmental delay (Jonas, 1993).

ii) Intraoperative factors

Although there are thought to be a multitude of intraoperative variables that could contribute to the neurological and neuropsychological dysfunction which may follow open-heart surgery, the literature in this area consistently highlights four main factors: reduced cerebral blood flow, microembolism, macroembolism and systemic inflammatory response.

The main form of neuroprotection in cardiac surgery on neonates and infants is through the use of hypothermic cardiopulmonary bypass with or without deep hypothermic circulatory arrest. During cardiac surgery, the body's normal process of varying the blood flow to match overall energy demands is temporarily controlled artificially via the bypass equipment. The use of hypothermia during cardiopulmonary bypass reduces the body's tissue oxygen consumption and cerebral metabolic rate for oxygen, thereby allowing for lower blood flow rates. Blood flow

is either reduced to 'low flow' or is stopped completely whilst the surgical techniques are performed. However, a number of questions remain regarding the extent to which reduced blood flow is sufficient to cause ischaemic cerebral injury in children and whether certain children are more vulnerable to these risks.

Another mechanism by which cerebral damage may occur is through the obstruction of blood in the small blood vessels that supply the brain. This can take place when gas bubbles are introduced from the cardiopulmonary bypass equipment (macroembolisation) or cellular particles arise as an inflammatory response to blood cells being in contact with the synthetic surfaces of the machine (microembolisation). These emboli may travel through the circulatory system and become lodged in the blood vessels of vital organs such as the brain, thus hindering the normal flow of blood and resulting in ischaemic-hypoxic damage.

The most visible sign of morbidity after cardiopulmonary bypass in neonates and infants is the development of swelling (oedema) in the whole body. Magnetic imaging of patients within 60 minutes after cardiac surgery demonstrated substantial diffuse brain swelling with the loss of the normal appearance in the folds (sulci) and ridges (gyri) of the brain (Harris, Smith, Taylor, Oatridge & Bydder, 1993). One possible explanation for this brain swelling is the systemic inflammatory response following cardiopulmonary bypass and illustrates the potentially subtle effects of open-heart surgery upon the brain.

The awareness of the hypoxic risks associated with hypothermic cardiac surgery has led to an increased focus upon other intraoperative factors such as the balance

between arterial oxygen and carbon dioxide levels (blood pH management), particularly in view of the susceptibility of general and cerebral circulation to changes in the latter.

iii) Postoperative Factors

Postoperative factors can also play an important role in a child's cognitive adjustment following cardiac surgery. One vital variable is that of blood flow around the brain (cerebral perfusion) in the initial phase after surgery, as this may be affected by low cardiac output, reduced oxygen delivery to the blood or altered cerebral blood flow (Mahle & Wernovsky, 2000). Seizures are also a frequently observed consequence of neonatal and infant cardiac surgery using circulatory arrest.

It is clear that there are many factors that influence the cognitive outcome for children with congenital heart disease, however, given that the majority of these children will require surgery at some time in their childhood, the effects of surgical factors upon normal development is an area which warrants further consideration. This review will, therefore, now discuss the current state of knowledge regarding the ways in which open-heart surgery can damage the brain both from an anatomical and functional perspective.

Areas of the brain affected by cardiac surgery

Although in adults the cardiopulmonary bypass pump can perfuse the body at normal flow, this is often not possible in children with congenital heart disease. As most of the repairs need to carried out within the heart, it is necessary to reduce the amount of blood flowing to enable the surgeon to perform the necessary procedures as

accurately and quickly as possible, thereby reducing time on bypass. In fact some of the more complex heart operations, where multiple anomalies or severe defects exist, necessitate complete cessation of the circulation during certain parts of the operation. Despite the protective strategy of deep hypothermic circulatory arrest, there are times during surgery that decreased tissue perfusion may place the vital organs at risk of ischaemic injury. The organ that is most sensitive to this type of injury is the brain.

It has been suggested that certain parts of the brain are particularly vulnerable to ischaemia and hypoxia as a result of this reduced global cerebral perfusion. However, a global ischaemic injury does not result in a uniform distribution of cell death (Meldrum, 1985). As the brain receives its blood supply from the internal carotid and vertebral arteries, a reduction in normal cerebral perfusion may be more likely to affect those areas of the brain that are served by the ends of the major cerebral arteries ('watershed' areas), such as the parieto-occipital region of the cortex. This region of the brain plays an important role in integrative sensory functions, such as linking touch with visual information or with memory. It also plays a role in visuo-spatial processing as well as being critical for attention (Stirling, 2002).

Another important cause of selective neuronal vulnerability relates to changes in metabolic demand at a cellular level during cardiac surgery. Areas of the brain known as the hippocampus, dentate gyrus and globus pallidus are particularly vulnerable to the effects of ischaemic-hypoxic injury (Hagberg, Andine & Lehmann, 1990). Each of these structures is vitally important in normal cognitive function and damage in any of these areas can have significant effects in terms of a child's normal

capabilities. The connections between the hippocampus and dentate gyrus means that damage to either region can impair information processing, new learning and the integration of long-term memories (Gould, 1998) and damage to the globus pallidus can result in impaired motor function.

Outcome studies of the effects of cardiac surgery

Many studies have attempted to define the effects of cardiac surgery upon the brain. Some studies have focused on the more physiological changes that may take place, including the anatomical changes that may occur in the brain (e.g. Brierley, 1963; Muroaka et al, 1981; Sotaniemi, Mononen & Hokkanen, 1986) whilst other studies have been interested in determining the ways in which cardiac surgery may affect cognitive skills and normal functional abilities (e.g. Aberg & Kihlgren, 1977; Sotaniemi, 1980).

Three main types of outcome studies are of interest, namely research relating to neuropathology, neuroimaging and neurological/ neuropsychological performance post-surgery. With regard to the first of these, neuropathology, the nature and distribution of any structural damage to the brain can be studied through histological examination. From a small number of cases, several factors have been implicated in the causation of brain damage following open-heart surgery, of which the main elements are thought to be reduced cerebral perfusion pressure due to systemic hypotension, and multiple embolism (Graham, 1990; Gravlee, Hudspeth & Toole, 1984).

i) Neuropathology Studies

In 1963, Brierley reported neuropathological findings from 11 participants, indicating the presence of focal or multifocal ischaemic lesions involving both grey and white matter. This ischaemic damage was found to be most severe in the hippocampus, basal ganglia and cerebellum with a relatively intact brainstem. Later a neuropathological study of 46 adults who had died after open-heart surgery, showed that only 9 individuals had normal brains (Brierley, 1967). The two major causes of brain damage identified were the presence of emboli or inadequate cerebral perfusion. Malone, Prior and Scholtz (1981) also found that brain damage was related to reduced cerebral perfusion which was found to cause ischaemic lesions in the watershed area in almost half of those studied after death. These findings were confirmed by Stockard, Bickford and Shauble (1973) who found damage of the hippocampus and caudate nucleus, although this occurred in only a small number of their participants.

Examination of pathological samples from children with congenital heart disease who have had open-heart surgery has provided some mixed results. In a review of children who had developed motor impairments with poor co-ordination and exaggerated movements (choreoathetosis), it was observed that there was a degeneration of myelinated fibres in the globus pallidus and pallidosubthalamic pathways but not elsewhere in the basal ganglia (Wong et al, 1992).

A detailed histological examination of children after open-heart surgery found that damage to the white matter tended to occur below the age of 3 months whilst damage in children above this age tended to occur in the grey matter (Bozóky et al, 1984).

Damage was observed in the frontal and parieto-occipital cerebral cortex, the hippocampus, the cerebellum, the white matter around the ventricles (periventricular) and the cingulate gyrus.

ii) Neuroimaging Studies

One of the main problems with histological examination is in determining whether neurological injury occurred prior to or during surgery. Neuroimaging of the brain has offered another way for researchers to attempt to identify structural cerebral damage following cardiac surgery. As magnetic resonance imaging (MRI) scans provide more detailed information and are sensitive to the presence of cerebral ischaemia, they tend to be preferred to computerised tomography (CT) scans (McConnell, 1993). Although the number of studies with adults who have had cardiac surgery is limited, even fewer of these studies have examined the effects of open-heart surgery upon paediatric patients.

Several studies have demonstrated cerebral injury in adults who have received open-heart surgery, although the incidence of cerebral injury appears to vary from one study to another. A retrospective study indicated that almost a quarter of adults who had received cardiopulmonary bypass had central nervous system symptoms. Of those patients who had undergone neuroimaging, a number had symptoms which were associated with intraoperative injury. However, this finding is questionable due to the absence of preoperative assessment and the problem of determining the age of an infarct through the use of conventional CT techniques (Boyajian, Sobel, De Laria & Otis, 1993).

A number of prospective studies have also identified the presence of postoperative lesions in adults following heart surgery, with the incidence of new post-operative abnormality on MRI ranging between 12.5% and 42% (Newman et al, 1993; Simonetta et al, 2000; Toner et al, 1993; Toner et al, 1994). Steinberg et al (1996), however, identified a higher incidence of 58% for post-operative cerebral abnormalities in a small sample of valve replacement or repair candidates. The new areas of damage identified in these studies, related to deep subcortical white matter lesions, periventricular hyperintensity, cerebral atrophy and small vessel white matter ischaemic changes. Damage to the 'watershed' area of the brain has been reflected in some of the adult studies (see e.g. Libman et al, 1996; Hise, Nipper & Schnitker, 1991).

Despite the identification of brain abnormalities as a consequence of cardiac surgery in adults, a number of prospective studies have found contradictory evidence. For example, Sellman, Hindmarsh, Ivert and Semb (1992) identified the presence of new lesions in only a small number of participants and some researchers have found no evidence of new abnormalities on post-operative MRI imaging (e.g. Vik et al, 1991; Schmidt et al, 1993; Simonsen et al, 1994; Anderson, Li, Hindmarsh, Settergren & Vaage, 1999). In addition to these contradictory findings, neuroimaging studies have been further complicated by the presence of preoperative lesions in a significant number of participants (Toner et al, 1994; Simonetta et al, 2000)

Although to a lesser extent, neuroimaging has also been used with children one such study used CT scans to examine 57 children pre- and postoperatively to assess the effects of cardiopulmonary bypass and deep hypothermic circulatory arrest on brain

morphology (Muraoka et al, 1981). Postoperatively, decreases in brain mass were observed in 14.7% of children who received conventional cardiopulmonary bypass and 16.7% of children who received total circulatory arrest. Interestingly, those children with abnormal CT findings did not exhibit any clinical signs of neurological dysfunction upon examination. Repeat CT scans were found to be normal in 6 to 11 weeks after surgery indicating the possible transient nature of this damage, although more subtle remaining deficits may have been missed.

MRI has also been used in a number of studies with children. Of note McConnell et al (1990) assessed 15 children, of whom one third showed enlarged ventricles (ventriculomegaly) and dilation of the subarachnoid spaces on preoperative images. No neurological symptoms or deficits were found during the preoperative clinical examination and any morphological changes were described as subclinical. In addition, four individuals developed postoperative subdural haematomas and one developed a post-operative infarction. Despite concerns about the generalisability of these findings they clearly indicate cerebral changes following surgery in children.

A more recent prospective study using MRI scans with 24 neonates with congenital heart disease (Mahle et al, 2002) also identified preoperative abnormalities in the form of lesions in the region around the ventricles (periventricular leukomalacia) in 16% and infarct in 8% of participants. Early postoperative MRI indicated that new or worsening of preoperative lesions had occurred in 67% of participants, although a further MRI 4 to 6 months later indicated resolution in almost half of those children re-tested. Unfortunately a large proportion of these children were not re-tested, which may have biased the data.

iii) Neurological and Neuropsychological Outcome Studies

Central nervous system dysfunction after cardiac surgery can be considered in two different ways depending upon the means by which it is detected, i.e. neurological dysfunction or neuropsychological dysfunction. Neurological examination and neuropsychological testing measure different but complementary functions, where the former evaluates cerebral areas associated primarily with motor, sensory, cerebellar and language functions, the latter assesses areas associated with higher cortical functions such as memory, attention, visuospatial skills, language and executive functioning.

In adults, the presence of overt neurological dysfunction such as fatal brain injury has been reported to range from 0.3 to 2% (e.g. Shaw, 1993; Sotaniemi, 1980). The most common cause of severe long-term neurological morbidity is stroke, involving problems such as hemiparesis, dysphasia and cortical blindness (e.g. Shaw, 1993). Other non fatal post-operative problems include reduced consciousness, confusion, agitation, perceptual distortion, paranoid ideation, intellectual dysfunction, seizures, opthalmological complications (such as visual blurring or difficulty reading) and rarely spinal cord injury (e.g. Shaw, 1993).

Despite the practical difficulties of neurological assessment with neonates, infants and children, a number of studies have assessed the neurological changes in the operative or perioperative period. The types of problems which have been identified include visual field defects (e.g. Hesz & Clark, 1988), hemiplegia, paraplegia, psychomotor retardation, motor co-ordination problems, marked speech delay (e.g. Puntis & Green, 1989) and seizures (e.g. Newburger et al, 1993). However, as many

types of congenital heart disease also have associated neurological abnormalities, prospective studies are required to disentangle pre-existing conditions from those which occur post-operatively (Medlock et al, 1993).

Neuropsychological assessment has been used for a number of years to examine the types of deficits which may be encountered following open-heart surgery. In order to inform the reader of the progress in this area to date and establish the way forward for future research it is first necessary to provide a brief overview of the neuropsychological findings related to adult cardiac surgery which will then be followed by a detailed review of the paediatric studies.

In the acute postoperative stages a number of studies have reported significant deficits in cognitive performance in adults (e.g. Bethune, 1982; Garvey et al, 1983; Hammeke & Hastings, 1988; Newman et al, 1987; Savageau, Stanton, Jenkins & Klein, 1982a, 1982b; Shaw et al, 1987). From a total of 12 single group studies conducted between 1972 and 1992, 10 authors reported a significant reduction in cognitive performance in the early postoperative period (e.g. Aris et al, 1986; Nevin, Colchester, Adams & Pepper, 1989; Shaw et al, 1985; Shaw et al, 1986). With longer test-retest intervals ranging from 3 months to 5 years, cognitive function has been found to improve (Frank, Heller, Kornfeld & Malm, 1972; Grote et al, 1992; Klonoff et al, 1989; Sotaniemi et al, 1986).

Comparison group studies have also yielded interesting findings in terms of cardiac patients' cognitive performance after surgery when compared with another surgical group or a healthy control. Despite various methodological concerns such as the

appropriateness of the control group due to age, pre-morbid functioning and variables related to the type of health problem, many of the studies identified a higher incidence of early neuropsychological dysfunction related to the use of cardiopulmonary bypass (e.g. Aberg & Kihlgren, 1977; Shaw et al, 1987; Blumenthal et al, 1991).

The majority of follow-up studies of this design have also indicated significant cognitive impairments more than six months after surgery in those individuals who received cardiopulmonary bypass (e.g. Di Carlo et al, 2001; Newman et al, 1990; Newman et al, 2001; Townes et al, 1989). This area is not without its share of controversy, as a more recent longitudinal study by Selnes and colleagues (Selnes et al, 2003) found no difference between individuals who had undergone coronary artery bypass grafting and a non-surgical coronary artery disease control group, even up to one year post-surgery.

Studies of adults who have undergone open-heart surgery highlight that a number of neuropsychological deficits may follow as a consequence of the procedures involved. Problems with sensation, attention and concentration, language, motor function, memory, spatial perception, orientation, perceptual speed and general mental status have been identified (e.g. Aberg & Kihlgren, 1974, 1980; Dahme et al, 1993; Newman, 1993; Sotaniemi, 1980; Vingerhoets, Van Nooten, Vermassen, de Soete & Jannes, 1997).

It has been suggested that in adults left hemisphere functions remain intact whilst the right hemisphere is susceptible to damage (Sotaniemi, 1980). However, other

authors have found that cardiac surgery may also affect left hemisphere functions particularly verbal memory (Newman, 1993; O'Brien et al, 1992; Vingerhoets et al, 1997). Longer-term follow-up studies have indicated that verbal memory can significantly improve when compared with baseline or control scores (Selnes et al, 2003; Vingerhoets et al, 1997).

The variability in the incidence and type of neuropsychological deficits has been associated with several factors related to the neuropsychological tests employed. For example, the number and type of tests adopted has varied widely between studies, with deficits more frequently identified when a larger number of tests have been used (Newman & Stygall, 2000). Test sensitivity is another factor that influences research findings, as measures differ in their capacity to detect subtle outcomes. The timing of testing is also important, partly because lowered mood prior to or after surgery can significantly affect neuropsychological functioning (Andrew, Baker, Kneebone & Knight, 2000; Dahme et al, 1993; Heller et al, 1970), but also because performance in the acute post-surgical phase may be influenced by transient neuropsychological deficits, analgesia, pain and tiredness (Newman & Stygall, 2000). Other factors such as study design, appropriateness of controls and patient related variables i.e. age and the extent of cardiac disease, are also thought to affect outcome.

Given the findings from adult research studies, which indicate that cardiac surgery can significantly impair neuropsychological functioning, attention has more recently focused on the ways in which open-heart surgery may affect the normal development of a child's brain. Some authors have identified significant impairments after surgery, with a higher risk of developmental delay following palliative treatment

than after corrective surgery (Dittrich et al, 2003). This study was limited by methodological problems such as a heterogeneous treatment group and inclusion of children with a non-significant heart defect into the non-surgical, healthy control group, however, other more well-controlled investigations of children with acyanotic heart defects have also identified post-surgical cognitive impairments (Yang, Liu & Townes, 1994).

A number of investigations of the effect of specific surgical procedures have also identified varying degrees of cognitive impairment in children who have received cardiac surgery. In a study comparing the effects of cardiopulmonary bypass with or without deep hypothermic circulatory arrest upon neuropsychological outcome, the latter was found to be more likely to affect intellectual and motor function adversely following closure of an acyanotic heart defect (ventricular septal defect), although postoperative information consisted only of clinical observations (Wright et al, 1979). This finding was also confirmed in a series of retrospective studies with children who have cyanotic heart problems (Newburger et al, 1993; Bellinger et al, 1995; Bellinger et al, 1999).

At one and four year longitudinal follow up the use of circulatory arrest was associated with an increased risk of delayed motor development, visuo-spatial and visual-motor integration deficits were also commonly noted. Neuropsychological assessment at four years of age demonstrated no difference in IQ scores between treatment groups (Bellinger at al, 1999). Unfortunately, despite the longitudinal and well-controlled design of these studies, measures were limited to IQ, language and

motor skills, and as such it is not possible to determine how these surgical treatments affect other aspects of cognitive development.

There are also conflicting findings regarding the risk of brain injury when deep hypothermic circulatory arrest is used for more than 30 minutes (Dickinson & Sambrooks, 1979; Bellinger et al, 1995; Haneda, Itoh, Togo, Ohmi & Mohri, 1996; Miller et al, 1994; Oates, Simpson, Cartmill & Turnbull, 1995; Wells, Coghill, Caplan & Lincoln, 1983). Unfortunately, the young age of the children recruited and choice of assessment tools has limited the conclusions that can be drawn from these studies.

A number of investigators have found that cardiac surgery, irrespective of the type of surgical procedure, does not adversely affect cognitive and psychomotor functioning in children. For example, an early study by Haka-Ikse et al (1978), which looked at the effects of deep hypothermic circulatory arrest, found that in the early postoperative stages the surgical group had significantly lower developmental quotient scores than a sibling control group but their scores were within the normal range at longer-term follow-up. This would seem to suggest that the effects of surgical procedures may be transient, although as sensitive measures of neuropsychological functioning were not included in the test battery it is not clear whether some aspects of cognitive functioning remained impaired but undetected.

Despite the methodological problems of the study by Haka-Ikse et al (1978), other studies have confirmed the absence of long-term effects on neuropsychological functioning from open-heart surgery. In a prospective study examining motor,

adaptive, language, personal and social development, Blackwood, Haka-Ikse & Steward (1986) found no significant difference in the developmental quotient values of children who had undergone cardiopulmonary bypass with or without deep hypothermic circulatory arrest, when compared with baseline scores. The scores were also found to be similar between the groups.

Further support for the non-detrimental effects of cardiac surgery on the paediatric brain was provided by Settergren et al (1982) in their retrospective interview study with parents of children who had received cardiopulmonary bypass with or without deep hypothermic circulatory arrest. A series of interviews up to three years post-surgery did not reveal any significant group differences. As previously mentioned, however, the effects of cardiac surgery upon the brain can result in subtle and sometimes, unobservable deficits, some of which may only be detected through sensitive tests such as those used during neuropsychological assessment.

Instead of focusing on the ways in which the type of surgical technique may affect cognitive functioning, other investigators have studied how children who have received open-heart surgery may compare with other surgical groups or healthy controls. One study of this nature, an unpublished dissertation (Dabek, 1983), prospectively compared the skills of children who were due to have open-heart surgery against a normal orthopaedic surgery group and a neurologically impaired control group. Although the author found no difference in preoperative IQ scores between groups, significant pre-operative sensori-motor impairments in the cardiac group were noted. It was suggested that surgery did not have any major impact upon intellectual functioning or 'neuropsychological' functioning at six week follow-up,

however as the 'neuropsychological' battery addressed mainly aspects of sensori-motor abilities, the extent to which other domains of cognitive abilities (e.g. memory, attention) had changed after surgery was not addressed.

A more recent prospective study (Wray & Sensky, 2001), compared a cardiac surgery group against a group of children awaiting bone marrow transplantation and a healthy control group. Preoperatively, overall IQ did not differ significantly between the cardiac and reference groups, although the former performed more poorly on information processing. At 12 month follow-up, the cyanotic subgroup's scores had declined on every subtest, although not to significant levels, whereas the acyanotic subgroup's results were generally unchanged. This contradicts the findings in some studies which have identified an increase in intelligence quotients after surgery, especially for children with cyanotic heart defects (Linde, Rasof & Dunn, 1970; Sunderland et al, 1973). Unfortunately, however, these researchers did not control for the type of surgical procedure used which, as discussed previously, is a potential source of variability. In addition, testing was constrained to intelligence quotients.

Given the retrospective design of the majority of existing studies in this area, some authors have attempted to clarify the extent to which the classification of congenital heart disease (i.e. cyanotic or acyanotic) and specific type of structural defect could contribute to preoperative cognitive impairments, later developmental problems and the risks related to cardiac surgery. Several researchers have suggested that cognitive development is more likely to be compromised in children with cyanotic lesions (e.g. De Maso, Beardslee, Silbert & Fyler, 1990; Feldt, Ewert, Stickler &

Weidman, 1969; O'Dougherty, Wright, Garmezy, Loewenson & Torres, 1983; Newburger, Silbert, Buckley & Fyler, 1984; Silbert, Wolff, Mayer, Rosenthal & Nadas, 1969). Although the mean IQ for cyanotic and non-surgical acyanotic children has been found to fall in the normal range, IQ of children with cyanotic heart disease has been found to be significantly lower due to degree of cyanosis rather than duration of hypoxemia (Aram, Ekelman, Ben-Shachar & Levinsohn, 1985).

The degree to which the duration of hypoxia and age of repair could impair cognitive function was investigated in a retrospective study of children with transposition of the great arteries (O'Dougherty et al, 1985). These authors found that those children who did not receive surgery until after 14 months of age were more likely to have cognitive impairments such as attentional difficulties and neurological abnormalities. Newburger et al (1984) also found an inverse relationship between age of correction and cognitive function.

In contrast, a more recent retrospective study by Oates et al (1995), comparing children with cyanotic or acyanotic congenital heart disease on a range of neuropsychological tests (IQ, verbal and visual memory, attention and executive functioning), found no evidence of detrimental effect of older age at operation. These authors suggest that the discrepancy between their findings and those of O'Dougherty et al (1985) may be due to insufficient statistical power in the latter.

Conclusions & Future Directions

Despite a general consensus in the adult cardiac literature regarding the possible deleterious effects of cardiac surgery upon neurological and neuropsychological functioning, to date, studies of children with congenital heart disease are of limited value. Of the existing outcome studies in this area, many are outdated due to the technical refinements that have occurred in surgery over the last decade or so. In addition, as surgery is often carried out in the neonatal period or during early infancy, researchers have struggled to obtain baseline measures of the child's preoperative abilities due to the limited neuropsychological tests available and problems regarding co-operation of the child during testing.

Furthermore, as research evidence highlights the possibility of pre-existing cognitive problems in children with congenital heart problems either as a consequence of the heart defect itself or associated abnormalities, the conclusions that can be derived from these studies have been restricted by their retrospective design (Aisenberg, Rosenthal, Nadas & Wolff, 1982; Aisenberg, Rosenthal, Wolff & Nadas, 1974; Samango-Sprouse & Suddaby, 1997). Future research studies need to be prospective, well-controlled and longitudinal in order to adequately assess the correlation between cardiac variables and cognitive development.

In addition to the retrospective nature of a significant proportion of the research, comparison of the findings between studies has also been hampered by the different methodologies employed, such as the time periods after surgery at which testing took place; the heterogeneous nature of the cardiac group (i.e. the combination of cyanotic and acyanotic heart defects or mix of different types of structural defect within each

of these classifications); the use of inappropriate control groups; the different periods of time after surgery at which testing took place; the absence of long-term follow-up; the age of the child when testing took place; and the choice of neuropsychological measures.

Some researchers have acknowledged that the assessment batteries have focused predominantly on IQ (e.g. Wray & Sensky, 2001) or developmental quotients, where younger participants were studied. However, general intelligence measures are not sufficiently sensitive to measure accurately responses to treatment in specific cognitive domains (Baron et al, 1995). Furthermore, developmental measures are even less satisfactory as they focus more heavily on sensori-motor function than other areas of development and their validity as a predictive measure of later intellectual skills is questionable.

The challenge for further research is to develop an appropriate test battery which will be sufficiently sensitive to detect subtle impairments in cognitive functioning following cardiac surgery. Ideally, future research will focus on targeted measurement of the different domains of cognitive functioning which are at risk following surgery. Although the research available does not provide conclusive evidence to indicate which areas of the brain are vulnerable to cognitive impairment following open-heart surgery, neuropathological and neuroimaging findings may help to inform this process.

Paediatric studies in these disciplines have suggested the potential vulnerability of several parts of the developing brain such as the frontal and the parieto-occipital

watershed region, as well as the hippocampus, cerebellum, periventricular white matter, cingulate gyrus and globus pallidus (e.g. Bozóky et al, 1984; McConnell et al, 1990; Wong et al, 1992). These anatomical findings support some of the evidence from neuropsychological research studies, which suggest that aspects of memory, attention, psychomotor development and executive functioning may be compromised in this population. In order to provide more concrete evidence regarding the possible cognitive risks of cardiac surgery, well-controlled studies of an exploratory nature will initially need to employ a broad range of assessment tools.

The cognitive domain which may be of particular interest is that of memory, as the post-operative vulnerability of the hippocampus, documented in studies of adults and animals (Baron et al, 1995) suggests that this may be an area of significant investigative priority in the paediatric population. The findings that verbal memory may be impaired in adults at least one month after open-heart surgery (O'Brien et al, 1990) raises the question about the pre and post-operative integrity of memory function in children following surgery and the potentially far-reaching effects that this may have upon their learning and the acquisition of new information. Unfortunately, despite the paramount importance of memory in normal everyday functioning, this area of cognition has received little attention in the paediatric literature.

The possible detrimental effects of paediatric open-heart surgery is an area of major research importance for two main reasons. Firstly, an understanding of the cognitive sequelae of cardiac surgery could inform the intra-operative interventions adopted and the post-surgical care provided for these children, and secondly, the early

identification of cognitive deficits could alert clinicians and educational professionals to the child's changing individual needs, thus increasing functional outcome.

One way in which future research could address the problems identified in the current literature would be to conduct small group or case control studies using a fixed neuropsychological assessment protocol across a number of cardiac surgery services. The use of baseline measures and appropriate control groups, would significantly improve upon the experimental design adopted in many of the existing studies. However, before studies of this nature are possible, preliminary investigations are required to ascertain the types of neuropsychological measures that would be appropriate for a wider scale assessment protocol. This evidence could then provide a useful foundation upon which further comparison group studies could be conducted.

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Empirical Paper

An Investigation of Neuropsychological Outcome after Paediatric Heart Surgery

Volume II of II

by

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ABSTRACT

Background. Numerous studies have been conducted with adults that indicate a variety of neuropsychological deficits after open-heart surgery (e.g. Vingerhoets, Van Nooten, Vermassen, de Soete & Jannes, 1997) which may be associated with the influence of ischaemic-hypoxic injury upon the brain. However, little is known about the effect of cardiac surgery upon the cognitive development of children.

Method. The current study was designed to explore the possible neuropsychological outcomes for paediatric patients following open-heart surgery. This investigation consisted of a series of five single case studies. Children (7 to 15 years) diagnosed with cardiac abnormalities, and age-matched controls, were assessed at three time points: 1) prior to surgery; 2) one month post surgery; and 3) three months post surgery using a battery of standardised neuropsychological tests to assess both global abilities and specific domains of cognitive functioning.

Results. Clinically significant improvements in intellectual functioning were identified in one child following surgery. Some improvements related to attention, executive functioning, verbal and visual memory were noted across the sample, however a pattern of significant decline in attention and verbal memory was identified for one patient participant. A less notable and more scattered pattern of decline was also observed in two other patient participants.

Conclusion. This study highlights the potential cognitive benefits of paediatric open-heart surgery, however, the results also appear to reflect some of the more subtle neuropsychological deficits indicated in the literature. Further research in the form of well-controlled prospective comparison studies is required.

INTRODUCTION

The introduction of open-heart surgery in the 1950's (Lillehei, 1955; Kirklin et al, 1955) to correct adult heart problems, led to significant concerns regarding the possible deleterious effects of these surgical procedures upon normal brain functioning (Newman & Stygall, 2000). The widespread use of a technique known as cardiopulmonary bypass, involving the redirection of blood away from the heart whilst maintaining oxygenation and blood flow to the rest of the body, was central to this controversy. Although this surgical advance offered significant benefits in terms of reduced mortality rates (Taylor, 1993), the cardiac research literature continues to report cerebral dysfunction as a major consequence.

Studies of adults who have undergone open-heart surgery highlight a number of neuropsychological deficits such as problems with sensation, attention and concentration, language, motor function, memory, general mental status, spatial perception, orientation and perceptual speed (e.g. Aberg & Kihlgren, 1974, 1980; Dahme et al, 1993; Newman, 1993; Sotaniemi, 1980; Vingerhoets, Van Nooten, Vermassen, de Soete & Jannes, 1997). These deficits appear to be related to damage which has been identified in the hippocampus, basal ganglia and cerebellum (Brierley, 1963; Stockard, Bickford & Shauble, 1973) as well as in the watershed area of the brain which is served by the major blood vessels.

A number of intraoperative variables are thought to be responsible for this cerebral damage, of which four main mechanisms are consistently reported: reduced cerebral blood flow; obstruction of the local blood supply to the brain due to the introduction of gas bubbles (macroemboli) or cellular particles (microemboli) and; a systemic

inflammatory response to the bypass machine, causing brain swelling (e.g. Taylor, 1993), all of which can potentially cause ischaemic-hypoxic cerebral damage. The neurological and neuropsychological deficits in adults as a consequence of these intraoperative factors have raised concerns regarding the impact of open-heart procedures upon children.

One of the more common paediatric heart problems requiring surgery is that of congenital heart disease (Baron, Fennell & Voeller, 1995), which occurs in approximately 6 to 8 per 1000 liveborn children (Clark, 1992; Perry, Neill, Ferencz, Rubin & Loffredo, 1993) and of whom more than a third will require surgical intervention early in infancy (Mahle & Wernovsky, 2000). Despite the relatively high incidence of neurological problems in these children, either as a consequence of the heart condition or its treatment, there still appears to be a lack of research evidence regarding cognitive complications (Fallon, Haw & Kirkham, in press).

Although many children do well, it is estimated that up to 30% experience detrimental effects following open-heart surgery (Bellinger et al, 1991; Ferry, 1990; Furlan et al, 1992; McConnell et al, 1990; Mendoza, Wilkerson & Reese, 1991; Miller, Rodichok, Baylen & Meyers, 1991; Newburger et al, 1993; Park and Neches, 1993) with problems such as cognitive deficits, seizures, involuntary motor activity with poorly co-ordinated and exaggerated movements (choreoathetosis), bilateral motor deficits and hemiparesis (Volpe, 1995). Although most children do not exhibit such obvious cerebral difficulties postoperatively, there is increasing concern regarding the high incidence of subtle long-term cognitive and motor deficits (Kirkham, 1998).

A small number of studies investigating the anatomical changes after surgery have identified certain parts of the paediatric brain that appear to be particularly vulnerable to damage. These include the frontal and parieto-occipital cerebral cortex, hippocampus, cerebellum, white matter around the ventricles (periventricular), cingulate gyrus, globus pallidus and pallidosubthalamic pathways (e.g. Bozóky, Bara & Kertész, 1984; Wong et al, 1992). Injury to these areas occurs primarily as a consequence of diffuse ischaemia, infarction, atrophy, subdural haematomas and loss of differentiation between white and grey matter (e.g. McConnell et al, 1990; Mahle et al, 2002; Muraoka et al, 1981). Importantly, normal follow-up scans for a number of children may indicate the possible transient nature of these defects (Mahle et al, 2002; Muraoka et al, 1981).

Despite the fairly consistent finding of neuropsychological deficits in a proportion of adults who had undergone open-heart surgery, the outcome for children is less clear and paediatric research is limited. Whilst some authors have identified significant cognitive impairments following surgery (e.g. Bellinger et al 1995; Dittrich et al, 2003; Yang, Liu & Townes, 1994) others have found either no detrimental effects following surgery (e.g. Blackwood, Haka-Ikse & Steward, 1986; Settergren et al, 1982) or a resolution of neuropsychological problems at longitudinal follow-up (e.g. Bellinger et al, 1999).

These findings are further complicated by the use of an additional technique of whole body hypothermia (deep hypothermic circulatory arrest) (Barratt-Boyes, Simpson & Neutze, 1970; Castadena, Lamberti, Sade, Williams & Nadas, 1974) designed to protect the heart, brain and other organs from ischaemic damage when the circulation

is stopped. Some studies comparing this method with cardiopulmonary bypass found it had detrimental effects upon cognitive functioning (e.g. Bellinger et al, 1995; Newburger et al, 1993; Wright, Hicks & Newman, 1979).

Comparison between the existing paediatric studies has been hampered by a variety of methodological problems. As surgery is often carried out in the neonatal period or during early infancy, it is difficult to obtain preoperative measures due to the lack of appropriate neuropsychological tools and problems of co-operation of the child during testing. Some researchers have attempted to overcome this problem by using preoperative developmental measures (e.g. Oates, Simpson, Cartmill & Turnbull, 1995), although these have limited value in predicting a child's cognitive skills later in life. The retrospective design of many studies is of concern particularly in view of the fact that a number of children with congenital heart disease have pre-surgical neurological and neuropsychological abnormalities as a consequence of their heart problem (Haka-Ikse, Blackwood & Steward, 1978; Jonas, 2000; Mahle & Wernovsky, 2000).

Prospective studies are required to disentangle pre-existing conditions from those which occur postoperatively (Medlock et al, 1993). However, although a small number of prospective studies exist (e.g. Wray & Sensky, 2001), the assessment tools tend to be limited to a measure of global intelligence quotients (IQ). This offers some information about the effects of surgery upon a child but these measures are not sufficiently sensitive to identify more specific cognitive problems.

The combination of different types of heart defect (i.e. cyanotic and acyanotic) in some studies (e.g. Dittrich et al, 2003) has also been problematic, especially as several researchers have identified compromised cognitive development in children with cyanotic lesions (e.g. De Maso, Beardslee, Silbert & Fyler, 1990; O'Dougherty, Wright, Garmezy, Loewenson & Torres, 1983; Newburger, Silbert, Buckley & Fyler, 1984), and lower preoperative IQ than children with acyanotic heart disease (Aram, Ekelman, Ben-Shachar & Levinsohn, 1985). As so little is known about the effects of surgery upon different cognitive domains, future research needs to be not only prospective in design, to control for pre-existing cognitive problems, but should also assess cardiac problems separately, although this may be premature until further exploratory studies have been conducted.

Due to the lack of well-controlled studies in this area and limitations of the existing research, the current study was designed to investigate the possible effect of heart surgery upon a child's cognitive functioning. It was anticipated that this could be achieved through pre and post-surgery assessment, using a comprehensive battery of neuropsychological tests to measure both global abilities (i.e. general intellectual functioning and academic performance) and specific areas of cognitive functioning. As factors such as type of heart defect, pre-operative cognitive abilities, type of surgical procedure and previous history of open-heart surgery could all potentially influence outcome, a series of five single case studies were used to allow for detailed neuropsychological assessment and to control for these factors.

In response to the best available evidence the following domains were assessed:

1) attention i.e. the ability to selectively attend to relevant stimuli, to sustain attention over a period of time, to divide attention between two stimuli simultaneously and to switch attention from one task to another (e.g. Manly, Robertson, Anderson & Nimmo-Smith, 1999);
2) executive functioning i.e. the ability to carry out tasks involving planning and organisation, problem solving, abstract thinking and mental flexibility (e.g. Anderson, 1998; Duncan, 1986);
3) memory i.e. the ability to learn and recall information presented through verbal and visual mediums (e.g. Stirling, 2002);
4) visuo-spatial skills i.e. the ability to carry out tasks involving visualisation and movement of objects in space (e.g. Kolb & Whishaw, 1996);
5) visuo-motor and sensori-motor skills i.e. the ability to carry out tasks requiring eye hand co-ordination and fine motor control (e.g. Beery, 1997; Korkman, Kirk & Kemp, 1998).

One area of particular interest was that of memory function following open-heart surgery, particularly verbal memory, as deficits in this area have been identified in adults at least up to one month post-surgery (O'Brien et al, 1992). As ongoing verbal memory problems could have far reaching effects upon learning and quality of life in paediatric patients, skills in this domain were investigated at both one and three months post-surgery.

It was hoped that this study would contribute to current understanding of the changing needs of a child with congenital heart disease in the post-surgical recovery

phase. In the absence of detailed neuropsychological outcome studies with paediatric heart patients, the current study was designed to explore the following research questions:

1. Do paediatric cardiac patients have normal pre-surgery cognition (i.e. general intellectual and academic skills, attention and executive functioning, visual and verbal memory, visuo-spatial, visuo-motor and sensorimotor skills) compared with age-matched healthy controls?

2. Do changes in general intellectual functioning occur after surgery?

3. How (if at all) do the specific domains of cognitive function change in paediatric heart patients following surgery?

METHOD

Participants

Five male children with congenital heart disease aged between 7 and 15 (7, 11, 11, 14 and 15 years) were recruited from the Cardiology Department's list of individuals awaiting open-heart surgery at a city general hospital. These patient participants will be referred to as P1, P2, P3, P4 and P5, respectively. The number, age and type of heart defect of the children who were recruited was dependent upon the pattern of referrals received by the hospital during the recruitment period November 2002 to February 2003.

An equal number of healthy children who matched the patient group in age and gender, were recruited to the control group (C1, C2, C3, C4 and C5). For P1, P4 and

P5 it was possible to recruit either a school friend or neighbour, however as this was not possible for P2 and P3 control participants were recruited from alternative sources. Children who had speech or hearing impairments, an identified learning disability or a specific genetic syndrome related to the heart defect (e.g. microdeletion of 22q 11.2) were excluded from this study. Children who had chronic or serious health conditions or who had also had heart surgery, were excluded from the control group.

Design

This study took the form of a series of five single case studies, for which repeated neuropsychological measures were taken at three time points (before surgery, one and three months after surgery). This design was chosen in preference to a group study for two main reasons: i) insufficient evidence regarding the effects of different types of congenital heart deficit upon cognitive functioning indicated that a group study would not be appropriate; ii) single case design allowed for a more extensive neuropsychological assessment of the cognitive abilities of each participant than has been achieved by previous studies in this area.

Neuropsychological Assessment

Following careful consideration, an extensive test battery was developed with the assistance of the Clinical Child Neuropsychologist at a city general hospital. Tests were included in the battery on the basis of their psychometric properties (i.e. reliability and validity), age appropriateness, availability of parallel versions and the time taken to complete them (i.e. to reduce the effects of fatigue upon performance). The battery was designed to explore all aspects of functioning that had been

implicated in previous research studies, such as emotional well-being; general intellectual and academic abilities; attention and executive functioning; verbal and visual memory; visuo-spatial, visuo-motor and sensorimotor abilities.

The test battery was piloted with two healthy children (aged 7 and 8 years), then shortened following pre-surgery assessment of the first two patient participants, due to testing fatigue. The final assessment battery took 2.5 hours to complete. Details of the psychometric properties of each measure used within these domains, is provided below.

Emotional Well-being

Child Behaviour Checklist (Achenbach, 1991)

To determine whether scores on the neuropsychological tests were affected by changes in levels of distress at the time of testing the Child Behaviour Checklist was used. This questionnaire has norms for children aged 4 to 18 years, good test-retest reliability and good content and construct validity. Parental responses to 113 questions on a three point scale were categorised into eight standardised domains (withdrawn, somatic complaints, anxious/ depressed, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour) which provided an indication of the severity of any problem behaviours (i.e. internalising and externalising behaviours). The same parent was asked to complete the questionnaire at each of the three time points, to reduce variability.

General Intellectual and Academic Functioning

Wechsler Intelligence Scale for Children - WISC-III (Wechsler, 1992)

This widely used UK standardised test was designed to measure the general intellectual ability of children between the ages of 6 and 16. Due to testing time constraints, a shortened version with good reliability and validity (Kaufman, Kaufman, Balgopal & McLean, 1996) was used for this study and consisted of two verbal subtests (Similarities and Arithmetic) and two non-verbal subtests (Picture Completion and Block Design). Scores on these subtests were used to calculate a Full Scale Intelligence Quotient. As parallel versions of the WISC-III have not been developed, the same assessment was conducted at the first (pre-surgery/ baseline) and last (three month post-surgery/ three month follow-up) time points.

Wechsler Individual Achievement Test – UK Quicktest – WIAT (Wechsler, 1995)

This test can be used with children aged 6 to 16 years of age, has good reliability and validity and was adopted to provide a brief overview of academic abilities. The Basic Reading subtest from the Wechsler Objective Reading Dimensions (WORD; Wechsler, 1993) and Mathematical Reasoning subtest from the Wechsler Objective Numerical Dimensions (WOND; Wechsler, 1996) were used.

Attention and Executive Functioning

Similarities and Arithmetic Subtests of the WISC-III

As described above in the general intellectual and academic functioning section, these subtests contribute to the Full Scale IQ scores. They were also used to measure abstract reasoning skills (Similarities) and mental manipulation/ calculation abilities (Arithmetic).

Test of Everyday Attention - TEA-Ch (Manly et al, 1999)

This is a standardised battery of tests with good reliability and validity for use with children between 6 and 16 years, which measures different aspects of a child's ability to attend in practical settings. The selected subtests assess sustained attention (Score!), selective/ focused attention (Sky Search), attentional control/ switching (Creature Counting) and sustained-divided attention (Sky Search DT and Score! DT). A parallel version was available for re-testing to reduce the influence of practice effects.

Working Memory Test Battery for Children – WMTB-C (Pickering and Gathercole, 2001)

This is a standardised battery for children aged 5 to 15, consisting of nine subtests which are designed to reflect the three component structure of the Working Memory Model (Baddeley & Hitch, 1974). Three subtests were selected: forward digit recall to assess phonological loop function; backward digit recall to assess central executive function; and block recall (forward) to assess visuo-spatial sketchpad function.

Verbal and Visual Memory

Rey Auditory-Verbal Learning Test - RAVLT (Rey, 1958)

This test was adopted to assess verbal learning and memory. It consists of free recall, 20 minute delayed recall and recognition trials. Although originally developed for adults, normative data are available for children aged 7 to 15 (Forrester & Geffen, 1991). This test was administered at each of the three time

points (before surgery, one month after surgery and three months after surgery). Controls were also tested at the same time points.

In order to reduce the possibility of practice effects, parallel versions were used at each of the three testing time points. At time point 1, list A (Taylor, 1959) and interference list B (Lezak, 1976) were used; at time point 2, list C (Lezak, 1983) and interference list D (Ryan, Geisser, Randall & Georgemiller, 1986); and at time point 3, list E and interference list F (Geffen, Butterworth & Geffen, 1994).

Rivermead Behavioural Memory Test for Children - RBMT-C (Wilson, Ivani-Chalian and Aldrich) and *Rivermead Behavioural Memory Test - RBMT* (Wilson, Cockburn and Baddeley, 1985).

This test was designed to measure memory abilities for everyday tasks and can be used with children aged 5 to 10 (RBMT-C) and 11 onwards (RBMT). Story recall was chosen because it measures immediate and delayed verbal memory and offered parallel versions. This test is described as having good reliability and validity.

Rey-Osterrieth Complex Figure Test - CFT (Taylor, 1969, 1979)

This test was used to measure visual memory skills and constructional ability. It requires the child to copy the design then recall it after three minutes (immediate recall) and 30 minutes (delayed recall) (Spreen & Strauss, 1998). An alternative form was used for repeated testing to reduce the risk of practice effects (Taylor, 1969, 1979). This test has good validity but moderate reliability (Berry, Allen & Schmitt, 1991), with the Rey figure being described as slightly harder (about 5 points) than the Taylor figure (Spreen and Strauss, 1998).

Visuo-spatial, Visuo-motor and Sensorimotor Abilities

Block Design and Picture Completion Subtests of the WISC-III

As described above in the general intellectual and academic functioning section, these subtests contribute to the Full Scale IQ scores. They were also used to assess visual recognition (Picture Completion) and visuo-spatial skills (Block Design).

Developmental Test of Visual-Motor Integration – VMI (Beery, 1997)

This standardised test was used to assess visuo-perceptual and motor skills and has age related normative data available for children aged from 3 to 16 years. The participant was assessed on their ability to copy 24 geometric designs, which follow a developmental gradient of difficulty. Parallel versions were not available but test-retest after a short period does not compromise the reliability.

Nepsy Developmental Neuropsychological Assessment (Korkman et al, 1998)

This is a comprehensive, standardised neuropsychological battery of tests for use with children between the ages of 3 and 12. One of the five domains (Sensorimotor Function) was used for this study as it provided a way of assessing each child's finger dexterity (Fingertip Tapping), ability to copy a hand position (Imitating Hand Positions), fine motor skills and hand-eye co-ordination (Visuomotor Precision).

Procedure

Approval was received from the Local Research Ethics Committee of the NHS Trust (see Appendix 2), Data Protection (Appendix 3) and Research & Development (Appendix 4). Patients awaiting open-heart surgery who met the inclusion criteria, were identified and approached at pre-surgery consultation. Age and gender

matched controls were identified by patient participants where possible. Information sheets were provided (see Appendix 5) and those interested were asked to complete a consent form at the first home visit (see appendix 6).

The comprehensive test battery was administered to the patient participants at two time points: 1) before surgery; and 2) three months after surgery. Each phase of testing was conducted in a single testing session. The measures were administered in the same order for each participant (see Appendix 7 for testing protocol) at each of the two time points, to eliminate the variability in performance that could be associated with test order. An additional testing time point, one month after surgery was introduced to assess verbal memory (RAVLT) and emotional well-being (CBCL). Control participants were assessed with the same test materials at time intervals which matched their patient participant as closely as possible.

At the second time point a short semi-structured interview was administered to parents (see Appendix 8), to gather information regarding their child's pattern of recovery and any observed difficulties post-surgery. Any changes in circumstances for the control participants were also noted at this time. Parents of patient and control participants were asked to complete a questionnaire (Child Behaviour Checklist) at each testing time point, as an observational measure of their child's current emotional state.

Tests were scored according to the relevant criteria and raw scores were converted using the statistical tables and normative data provided in the test manuals or associated literature. A random sample of results was scored by the Clinical Child

Neuropsychologist for inter-rater reliability. Small deviations in scoring for the Rey Osterrieth Complex Figure Test were observed and although these were not at sufficiently high levels to be of concern the researcher reviewed the scoring for this test. It is planned that in due course a summary of the findings will be sent to each participant. Any specific problems identified will be resolved on an individual basis in association with the Consultant Paediatric Cardiologist.

Analysis

Despite varying definitions of statistically significant change in single case studies, for the purpose of this research, significant change was taken to be a change in scores of one or more standard deviations (Bellinger, 2003). The responses for each child were scored according to test specific criteria as outlined below. This criterion allows for the possibility of practice effects e.g. FSIQ from the WISC-III can increase by 7 to 8 points if retesting occurs within six months, however a clinically significant change of 15 or more points should have controlled for this difficulty (Wechsler, 1992).

Emotional well-being was calculated according to the parental ratings on each question of the Child Behaviour Checklist. Questions were categorised according to specific behaviours and the responses (ranging from 0 to 2) were summed to provide a raw score for 'internalising' behaviours (withdrawn, somatic complaints, anxious/ depressed) and 'externalising' behaviours (delinquent and aggressive behaviour). The raw score for each category was converted into a T score using the CBCL analysis sheets (M = 50; SD = 10). T scores between 60 and 63 indicated problem

behaviours in the borderline clinical range and scores above 63 indicated problem behaviours in the clinical range.

On the WISC-III, scores on the four subtests (Similarities, Arithmetic, Picture Completion, Block Design) were translated into age related scaled scores using normative data. Scaled scores (M = 10; SD = 3) were used to calculate a Full Scale Intelligence Quotient (FSIQ, M = 100; SD = 15) for each child using a formula provided by Kaufman et al (1996).

For the WIAT Quicktest, the subtest raw score (i.e. number of items correct) was calculated and converted into standard scores (M = 100; SD = 15) using UK standardised norms. As parallel forms of this test were not available, the researcher was mindful that test-retest scores can increase by up to three standard score points when the retest period is short (Wechsler, 1995).

RAVLT raw scores derived from the total number of items recalled over the 5 trials (learning), after a 30 minute delay (delayed recall) and number of first list items correctly recognised from a group of words (recognition), were converted into standardised scores using the published normative data (Forrester & Geffen, 1991).

On the RBMT and RBMT-C, raw scores were calculated for the total number of correct ideas (or close synonyms) recalled immediately after presentation of the story and after a 20 minute delay. For the children aged 11 years and above, RMBT normative data were used, as although the original normative data were from adults the authors state that this does not differ significantly from data collected from

children aged 11 to 14 years (Wilson, Forester, Bryant & Cockburn, 1990). As appropriate age related means and standard deviations for the story recall subtest were unavailable for the RBMT-C, from either previous research (Aldrich & Wilson, 1991) or the author (Wilson, B. 2003, personal communication), a percentage change in score from pre-surgery/ baseline to follow-up was determined for the 7 year old participants, using clinical judgement to determine the significance of this change.

The CFT drawings were scored according to the Taylor criteria (Spreen & Strauss, 1998). Normative data for children aged 6 to 16 years (Kolb & Whishaw, 1990), were used to convert raw scores into standard scores. Normative data were not available to convert immediate recall raw scores into standard scores.

On the TEA-Ch, raw scores for each subtest were converted into age scaled scores (M = 10; SD = 3) using the normative data provided in the manual. Raw scores on the VMI and WMTB-C were converted into standard scores using the available standardised norms (M = 100; SD = 15). Some caution may be required when interpreting the scores of block recall as this was described as having lower test-retest reliability than other subtests on the WMTB-C (Pickering & Gathercole, 2001).

Nepsy subtest raw scores were converted into age scaled scores (M = 10; SD = 3). However, as standardised data was only available for children up to the age of 12 years, the scores of older children recruited to this study were converted using the data for children aged 12 years 11 months.

Descriptive statistics were used to analyse the results for each individual. The single case design of this study precluded extensive statistical analysis, however, comparisons of scores between the patient and control participants were made through the use of normative data and z scores.

RESULTS

Of the five patient participants who were recruited to this study, three had previously undergone heart surgery within their first two years of life (P2, P4 and P5). One child had undergone several heart repair procedures (P5) prior to the current admission. All patient participants had received an early post-natal diagnosis of congenital heart disease except for P3 who had been diagnosed more recently. Three patient participants received an original diagnosis of acyanotic heart disease (P1, P2, P3), namely atrial septal defect (Appendix 1) and the other two received an original diagnosis of cyanotic heart disease (P4, P5), namely tetralogy of Fallot. (Appendix 1). Unfortunately as most of the children had not been born locally, it was not possible to obtain information about their general neonatal health and blood oxygen saturation immediately after birth. All available details regarding each child's developmental characteristics and surgical history can be found in Table 1.

Insert Table 1 about here.

For a clearer analysis of the findings from this study, each patient participant's scores will be discussed in turn within the context of comparison data from their matched

control and available normative data. Changes in performance from pre-surgery (baseline for controls) to post-surgery assessment (follow-up for controls) will be considered with regard to each of the assessment domains. With reference to the results, the term 'significant' is used to denote statistical significance.

Insert Tables 2 to 6 about here

Participant Pair One (Patient P1 and Control C1)

P1's acyanotic heart disease had been diagnosed several years prior to the current admission, although he had not previously required surgery. Surgery was required for closure of an atrial septal defect (hole in the right atrium, see Appendix 1 for details), which was achieved whilst he was on cardiopulmonary bypass for 26 minutes without deep hypothermic circulatory arrest.

P1 was 7 years 4 months at the time of the initial assessment. Assessments were also conducted at four and 12 weeks after surgery. The control participant was assessed within one week of testing P1. P1 and C1 attended the same primary school, where they were both in year 2. P1 was three months and two weeks older than his control. According to parents, both children were performing well at school from a social and academic perspective at pre-surgery/ baseline, with no specific learning difficulties or neurological disorders reported. No major physical or cognitive problems were

reported for either child during the semi-structured interview at one month post-surgery/ follow-up.

CBCL emotional well-being scores for P1 and C1 (Table 2) were in the normal range before and after surgery, with externalising scores for P1 improving significantly after surgery ($z = -1.1$). P1's pre-surgery Full Scale IQ (low range) was significantly lower than the mean ($z = -1.7$) and C1's baseline scores, with no significant change in intellectual or academic functioning for either participant at follow-up.

P1's pre-surgery attention scores (table 4) were within the average to low ranges, with a significant improvement in sustained attention ($z = +1.7$) and sustained-divided attention ($z = +1.7$ and $+1.0$) after surgery. The improvements in sustained-divided auditory attention probably reflects the improvements in sustained auditory attention. C1's scores only improved significantly for sustained-divided attention ($z = +2.3$). P1's pre-surgery working memory scores were in the average to low ranges, with no significant difference from C1, however at follow-up, the significant improvements in C1's scores for digit recall forwards ($z = +1.6$) and digit recall backwards ($z = +2.1$) were not reflected in P1's scores, for which a significant decline was observed on digit recall backwards scores ($z = -1.1$). However, unlike P1, C1's scores were observed to decline significantly on block recall. There were no other significant changes on executive functioning.

P1's pre-surgery verbal learning and delayed verbal recall (Table 5), which were in the average range, were significantly lower than baseline scores for C1. Significant post-surgery improvements in verbal memory were observed for P1 on list learning

(z = +1.7), delayed list recall (z = +1.1) and immediate story recall (+26%). For C1, significant declines were observed on list learning (z = -1.0) and list recognition (z = -1.5), accentuating the improvements of P1 on verbal learning. Improvements were also noted in P1's delayed non-verbal memory (z = +1.9) (Table 5). P1's visuo-motor integration skills (Table 6) improved significantly at post-surgery follow-up, with no other changes in visuo-motor or sensorimotor skills.

Participant Pair Two (Patient P2 and Control P2)

P2's acyanotic heart disease (Co-arctation of the aorta, see Appendix 1) had been diagnosed in early infancy with open-heart surgery at two years old. The current admission was to repeat this surgical repair, for which he was on cardiopulmonary bypass for 2 hours and 25 minutes. Deep hypothermic circulatory arrest was used during the operation for 39 minutes.

P2 was 11 years 3 months at the time of the initial assessment, which was conducted one week before surgery, with follow-up assessments at four and 12 weeks. As P2 had been tutored at home for the previous two years, it was not possible to identify a suitable control from age matched friends or neighbours. C2 was two months older and in an equivalent academic year. At pre-surgery/ baseline no specific learning difficulties or neurological disorders were reported. No major physical or cognitive problems were reported for either child during the semi-structured interview at one month post-surgery/ follow-up.

P2's emotional-well being scores on the CBCL (Table 2) were all within the normal range, with no significant change from pre to post-surgery. C2's emotional well-

being baseline scores were significantly higher than for P2 with problem behaviours in the borderline to clinical ranges, although significant improvements in internalising ($z = -2.5$) and externalising ($z = -1.6$) scores placed these in the normal range at follow-up. Pre-surgery IQ scores (Table 3) for P2 and C2 were in the average range, with a significant increase in P2's IQ score ($z = +1.7$) at post-surgery follow-up. Academic functioning did not change significantly for either participant.

On attention tasks, (Table 4) P2's pre-surgery scores did not deviate significantly from C2, except for P2's significantly lower score for sustained-divided auditory attention, which improved significantly at post-surgery follow-up ($z = +1.0$). A significant decline in sustained attention ($z = -1.3$) was observed for C2, however a significant improvement in scores was found in selective attention ($z = +1.0$), which may have been associated with improvements in emotional well-being scores. Pre-surgery working memory skills (i.e. digit recall forwards) were significantly lower than for C2, with no significant changes for either participant in this area. P2's improvements in mental calculation ($z = +2.0$) and verbal reasoning ($z = +2.0$) were not reflected in C2's scores.

P2's preoperative verbal memory was in the average to high average range (Table 5), with improvements in list learning at both of the post-surgery assessments leading to a significant increase in scores by three month follow-up ($z = +1.2$). In contrast C2's scores declined at T2 and improved again by T3, but not to a significant level. A significant decline in C2's list recognition scores was observed at three month follow-up ($z = -1.2$).

P2's ability to copy and recognise visual detail (Table 6) also improved significantly, although no significant change was observed in visual memory, unlike C2, whose visual memory improved significantly (z = +1.0). There were no significant changes in visuo-spatial, visuo-motor or sensorimotor skills for P2 across time, although C2's visuo-motor precision scores were found to improve significantly at follow-up (z = +1.3).

Participant Pair Three (Patient P3 and Control C3)

P3's acyanotic heart disease was first diagnosed 10 months prior to current admission. Surgery was required for closure of a hole in the right atrium, which was achieved with cardiopulmonary bypass and mild hypothermia for 34 minutes. P3 was 11 years 9 months at the time of the initial assessment, which was conducted three days before surgery, with follow-up assessments at five and 14 weeks after surgery. P3 had been unable to identify a friend to participate in the study so C3, who was nine months younger, was recruited. At pre-surgery/ baseline no specific learning difficulties or neurological disorders were reported. No major physical or cognitive problems were reported for either child during the semi-structured interview at one month post-surgery/ follow-up. P3 had a bruised eye at three month follow-up, although this did not appear to interfere with his performance.

All CBCL scores of emotional well-being for P3 and C3 were in the normal range (Table 2). Although there was no significant change in P3's internalising scores at post-surgery follow-up, an increase in externalising scores did indicate a significant deterioration in behaviour (z = +1.0). Pre-surgery/ baseline Full Scale IQ scores and mathematics reasoning skills were significantly above the mean for P3 and C3 (Table

3). Pre-surgery basic reading scores, although within the average range, were significantly lower than for C3. No significant change in IQ or academic functioning at follow-up was noted for either participant.

P3's pre-surgery attentional scores were within the low average to high average range (Table 4), with a significant post-surgery decline in scores for sustained attention ($z = -2.0$), sustained-divided auditory attention ($z = -2.3$) and switching attention ($z = -1.0$). A significant decline in switching attention scores ($z = -1.0$) was also observed for C3. C3's significant improvement in sustained attention at follow-up ($z = +1.0$) exaggerated the difference between P3 and C3's scores, although C3's low baseline score for this subtest allowed more room for improvement. On executive functioning tasks, P3 showed a significant increase in scores for mental calculation ($z = +1.0$) whilst C3 showed improvements in abstract verbal reasoning ($z = +1.0$)

On verbal memory tasks P3's pre-surgery verbal learning and delayed verbal recall scores (Table 5) were in the exceptionally high range but were not significantly different from C3. A significant post-surgery decline was found for P3's scores on immediate story recall ($z = -1.1$) and delayed recall for both lists ($z = -1.4$) and stories ($z = -1.1$), although his scores improved for list recognition ($z = +1.2$). An improvement in C3's list learning ($z = +1.2$) was not reflected by P3. Pre-surgery scores for visuo-spatial, visuo-motor and sensorimotor tasks were in the average range, except for visuo-motor precision scores which were in the low range and were significantly lower than C3 suggesting preoperative difficulties in this area. C3's

scores on visuo-motor precision (z = -1.0) and visuo-motor integration (z = -1.1) declined significantly at follow-up

Participant Pair Four (Patient P4 and Control C4)

P4's cyanotic heart disease (tetralogy of Fallot, Appendix 1) was corrected at 18 months. Surgery was to repair the pulmonary valve and P4 was on cardiopulmonary bypass for 55 minutes without deep hypothermic circulatory arrest. P4 was 13 years 11 months at the time of the initial assessment (although he was 14 years old six days later). C4 was a close friend who was in the same academic year at a different school. P4 required Speech and Language Therapy in primary school, for a 'word order problem'. During the semi-structured interview at one month post-surgery follow-up, P4 reported some memory difficulties but at three months post-surgery follow-up, this had resolved. No difficulties were reported regarding C4.

P4's pre-surgery emotional well-being scores on the CBCL (Table 2) were within the normal range, with a significant improvement in internalising behaviours at post-surgery follow-up (z = -1.1). His pre-surgery Full Scale IQ score (Table 3), which was in the low average range, was significantly lower than C4's and did not change significantly after surgery. P4's pre-surgery academic skills were in the average to low average range, with basic reading scores significantly higher than for C4.

P4's pre-surgery attention scores (Table 4) varied from the high average to low average ranges. Skills in selective attention improved significantly at post-surgery follow-up (z = +1.0), although this was also the case for C4. P4's pre-surgery verbal memory (learning and delayed recall of word lists) was in the low average range,

however list recognition scores were exceptionally low (Table 5). Significant improvements in list learning (z = +1.5), delayed word recall (z = +3.1) and list recognition (z = +3.3) were noted at three month follow-up, although verbal learning improvements were also found in C4's scores (z = +1.7). Delayed visual memory skills, which were significantly below the mean before surgery, improved significantly at three month follow-up (z = +2.4).

P4's pre-surgery scores for visual recognition, visuo-spatial and visuo-motor skills (Table 6) were within the average to low average range, with significantly lower scores than C4 for visual recognition and visuo-motor precision. No significant post-surgery changes were observed for P4, although C4's scores significantly increased in visuo-motor precision at follow-up (z = +1.3).

Participant Pair Five (Patient P5 and Control P5)

P5's cyanotic heart disease (tetralogy of Fallot, see Appendix 1) had previously been treated at the ages of one week, 17 months, 5 and 8 years. The current surgery was required for valve repair, which was accomplished with cardiopulmonary bypass for 40 minutes without deep hypothermic circulatory arrest. P5 was 15 years 3 months at the time of the initial assessment, with follow-up assessments at four and 12 weeks after surgery. P5 and C5 attended the same school and were in the same academic year. At pre-surgery/ baseline no specific learning difficulties or neurological disorders were reported. No major physical or cognitive problems were reported for either child during the semi-structured interview at one month post-surgery/ follow-up.

P5's pre-surgery externalising scores were in the clinical range for problem behaviours (Table 2), with significant improvements noted for internalising scores at post-surgery follow-up (z = -1.0). P5's pre-surgery full scale IQ and academic abilities were within the average range (Table 3), although mathematics reasoning scores were significantly lower than C5. No significant change from pre-surgery/ baseline to follow-up was noted for either participant.

P5's pre-surgery attention scores (sustained attention, selective attention, sustained-divided attention) were significantly lower than the mean and/ or C5's baseline scores (Table 4). Significant improvements were observed at three month post surgery follow-up in selective attention (z = +1.0), sustained-divided (visual/ auditory) attention (z = +2.0) and switching attention (z = +1.0). With improvements in C5's switching attention scores (z = +1.0) also observed at follow-up. P5's pre-surgery working memory scores (digit recall forwards and backwards) were significantly lower than the mean, with the former also significantly lower than C5's baseline score. Although no significant changes in working memory were noted for P5, C5's block recall scores declined significantly at follow-up (z = -2.3).

P5's pre-surgery verbal memory scores (Table 5) were within the average range except for list learning which was significantly above the mean. Pre-surgery delayed recall scores were significantly lower than for C5. Post-surgery follow-up indicated a significant deterioration in P5's scores for list learning (z = -1.3) and list recognition (-2.3). P5's ability to copy a complex design deteriorated significantly (z = -1.1), although his visual memory did not change significantly post-surgery. C5's

delayed visual memory scores did, however, improve significantly at follow-up (z = +1.2).

P5's pre-surgery visual recognition skills and visuo-spatial skills were within the average range, although the latter was significantly better than baseline scores for C5. Pre-surgery scores for sensorimotor and visuo-motor skills were in the average range for P5 and C5. No significant changes were observed in these scores at follow-up for either participant.

Summary of Findings

Emotional Well-being

Generally pre-surgery emotional well-being scores for the patient participants were in the normal range, with the exception of P5's externalising score. A number of significant post-surgery improvements were found for internalising (P4 and P5) and externalising scores (P1), although a deterioration in externalising behaviour was also observed for one patient (P3). Baseline scores for C2 were in the borderline to clinical range with significant improvements at follow-up.

Intellectual and Academic Functioning

Pre-surgery IQ scores varied from the low (P1) to high (P3) ranges, and pre-surgery academic skills were generally in the average range. P2's significant increase in IQ scores was greater than expected from practice effects. No other significant changes were observed at follow-up for patients or controls.

Attention and Executive Functioning

Preoperative attention skills varied widely for both patients and controls, with scores ranging from high average to exceptionally low. Working memory skills were in the average to low range for both groups, with controls generally obtaining higher scores on digit recall forwards and block recall. At follow-up, a number of significant improvements on tasks of attention were found in both groups. Mental calculation scores improved only in P2 and P3. C3 improved on a task of abstract reasoning and C1 on working memory.

P3, however, showed a significant deterioration on three of the attentional subtests (sustained attention, sustained-divided auditory attention, switching attention). Although C2 and C4 demonstrated some deterioration on attention, this was not as consistent or as marked a decline as in P3. A significant decline on a task of working memory (digit recall backwards) was also identified in P1. The scores for C1 and C5 showed a decline in block recall, which was not reflected in patient participants.

Verbal and Visual Memory

Apart from P4's low average to exceptionally low verbal memory skills, scores for both groups were in the average to exceptionally high range before surgery. Improvements in verbal memory were found in the scores of several patient participants, however, a significant decline in scores for P3 was observed on immediate story recall and delayed recall for both word lists and stories. P5's scores were also found to decline but for list learning and word recognition. Controls' scores were more varied with C4 improving on list learning and recognition: C1 deteriorating on list learning and list recognition; and C2 deteriorating on

recognition. Pre-surgery delayed visual memory scores were in the average to low range and were slightly lower than controls' scores which were in the high average to low average range. P1 and P4 improved significantly at post-surgery follow-up, although improvements were also identified for C2 and C5.

Visuo-spatial, Visuo-motor and Sensorimotor Skills

Scores were in the high average to low average range for both groups, although P1's visual recognition and visuo-spatial skills were in the low range. P1 and P3's visuo-motor precision skills were significantly below the mean. P1 and P4 improved on visuo-motor integration tasks following surgery. Control's scores on visuo-motor precision varied, with scores improving for C2 and C4 and deteriorating for C3 and C5. Visuo-motor integration scores declined significantly for C3.

DISCUSSION

These results highlight a number of interesting and clinically potentially important findings.

Q1. Do paediatric cardiac patients have normal pre-surgery cognition compared with age-matched healthy controls?

Pre-surgery IQ for the patient participants varied from the low to high range, with P1 and P4's scores significantly lower than controls. As global intellectual skills can influence other aspects of cognitive functioning, the difference in IQ between pairs 1 and 4 could possibly account for the pre-surgery differences observed in other domains.

Scores in domains other than general intellectual functioning tended to be variable, with some pre-surgery problems identified in attention (which were particularly severe in one of the cyanotic patient participants i.e. P5), working memory (digit span forwards and block span), verbal memory (for which significant impairments were noted for one of the cyanotic patient participants i.e. P4), visual memory, visual recognition, visuo-spatial skills and visuo-motor precision. It is, however, important to note that generally the findings were variable and were not indicative of a specific pattern of deficit in the group of children as a whole.

Some of the paediatric literature, which highlights compromised cognitive development in children with cyanotic lesions (e.g. De Maso et al, 1990; O'Dougherty et al, 1983; Newburger et al, 1984) and lower preoperative IQ than children with acyanotic heart disease (Aram et al, 1985) was therefore supported to some degree, as full scale IQ for one of the cyanotic patient participants was significantly lower than the scores of 2 of the 3 acyanotic patient participants. Other cognitive difficulties were also identified for the two children with cyanotic heart conditions. However, as the IQ of P1, an acyanotic child, was significantly lower than all participants, it is difficult to be conclusive about preoperative differences between cyanotic and acyanotic children, particularly as these findings are based on a very small number of participants.

Q2. Do changes in general intellectual functioning occur after surgery?

The only change that was noted for intellectual functioning scores was for P2, an acyanotic patient, whose IQ scores changed from 100 to 126 at post-surgery follow-up which was not thought to reflect practice effects as it exceeds the suggested

increase of 7 or 8 standard score points. This result supports the findings of some researchers (Linde, Rasof & Dunn, 1970; Sunderland et al, 1973), who also found increases in IQ following surgery.

There are a number of possible influences which may have contributed to this change, one of which could be related to the surgical procedure used, as he was the only child for whom deep hypothermic circulatory arrest was used. This would appear to conflict with some previous retrospective studies (Newburger et al, 1993; Bellinger et al, 1995; Bellinger et al, 1999), which suggest that this technique can adversely affect cognitive functioning. However, these studies were conducted with children who had a cyanotic heart problem and were also retrospective in design both of which would limit their applicability to this study.

Even if this technique offered the neuroprotection from ischaemic injury for which it is adopted, this alone would not explain the increase in IQ scores. It is likely that other factors may have influenced these findings, for example, at pre-surgery assessment P2 was being tutored at home, having been too unwell for the last two years to attend school. It is acknowledged that children with a chronic illness experience frequent interruptions in regular schooling, restricted mobility and participate in a reduced number of activities, all of which can have consequences upon physical, social, psychological and cognitive functioning (Krol et al, 2003). It is possible, therefore, that the improved efficiency of his heart function following repair, increased activity and recent school attendance may have combined to influence the changes in his IQ scores.

Q3. How (if at all) do the specific domains of cognitive function change in paediatric heart patients following surgery?

The findings of this study highlight a number of interesting post-surgery changes in cognitive functioning with both improvements and deteriorations in performance being noted. Improvements were observed for four of the patient participants in attention and executive functioning (i.e. mental flexibility and abstract reasoning), although there was not a consistent pattern regarding the type of attention that changed following surgery. Each control participant's attention scores also improved on at least one subtest, and although this suggests that these results should be regarded with some caution, the changes in patient participants' scores were more numerous, with P1 and P5 improving on three of the five subtests.

Patient's verbal memory scores at one month follow-up did not indicate a consistent decline in skills as suggested in the adult literature (O'Brien et al, 1992). Significant improvements in verbal memory were noted at three month follow-up, with four patient participants demonstrating improvements in one or more of the areas of learning, delayed recall or recognition. This supports some of the adult literature which has identified verbal memory improvements at longer-term follow-up (e.g. Vingerhoets et al, 1997). Although some improvements were also found in controls' verbal memory scores these were not as frequent as for patient participants and may underscore the significance of the improvements in patient verbal memory. A significant improvement in delayed visual memory scores was found at post-surgery follow-up (P1 and P4), although as two controls' scores also improved it is not clear whether this can be attributed to the surgical experiences of the patient participants.

A number of significant deteriorations in scores were also observed at three months post-surgery, the most notable of which was the decline in P3's attention scores (sustained attention, sustained-divided auditory attention and switching attention) and verbal memory (immediate story recall and delayed recall for words and stories). It is not clear to what extent these scores are associated with the increase in P3's externalising problem behaviours following surgery, although research in this area by Yang et al (1994), who also found a deterioration in externalising behaviours in their patient participants, suggests that this change may be associated with surgery. It should be noted, however, that despite these changes, scores generally remained within normal limits and were, therefore, suggestive of more subtle deficits which may have gone undetected without neuropsychological assessment. These discrete changes highlight the fact that although a child may function within normal limits following surgery, this may not be to their full potential.

Other patient participants' scores also reflected a significant deterioration in working memory (digit recall backwards for P1), verbal memory (list learning and recognition for P5) and design copy (P5). Some deterioration was noted in controls' scores for attention (sustained, switching), working memory (block recall), verbal memory (list learning and recognition) and visuo-motor skills (visuo-motor precision). Although it is not clear why these changes occurred in the controls, it is possible that they may be related to external influences such as environmental factors.

It is possible that the decline in patients' scores could be associated with the adverse effects of cardiopulmonary bypass (e.g. Yang et al, 1994) and supports previous studies which indicate a significant decline in attention and verbal memory (e.g.

Dahme et al, 1993; Newman, 1993) following surgery. Indeed this pattern of decline may be consistent with changes in regions of the brain such as the parietal lobes and hippocampus which have been implicated in previous anatomical studies but prospective neuroimaging data are required to establish this with confidence. This finding does, however contradict the suggestion that surgical techniques affect only the right hemisphere of the brain (Sotaniemi, 1980).

Despite the identification of a variety of theoretically and clinically important findings, these results should be understood within the context of a number of unavoidable methodological difficulties. The first of these issues relates to the assessment tools that were used in this study. Where possible, tests that had good psychometric properties and standardised normative data were adopted. However, there are a limited number of tests available to measure different cognitive domains in children particularly those with parallel forms to reduce the risk of practice effects. Parallel forms were not available for all tests although the data were interpreted with this issue in mind. Even where parallel forms were available, the repetitive nature of testing may have contributed to improved performance as evidenced by improvements in for example, controls scores on the RAVLT.

For two tests, the RBMT-C and the Nepsy, normative data were not available for some of the participants. Clinical judgement was used to determine significant change and this may have led to a less objective analysis of these data. Future research should attempt to adopt tests where normative data exists and although this is not possible for story recall, for which no tests with parallel versions have come to the attention of the researcher, the Wide Range Assessment of Visual Motor Abilities

(Adams & Sheslow, 1995), may offer a possible alternative to the Nepsy for measuring fine motor skills.

Factors related to the child should also be considered with regard to these results. For example, with reference to two of the patient participants (P3 and P4), it was acknowledged that their move from one age band to another (e.g. from age 13 to 14) between the pre and post-surgery assessments could have contributed to a change in scaled scores on tests such as the WISC-III. Analysis of the raw data, however, suggested that this factor was not significant in either case.

In addition, other issues related to the child's performance may also be relevant. For example, although regular breaks were taken, as tests were administered in a single session at each time point, some children fatigued more easily than others. This may have affected their testing motivation, ability to concentrate and performance, particularly on the latter tasks. The order in which the measures were administered was kept constant for each participant and at each time point, which to some extent may have controlled for variability of performance across participants.

For the patient participants, their pre-surgery health as well as the possibility of anxiety about the operation could all have contributed to impaired pre-surgery scores thus accounting for improvements at follow-up. Due to recruitment difficulties and time constraints, it was not possible to employ a non-surgical control group, although this would have been particularly helpful in ascertaining whether these improvements were related purely to the surgical experience.

Where control's scores significantly declined, it is possible that factors such as the sensitivity of the test, environmental changes, mood, fatigue and motivation could have all contributed to these findings, thus exaggerating the changes observed in the patient participants' scores. Finally, P3 had a bruised eye at post-surgery follow-up, which may have impaired his performance on visual tasks, although as he also demonstrated impairments on verbal tasks it is unlikely that this injury had any influence on his performance.

It can be concluded that this study highlights the possibility of cognitive improvements following cardiac surgery. Some decline in cognitive skills was also noted, although to a lesser extent, which may indicate the more subtle effects of cardiac surgery upon a child's cognitive functioning, and is suggestive of a higher incidence of neuropsychological deficits than the 1 to 30% documented in previous studies (Bellinger et al, 1991; Ferry, 1990; Furlan et al, 1992; McConnell et al, 1990; Mendoza et al, 1991; Miller et al, 1991; Newburger et al, 1993; Park & Neches, 1993).

These findings may relate to the extensive battery of tests used in this study as this could have led to the identification of subtle cognitive deficits that may not have otherwise been detected. Comparison with other studies is, however, almost impossible because of differences in design and the varying definitions of significant change used (Bellinger, 2003). It should also be noted that this study's use of one standard deviation or above to represent significant change is not a stringent test and may have been over-inclusive in the identification of cognitive change.

The purpose of this study was to explore in detail the possible areas of cognitive functioning that may be affected by cardiac surgery. Although improvements in intellectual functioning, attention, executive functioning, verbal and visual memory, and visuo-motor-skills were noted in this study, the findings also indicate the possible adverse effects of surgery. Deterioration in patients' scores was noted for behaviour, attention (sustained, auditory sustained-divided and switching), verbal memory (list learning, immediate story recall, delayed recall for list and stories and list recognition), working memory (digit recall backwards) and visuo-motor skills (design copy). As a number of changes in behaviour, attention, executive functioning, memory and visuo-motor skills were also noted for controls, more research is required to verify these findings.

Despite the interesting findings outlined above, it is not possible to definitively conclude, on the basis of this study alone, that the cognitive changes observed were due to cardiac surgery. Nevertheless, these findings highlight the need for further investigation in this area and as such it is hoped that this study could serve as a basis for further, more extensive, controlled comparison research, for example through the recruitment of children in multi-centre studies using a standardised protocol matched for heart defect. However, researchers should be alert to the potential difficulty that comparison groups may mask the subtle individual neuropsychological differences identified by this study. Improved methodological design of future research could have major implications as these could not only provide the basis for routine monitoring of a child's progress following surgery, but could also play a significant role in the evaluation and improvement of current treatment techniques.

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Table 1: Developmental characteristics and surgical history of patient participants

Patient participant	Type of defect	Age at current operation	Gestational age in weeks	Birth weight (Kg)	Developmental problems	SCBU? Duration (days)	Previous heart surgery (approximate age)	Current operation	Oximetry SaO_2 (%)	
									Pre-surgery	Post-surgery
P1	ASD	7	39	2.99	Speech and motor delay	2	None	Closure ASD	99	95-99
P2	ASD	11	FT	3.7	None	No	Resection of Co-arc (2yrs)	Redo co-arc	97	97-99
P3	ASD	11	35	NK	None	No	None	Closure ASD	97	98
P4	TOF	14	41	3.32	Speech Delay	No	Repair TOF (18mths)	PV repair	96	98
P5	TOF	15	37	3.62	None	2 days	Blalock shunt (1 week) Repair TOF (17 mths) Balloon PA (5 years) Balloon Stent (8 years)	Aortic homograft	100	94-98

Note: ASD = Atrial Septal Defect; TOF = Tetralogy of Fallot; PV = Pulmonary valve; PA = Pulmonary artery; Co-arc = Co-arctation of the aorta; FT = full term, where actual gestational age is not known; NK = not known; oximetry SAO_2 = percentage blood oxygen saturation: as at post-surgery this measure was taken on several occasions, a range is provided.

Table 2: Internalising and externalising scores for patient and control participants on the Child Behaviour Checklist

Measure	Pair	Patient participant scores				Control participant scores			
		Pre-surgery	1 month post-surgery	3 months post-surgery	Change in scores	Baseline	1 month follow-up	3 month follow-up	Change in scores
CBCL		T1	T2	T3		T1	T2	T3	
Internalising score	1	55 (+0.5)	43 (-0.7)	51 (+0.1)	-4 (-0.4)	49 (-0.1)	40 (-1.0)	43 (-0.7)	-6 (-0.6)
	2	43 (-0.7)	40 (-1.0)	49 (-0.1)	+6 (+0.6)	71 (+2.1)	61 (-1.1)	46 (-0.4)	**-25 (-2.5)**
	3	46 (-0.4)	43 (-0.7)	45 (-0.5)	-1 (-0.1)	46 (-0.4)	43 (-0.7)	40 (-1.0)	-6 (-0.6)
	4	43 (-0.7)	39 (-1.1)	32 (-1.8)	**-11 (-1.1)**	55 (+0.5)	51 (+0.1)	57 (+0.7)	+2 (+0.2)
	5	58 (+0.8)	45 (-0.5)	48 (-0.2)	**-10 (-1.0)**	57 (+0.7)	64 (+1.4)	50 (0)	-7 (-0.7)
Externalising score	1	46 (-0.4)	35 (-1.5)	35 (-1.5)	**-11 (-1.1)**	52 (+0.2)	46 (-0.4)	49 (-0.1)	-3 (-0.3)
	2	43 (-0.7)	52 (+0.2)	52 (+0.2)	+9 (-0.9)	60 (+1.0)	46 (-0.4)	44 (-0.6)	**-16 (-1.6)**
	3	46 (-0.4)	41 (-0.9)	56 (+0.6)	**+10 (+1.0)**	43 (-0.7)	41 (-0.9)	43 (-0.7)	0 (0.0)
	4	40 (-1.0)	32 (-1.8)	32 (-1.8)	-8 (-0.8)	53 (+0.3)	53 (+0.3)	52 (+0.2)	-1 (-0.1)
	5	67 (+1.7)	58 (+0.8)	58 (+0.8)	-9 (-0.9)	43 (-0.7)	43 (-0.7)	40 (-1.0)	-3 (-0.3)

Note: CBCL = Child Behaviour Checklist in T scores (z score); internalising score = T scores representing combined scores for withdrawn, somatic complaints, anxious/ depressed; externalising score = T scores representing combined scores for delinquent behaviour and aggressive behaviour; Change in scores = change from T1 to T3, where an increase/ decrease in scores indicates deterioration/ improvement (respectively) in behaviour over time; significant change of one or more standard deviations in T scores is illustrated in bold writing.

Table 3 General intellectual and academic functioning scores for patient and control participants

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3 months post-surgery	Change in scores	Baseline	3 month follow-up	Change in scores
WISC-III		T1	T3		T1	T3	
FSIQ	1	75 (-1.7)	80 (-1.3)	+5 (+0.3)	117 (+1.1)	114 (+0.9)	-3 (-0.2)
	2	100 (0)	126 (+1.7)	**+26 (+1.7)**	108 (+0.5)	118 (+1.2)	+10 (+0.7)
	3	121 (+1.4)	126 (+1.7)	+5 (+0.3)	121 (+1.4)	134 (+2.3)	+13 (+0.9)
	4	82 (-1.2)	87 (–0.9)	+5 (+0.3)	97 (-0.2)	92 (-0.5)	-5 (-0.3)
	5	99 (-0.1)	100 (0)	1 (+0.1)	92 (-0.5)	99 (-0.1)	+7 (+0.5)

Note: WISC-III = Wechsler Intelligence Scale for Children in scaled score (z score); Change in scores = number of points change in standard score from pre to post surgery for patient participants or from baseline to follow-up for control participants; significant change of one or more standard deviations is illustrated in bold writing.

Table 3 General intellectual and academic functioning scores for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3 months post-surgery	Change in scores	Baseline	3 month follow-up	Change in scores
WIAT		T1	T3		T1	T3	
Basic Reading	1	95 (-0.3)	89 (-0.7)	-6 (-0.4)	112 (+0.8)	105 (+0.3)	-7 (-0.5)
	2	90 (-0.7)	87 (-0.9)	-3 (-0.2)	108 (+0.5)	111 (+0.7)	+3 (+0.2)
	3	91(-0.6)	91 (-0.6)	0 (0.0)	108 (+0.5)	111 (+0.7)	+3 (+0.2)
	4	93 (-0.5)	83 (-1.1)	-10 (-0.7)	73 (-1.8)	79 (-1.4)	+6 (+0.4)
	5	100 (0)	97 (-0.2)	-3 (-0.2)	95 (-0.3)	100 (0)	+5 (+0.3)
Maths Reasoning	1	101 (0.1)	102 (0.1)	+1 (+0.1)	117 (+1.1)	116 (+1.1)	-1 (+0.1)
	2	118 (+1.2)	122 (+1.5)	+4 (+0.3)	124 (+1.6)	125 (+1.7)	+1 (+0.1)
	3	126 (+1.7)	124 (+1.6)	-2 (-0.1)	115 (+1.0)	125 (+1.7)	+10 (+0.7)
	4	89 (-0.7)	93 (-0.5)	+4 (+0.3)	101 (+0.1)	101 (+0.1)	0 (0.0)
	5	93 (-0.5)	97 (-0.2)	+4 (+0.3)	111 (+0.7)	102 (+0.1)	-9 (-0.6)

Note: WIAT = Wechsler Individual Attainment Test (Quicktest) in standard score (z score); Change in scores = number of points change in standard score from pre to post surgery for patient participants or from baseline to follow-up for control participants; significant change of one or more standard deviations is illustrated in bold writing.

Table 4: Attention and executive functioning scores for patient and control participants

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3mth post-surgery	Change in	Baseline	3mth follow-up	Change in
TEA-Ch		T1	T3	scores	T1	T3	scores
Sustained attention	1	7 (-1.0)	12 (0.7)	**+5 (+1.7)**	7 (-1.0)	7 (-1.0)	0 (0.0)
(Score!)	2	13 (+1.0)	13 (+1.0)	0 (0)	13 (+1.0)	9 (-0.3)	**-4 (-1.3)**
	3	13 (-1.0)	7 (-1.0)	**-6 (-2.0)**	4 (-2.0)	7 (-1.0)	**+3 (+1.0)**
	4	8 (-0.7)	8 (-0.7)	0 (0.0)	12 (+0.7)	8 (-0.7)	**-4 (-1.3)**
	5	1 (-3.0)	1 (-3.0)	0 (0.0)	12 (+0.7)	11 (+0.3)	-1 (-0.3)
Selective attention	1	8 (-0.7)	9 (-0.3)	+1 (0.3)	10 (0.0)	11 (+0.3)	+1 (+0.3)
(Sky Search)	2	11 (+0.3)	11 (+0.3)	0 (0.0)	9 (-0.3)	12 (+0.7)	**+3 (+1.0)**
	3	10 (0.0)	10 (0.0)	0 (0.0)	9 (-0.3)	11 (+0.3)	+2 (+0.7)
	4	6 (-1.3)	9 (-0.3)	**+3 (+1.0)**	10 (0.0)	14 (+1.3)	**+4 (+1.3)**
	5	7 (-1.0)	10 (0)	**+3 (+1.0)**	9 (-0.3)	11 (+0.3)	+2 (+0.7)

Note: TEA-Ch = Test of Everyday Attention for Children in scaled score (z score); Change in scores = difference in scaled score points from T1 to T3 (z score); significant change of one or more standard deviations is illustrated in bold writing.

Table 4: Attention and executive functioning scores for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3mth post-surgery	Change in	Baseline	3mth follow-up	Change in
TEA-Ch		T1	T3	scores	T1	T3	scores
Sustained-divided	1	6 (-1.3)	11 (0.3)	**+5 (+1.7)**	5 (-1.7)	12 (+0.7)	**+7 (+2.3)**
attention (vis/ aud)	2	7 (-1.0)	8 (-0.7)	+1 (+0.3)	9 (-0.3)	8 (-0.7)	-1 (-0.3)
(Sky Search DT)	3	7 (-1.0)	9 (-0.3)	+2 (+0.7)	9 (-0.3)	9 (-0.3)	0 (0.0)
	4	10 (0.0)	9 (-0.3)	-1 (-0.3)	7 (-1.0)	5 (-1.7)	-2 (-0.7)
	5	2 (-2.7)	8 (-0.7)	**+6 (+2.0)**	6 (-1.3)	7 (-1.0)	+1 (+0.3)
Sustained-divided	1	6 (-1.3)	9 (-0.3)	**+3 (+1.0)**	6 (-1.3)	7 (-1.0)	+1 (+0.3)
attention (auditory)	2	8 (-0.7)	11 (+0.3)	**+3 (+1.0)**	12 (+0.7)	14 (+1.3)	+2 (+0.7)
(Score DT!)	3	14 (+1.3)	7 (-1.0)	**-7 (-2.3)**	6 (-1.3)	7 (-1.0)	+1 (+0.3)
	4	8 (-0.7)	9 (-0.3)	+1 (+0.3)	9 (-0.3)	8 (-0.7)	-1 (-0.3)
	5	5 (+1.7)	3 (+1.0)	-2 (-0.7)	9 (-0.3)	7 (-1.0)	-2 (-0.7)

Note: TEA-Ch = Test of Everyday Attention for Children in scaled score (z score); vis/aud = visual and auditory stimuli; change in scores = difference in scaled score points from T1 to T3 (z score); significant change of one or more standard deviations is illustrated in bold writing.

Table 4: Attention and executive functioning scores for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery T1	3 mths post-surgery T3	Change in scores	Baseline T1	3 mths follow-up T3	Change in scores
TEA-Ch							
Switching attention	1	5 (-1.7)	6 (-1.3)	+1 (+0.3)	12 (+0.7)	14 (+1.3)	+2 (+0.7)
(Creature Counting)	2	13 (+1.0)	13 (+1.0)	0 (0.0)	13 (+1.0)	13 (+1.0)	0 (0.0)
	3	13 (+1.0)	10 (0.0)	**-3 (-1.0)**	13 (+1.0)	10 (0.0)	**-3 (-1.0)**
	4	14 (+1.3)	14 (+1.3)	0 (0.0)	14 (+1.3)	9 (-0.3)	**-5 (-1.7)**
	5	11 (+0.3)	14 (+1.3)	**+3 (+1.0)**	11 (+0.3)	14 (+1.3)	**+3 (+1.0)**
WMTB-C							
Digit recall	1	104 (+0.3)	109 (+0.6)	+3 (+0.2)	118 (+1.2)	142 (+2.8)	**+24 (+1.6)**
(forwards)	2	83 (-1.1)	89 (-0.7)	+6 (+0.4)	113 (+0.9)	118 (+1.2)	+5 (+0.3)
	3	89 (-0.7)	86 (-0.9)	-3 (-0.2)	91 (-0.6)	94 (-0.4)	+3 (+0.2)
	4	76 (-1.6)	71 (-1.9)	-5 (-0.3)	88 (-0.8)	96 (-0.3)	+8 (+0.5)
	5	79 (-1.4)	74 (-1.7)	-5 (-0.3)	95 (-0.3)	100 (0)	+5 (+0.3)

Note: TEA-Ch = Test of Everyday Attention for Children in scaled score (z score); switching attention scores are based on the child's accuracy to perform the task; change in scores = difference in scaled score points from T1 to T3 and (z score); WMTB-C = Working Memory Test Battery for Children in standard score (z score); significant change of one or more standard deviations is illustrated in bold writing

Table 4: Attention and executive functioning scores for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery T1	3 mths post-surgery T3	Change in scores	Baseline T1	3 mths follow-up T3	Change in scores
WMTB-C							
Digit recall	1	83 (-1.1)	67 (-2.2)	**-16 (-1.1)**	77 (–1.5)	109 (+0.6)	**+32 (+2.1)**
(backwards)	2	92 (-0.5)	105 (+0.3)	+13 (+0.9)	98 (-0.1)	88 (-0.8)	-10 (-0.7)
	3	81 (-1.3)	88 (-0.8)	+7 (+0.5)	92 (-0.5)	105 (+0.3)	+13 (+0.9)
	4	77 (-1.5)	79 (-1.4)	+2 (+0.1)	87 (-0.9)	79 (-1.4)	-8 (-0.5)
	5	85 (-1.0)	90 (-0.7)	+5 (+0.3)	96 (-0.3)	90 (-0.7)	-6 (-0.4)
Block recall	1	79 (-1.4)	81 (-1.3)	+2 (+0.1)	122 (+1.5)	103 (+0.2)	**-19 (-1.3)**
(forwards)	2	97 (-0.2)	89 (-0.7)	-8 (-0.5)	105 (+0.3)	109 (+0.6)	+4 (+0.3)
	3	81 (-1.3)	81 (-1.3)	0 (0.0)	97 (-0.2)	93 (-0.5)	-4 (-0.3)
	4	82 (–1.2)	82 (-1.2)	0 (0.0)	96 (-0.3)	103 (+0.2)	+7 (+0.5)
	5	86 (-0.9)	89 (-0.7)	+3 (+0.2)	89 (-0.7)	55 (-3.0)	**-34 (-2.3)**

Note: WMTB-C = Working Memory Test Battery for Children in standard score (z score); significant change of one or more standard deviations is illustrated in bold writing.

Table 4: Attention and executive functioning scores for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery T1	3mth post-surgery T3	Change in scores	Baseline T1	3mth follow-up T3	Change in scores
WISC-III							
Mental Calculation	1	7 (-1.0)	9 (-0.3)	+2 (+0.7)	10 (0.0)	8 (-0.7)	-2 (-0.7)
(Arithmetic)	2	9 (-0.3)	15 (+1.7)	**+6 (+2.0)**	15 (+1.7)	17 (+2.3)	+2 (+0.7)
	3	13 (+1.0)	16 (+2.0)	**+3 (+1.0)**	15 (+1.7)	17 (+2.3)	+2 (+0.7)
	4	6 (-1.3)	8 (-0.7)	+2 (+0.7)	7 (-1.0)	6 (-1.3)	-1 (-0.3)
	5	11 (+0.3)	12 (+0.7)	+1 (+0.3)	11 (+0.3)	12 (+0.7)	+1 (+0.3)
Verbal Reasoning	1	8 (-0.7)	7 (-1.0)	+1 (-0.3)	12 (+0.7)	12 (+0.7)	0 (0.0)
(Similarities)	2	9 (-0.3)	15 (+1.7)	**+6 (+2.0)**	10 (0)	12 (+0.7)	+2 (+0.7)
	3	11 (+0.3)	11 (+0.3)	0 (0.0)	12 (+0.7)	15 (+1.7)	**+3 (+1.0)**
	4	5 (-1.7)	6 (-1.3)	+1 (+0.3)	7 (-1.0)	6 (-1.3)	-1 (-0.3)
	5	10 (0.0)	10 (0.0)	0 (0.0)	10 (0.0)	11 (+0.3)	+1 (+0.3)

Note: WISC III = Wechsler Intelligence Scales for Children in scaled score (z score); significant change in scores is illustrated in bold writing; significant change of one or more standard deviations is illustrated in bold writing.

Table 5: Verbal and visual memory scores for patient and control participants

Measure	Pair	Patient participant scores					Control participant scores				
		Pre-surgery	1 month post-surgery	Change in scores at 1 month	3 months post-surgery	Change in scores at 3 months	Baseline	1 month follow-up	Change in scores at 1 month	3 month follow-up	Change in scores at 3 months
RAVLT		T1	T2				T1	T2		T3	
Learning	1	102 (+0.1)	117 (+1.1)	+15 (+1.0)	127 (+1.8)	**+25 (+1.7)**	117 (+1.1)	110 (+0.7)	-7 (-0.5)	102 (+0.1)	**-15 (-1.0)**
	2	121 (+1.4)	142 (+2.8)	+21 (+1.4)	139 (+2.6)	**+18 (+1.2)**	130 (+2.0)	100 (0.0)	-30 (-2.0)	121 (+1.4)	-9 (-0.6)
	3	130 (+2.0)	133 (+2.2)	+3 (+0.2)	133 (+2.2)	+3 (+0.2)	139 (+2.6)	163 (+4.2)	+24 (+1.6)	157 (+3.8)	**+18 (+1.2)**
	4	87 (-0.9)	84 (-1.1)	-3 (-0.2)	109 (+0.6)	**+22 (+1.5)**	121 (+1.4)	123 (+1.5)	+2 (+0.1)	141 (+2.7)	**+20 (+1.7)**
	5	133 (+2.2)	118 (+1.2)	-15 (-1.0)	114 (+0.9)	**-19 (-1.3)**	123 (+1.5)	123 (+1.5)	0 (0.0)	133 (+2.2)	+10 (+0.7)
Delayed	1	98 (-0.1)	104 (+0.3)	+6 (+0.4)	115 (+1.0)	**+17 (+1.1)**	121 (+1.4)	92 (-0.5)	-29 (+1.9)	115 (+1.0)	-6 (-0.4)
Recall	2	136 (+2.4)	147 (+3.1)	+11 (+0.7)	136 (+2.4)	0 (0.0)	147 (+3.1)	126 (+1.7)	-21 (-1.4)	136 (+2.4)	-11(-0.7)
	3	147 (+3.1)	147 (+3.1)	0 (0.0)	126 (+1.7)	**-21 (-1.4)**	147 (+3.1)	158 (+3.9)	+11 (+0.7)	147 (+3.1)	0 (0.0)
	4	84 (+1.1)	91 (-0.6)	+7 (+0.5)	130 (+2.0)	**+46 (+3.1)**	124 (+16)	124 (+1.6)	0 (0.0)	124 (+1.6)	0 (0.0)
	5	110 (+0.7)	104 (+0.3)	-6 (-0.4)	97 (-0.2)	-13 (-0.9)	130 (+2.0)	124 (+1.6)	-6 (-0.4)	124 +1.6)	-6 (-0.4)

Note: RAVLT = Rey Auditory Verbal Learning Test in standard score (z score); Change in scores at 1 month = the difference in standard scores from T1 (pre-surgery/ baseline) to T2 (1 month post-surgery/ follow-up); Change in scores at 3 months = the difference in standard scores from T1 (pre-surgery/ baseline) to T3 (3 months post-surgery/ follow-up); significant change of one or more standard deviations is illustrated in bold writing.

Table 5: Verbal and visual memory scores for patient and control participants (continued)

Measure	Pair	Patient participant scores					Control participant scores				
		Pre-surgery T1	1 month post-surgery T2	Change in scores at 1 month	3 months post-surgery T3	Change in scores at 3 months	Baseline T1	1 month follow-up T2	Change in scores at 1 month	3 month follow-up T3	Change in scores at 3 months
RAVLT Recognition	1	111 (+0.7)	111 (+0.7)	0 (0.0)	111 (+0.7)	0 (0.0)	111 (+0.7)	89 (-0.7)	-22 (-1.5)	89 (-0.7)	**-22 (-1.5)**
	2	109 (+0.6)	109 (+0.6)	0 (0.0)	109 (+0.6)	0 (0.0)	109 (+0.6)	109 (+0.6)	0 (0.0)	91 (-06)	**-18 (-1.2)**
	3	91 (+0.5)	72 (-1.9)	-19 (-1.3)	109 (+0.6)	**+18 (+1.2)**	109 (+0.6)	109 (+0.6)	0 (0.0)	109 (+0.6)	0 (0.0)
	4	62 (-2.5)	62 (-2.5)	0 (0.0)	112 (+0.8)	**+50 (+3.3)**	95 (-0.3)	112 (+0.8)	+17 (+1.1)	112 (+0.8)	**+17 (+1.1)**
	5	112 (+0.8)	112 (+0.8)	0 (0.0)	78 (-1.5)	**-34 (-2.3)**	112 (+0.8)	95 (-0.3)	-17 (-1.1)	112 (+0.8)	0 (0.0)

Note: RAVLT = Rey Auditory Verbal Learning Test in standard score (z score); Change in scores at 1 month = the difference in standard scores from T1 (pre-surgery/ baseline) to T2 (1 month post-surgery/ follow-up); Change in scores at 3 months = the difference in standard scores from T1 (pre-surgery/ baseline) to T3 (3 months post-surgery/ follow-up); significant change of one or more standard deviations is illustrated in bold writing.

Table 5: Verbal and visual memory scores for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3 mths post-surgery	Change	Baseline	3 mths follow-up	Change
RBMT[1]		T1	T3	In scores	T1	T3	in scores
Story recall	1	12	20	**+8 (+26%)**	23.5	25	+1.5 (+5%)
(immediate)	2	9 (-0.2)	12 (+0.6)	+3 (+0.6)	11 (+0.3)	9.5 (-0.1)	-1.5 (-0.4)
	3	14 (+1.1)	9.5 (-0.1)	**-4.5 (-1.1)**	13.5 (+0.9)	11.5 (+0.4)	-2 (-0.5)
	4	6.5 (-2.5)	3.5 (-1.6)	-3 (-0.8)	13 (+0.8)	10.5 (+0.2)	-2.5 (-0.6)
	5	10 (+0.1)	12.5 (+0.6))	+2.5 (+0.6)	10 (+0.1)	9 (-0.2)	-1 (-0.3)
Story recall	1	13	12.5	-0.5 (-1%)	23 (+1.8)	22.5 (+1.7)	-0.5 (-1%)
(delayed)	2	10 (+0.3)	11 (+0.6)	+1 (+0.2)	11 (+0.6)	7.5 (-0.3)	-3.5 (-0.9)
	3	12 (+0.8)	7.5 (-0.3)	**-4.5 (-1.1)**	10.5 (+0.5)	11.5 (+0.7)	+1 (+0.2)
	4	3.5 (-1.3)	2.5 (-1.5)	-1 (-0.2)	14 (+1.3)	12 (+0.8)	-2 (-0.5)
	5	8.5 (0.0)	11 (+0.3)	+2.5 (+0.6)	9 (+0.1)	7.5 (-0.3)	-1.5 (-0.2)

Note: RBMT = Rivermead Behavioural Memory Test in raw score (z score); RBMT[1] = pair 1 were administered children's version, for which the percentage change in scores over time was calculated; significant change of one or more standard deviations is illustrated in bold writing.

Table 5:Verbal and visual memory scores for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3 mths post-surgery	Change	Baseline	3 mths follow-up	Change
CFT		T1	T3	In scores	T1	T3	in scores
Copy	1	93 (-0.5)	103 (+0.2)	+10 (+0.7)	89 (-0.7)	104 (+0.3)	**+15 (+1.0)**
	2	95 (-0.3)	126 (+2.2)	**+31 (+2.6)**	107 (+0.5)	109 (+0.6)	+2 (+0.1)
	3	105 (+0.3)	93 (-0.5)	-12 (-0.8)	105 (+0.3)	109 (+0.6)	+4 (+0.3)
	4	89 (-0.7)	88 (-0.8)	-1 (-0.1)	93 (-0.6)	88 (-0.8)	-5 (-0.3)
	5	97 (-0.2)	82 (+1.2)	**-16 (-1.1)**	93 (-0.6)	97 (-0.2)	+4 (+0.3)
Delayed memory	1	78 (-1.5)	107 (+0.5)	**+29 (+1.9)**	84 (-1.1)	95 (-0.3)	+11 (+0.7)
	2	105 (+0.3)	109 (+0.6)	+4 (+0.3)	104 (+0.3)	119 (+1.3)	**+15 (+1.0)**
	3	108 (+0.5)	104 (+0.3)	-4 (-0.3)	112 (+0.8)	119 (+1.3)	+7 (+0.5)
	4	77 (-1.5)	113 (+0.9)	**+36 (+2.4)**	99 (-0.1)	108 (+0.5)	+9 (0.6)
	5	81 (-1.3)	93 (-0.5)	+12 (+0.8)	91 (+0.5)	109 (+0.6)	**+18 (+1.2)**

Note: CFT = Rey Osterrieth Complex Figure Test in standard score (z score); significant change of one standard deviation or more is illustrated in bold writing.

Table 6: Visuo-spatial, visuo-motor and sensorimotor scores for patient and control participants

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3 months post-surgery	Change in scores	Baseline	3 month follow-up	Change in scores
WISC-III		T1	T3		T1	T3	
Visual recognition	1	5 (-1.7)	7(-1.0)	+2 (+0.7)	14 (+1.3)	14 (+1.3)	0 (0.0)
(Picture completion)	2	10 (0.0)	13 (+1.0)	**+3 (+1.0)**	10 (0)	12 (+0.7)	+2 (+0.7)
	3	14 (+1.3)	16 (+2.0)	+2 (+0.7)	15 (+1.7)	16 (+2.0)	+1 (+0.3)
	4	9 (-0.3)	11 (+0.3)	+2 (+0.7)	13 (+1.0)	13 (+1.0)	0 (0.0)
	5	8 (+0.7)	9 (-0.3)	+1 (+0.3)	7 (-1.0)	9 (-0.3)	+2 (+0.7)
Visuo-spatial skills	1	5 (-1.7)	5 (-1.7)	0 (0.0)	14 (+1.3)	14 (+1.3)	0 (0.0)
(Block design)	2	12 (+0.7)	13 (+1.0)	+1 (+0.3)	10 (0.0)	10 (0.0)	0 (0.0)
	3	15 (+1.7)	13 (+1.0)	-2 (-0.7)	11 (+0.3)	13 (+1.0)	+2 (+0.7)
	4	9 (-0.3)	7 (-1.0)	-2 (-0.7)	11 (+0.3)	10 (0.0)	-1 (-0.3)
	5	10 (0.0)	9 (-0.3)	-1 (-0.3)	7 (-1.0)	7 (-1.0)	0 (0.0)

Note: WISC-III = Wechsler Intelligence Scale for Children in scaled score (z score); significant change of one or more standard deviations is illustrated in bold writing.

Table 6: Visuo-spatial, visuo-motor and sensorimotor tasks for patient and control participants (continued)

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3 months post-surgery	Change in scores	Baseline	3 month follow-up	Change in scores
Nepsy		T1	T3		T1	T3	
Fingertip tapping	1	13 (+1.0)	12 (+0.7)	-1 (-0.3)	14 (+1.3)	14 (+1.3)	0 (0.0)
	2	13 (+1.0)	13 (+1.0)	0 (0.0)	13 (+1.0)	14 (+1.3)	+1 (+0.3)
	3	14 (+1.3)	13 (+1.0)	-1 (-0.3)	10 (0.0)	11 (+0.3)	+1 (+0.3)
	4	14 (+1.3)	15 (+1.7)	+1 (+0.3)	14 (+1.3)	13 (+1.0)	-1 (-0.3)
	5	13 (+1.0)	13 (+1.0)	0 (0.0)	13 (+1.0)	13 (+1.0)	0 (0.0)
Imitating hand Positions	1	11 (+0.3)	13 (+1.0)	+2 (+0.7)	14 (+1.3)	14 (+1.3)	0 (0.0)
	2	13 (+1.0)	13 (+1.0)	0 (0.0)	13 (+1.0)	13 (+1.0)	0 (0.0)
	3	13 (+1.0)	13 (+1.0)	0 (0.0)	13 (+1.0)	13 (+1.0)	0 (0.0)
	4	13 (+1.0)	13 (+1.0)	0 (0.0)	13 (+1.0)	13 (+1.0)	0 (0.0)
	5	9 (-0.3)	8 (-0.7)	-1 (-0.3)	13 (+1.0)	13 (+1.0)	0 (0.0)

Note: Nepsy = Nepsy Developmental Neuropsychological Assessment in scaled score (z score); significant change of one or more standard deviations is illustrated in bold writing.

Table 6: Visuo-spatial, visuo-motor and sensorimotor tasks for patient and control participants (continued).

Measure	Pair	Patient participant scores			Control participant scores		
		Pre-surgery	3 months post-surgery	Change in scores	Baseline	3 month follow-up	Change in scores
Nepsy		T1	T3		T1	T3	
Visuo-motor	1	7 (-1.0)	5 (-1.7)	-2 (-0.7)	7 (-1.0)	7 (-1.0)	0 (0.0)
Precision	2	11 (+0.3)	11 (+0.3)	0 (0.0)	11 (+0.3)	15 (+1.7)	**+4 (+1.3)**
	3	4 (-2.0)	3 (-2.3)	-1 (-0.3)	10 (0.0)	7 (-1.0)	**-3 (-1.0)**
	4	10 (0.0)	11 (+0.3)	+1 (+0.3)	10 (0.0)	14 (+1.3)	**+4 (+1.3)**
	5	11 (+0.3)	9 (–0.3)	-2 (-0.7)	14 (+1.3)	8 (-0.7)	**-6 (-2.0)**
VMI	1	94 (-0.4)	109 (+0.6)	**+15 (+1.0)**	92 (-0.5)	98 (-0.1)	+6 (+0.4)
	2	112 (+0.8)	115 (+1.0)	+3 (+0.2)	112 (+0.8)	117 (+1.1)	+5 (+0.3)
	3	98 (-0.1)	95 (-0.3)	-3 (-0.2)	127 (+1.8)	111 (+0.7)	**-16 (-1.1)**
	4	87 (-0.9)	103 (+0.2)	**+16 (+1.1)**	105 (+0.3)	97 (-0.2)	-8 (-0.5)
	5	99 (-0.1)	85 (-1.0)	-14 (-0.9)	92 (-0.5)	100 (0.0)	+8 (+0.5)

Note: Nepsy = Nepsy Developmental Neuropsychological Assessment in scaled score (z score); VMI = The Developmental Test of Visual Motor integration in standard score (z score); significant changes in scores are illustrated in bold writing.

LIST OF APPENDICES

APPENDIX 1

Common types of congenital heart defects

Common Types of Congenital Heart Defects

i) Acyanotic congenital heart abnormalities

Ventricular and Atrial Septal Defects (VSD/ ASD)

The most common form of congenital heart defect is called ventricular septal defect (VSD). This refers to the presence of a hole in the wall (septum) separating the ventricles and with the pumping action of the heart, this hole allows oxygenated blood, to be forced under high pressure to the right side of the heart (left-to-right shunt). As a consequence, this oxygenated blood (mixed with deoxygenated blood) is sent back to the lungs and the left side of the heart again. Many patients are asymptomatic with fewer than 10% requiring surgery as the hole either closes spontaneously or is so small that it presents no serious problems.

An atrial septal defect is similar to the VSD in that it causes a left-to-right shunt, however in this instance the hole occurs in the wall between the atria causing some oxygenated blood to pass from the left atrium to the right atrium rather than going via the aorta to the body. An ASD tends to cause fewer symptoms than a VSD and although this can close spontaneously in a number of cases, open-heart surgery is frequently required.

Pulmonary and Aortic Stenosis

A narrowing of the pulmonary valve occurs in pulmonary stenosis, causing an obstruction of varying severity that restricts blood flow from the right ventricle, requiring it to work harder to overcome the defect. Non-surgical techniques can be

used to widen the area where the obstruction occurs (balloon valvuloplasty), although in severe cases, surgery may be required.

Similarly aortic stenosis results in an obstruction of the aortic valve, which has consequences for the efficient flow of oxygenated blood via the aorta to the body. The degree of stenosis can vary and correction using balloon valvuloplasty, surgical valvotomy or valve replacement would only occur in cases of moderate or severe obstruction.

Patent Ductus Arteriosus (PDA)

A foetus relies on the ductus arteriosus (connection between the aorta and pulmonary artery) for a right-to-left shunt of blood to bypass the lungs. This system is open (patent) in the foetus but closes soon after birth when the lungs begin to function. Problems occur, however, when the ductus does not close after birth as some oxygenated blood from the left ventricle flows back into the lungs through the ductus, causing a left-to-right shunt. This type of defect is likely in premature infants, but can also occur in full term infants. Pharmacological treatment may resolve the problem in premature infants, although transcatheter occlusion or open-heart surgery may be required in a number of instances where pharmacological treatment is unsuccessful or with older patients.

Coarctation of the Aorta

Blood vessels that supply the body parts arise along the aortic arch. As coarctation of the aorta involves a localised constriction of the aorta, the site of this constriction differentially affects the supply of blood to different parts of the body. This may

present itself as congestive heart failure several days after birth or may not be identified until older childhood following symptoms such as leg pain or weakness after exercise. Surgical correction is required to resolve the defect.

Atrioventricular Canal Defect

In this condition, a large hole is present at the centre of the heart where the four chambers meet and also involves the tricuspid and mitral valves. A single large valve crosses the hole and allows oxygenated blood from the left side of the heart to pass into the right side where it is returned, with deoxygenated blood, to the lungs. The increased workload and blood flow to the lungs leads to an enlargement of the heart and pulmonary hypertension. Surgical correction usually occurs within the first year of life.

ii) Cyanotic congenital heart abnormalities

Tetralogy of Fallot

This type of defect combines four problems: a VSD causing a right to left shunt, where some deoxygenated blood is returned to the body through the aorta before passing the lungs, and is associated with cyanosis; pulmonary stenosis which blocks blood flow to the lungs; an overriding aorta lying directly over the VSD; and right ventricular hypertrophy. Surgical repair tends to occur when the child is about 1 year old although a palliative technique can be adopted if early correction is not possible.

Transposition of the Great Arteries

This occurs where the aorta and pulmonary artery are transposed, arising from the opposite ventricles than in a normal heart. This means that deoxygenated blood

instead of being carried by the pulmonary artery to the lungs for re-oxygenation, is carried to the body. Under these circumstances profound cyanosis occurs soon after birth. A palliative procedure (balloon atrial septostomy) opens the defect between the atria to increase mixing of the oxygenated and deoxygenated blood, therefore reducing cyanosis on a temporary basis until surgery a few days after birth. Most surgeons currently adopt a procedure which severs and correctly reconnects the blood vessels (arterial switch).

Hypoplastic Left Heart Syndrome (HLHS)

This refers to a range of abnormalities in which parts of the heart are under-developed e.g. left ventricle, aorta, mitral valve and is responsible for approximately 15% of all neonatal congenital heart disease deaths in the first month of life. As genetic and chromosomal anomalies are associated with this type of heart defect, these children often also have other organ defects, including brain anomalies.

APPENDIX 2

Local Research Ethics Committee Approval

SOUTHAMPTON & SOUTH WEST HANTS
LOCAL RESEARCH ETHICS COMMITTEES

Chairman: Dr Audrey Kermode/Dr David Briggs

Manager: Mrs Clair Wright
1st Fioor
Regents Park Surgery
Park Street
Shirley
Southampton S016 4RJ

Tel: (023) 8036 2466
Fax: (023) 8036 4110

Ref: CPW/ch

28 August 2002

Mrs P Young-Raybold (Trainee Clinical Psychologist)
Doctoral Programme in Clinical Psychology
Shackleton Building (no 44)
University of Southampton
Highfield

Dear Mrs Young-Raybold,

Submission No: m223/02/t – An investigation of Neuropsychological Outcome for Paediatric Heart Sugery Patients

Following the conditional approval and in response to your letter dated 5th August 2002, I am pleased to confirm **full approval** having responded satisfactorily to the committees concerns.

The following documents were re-considered:

- Consent Form, version 1, dated 20th July 2002
- Patient Information Sheet for adults, version 2, dated 20th July 2002
- Patient Information Sheet for Children, version 2, dated 20th July 2002

This approval was granted under Chairman's action by the Chairman Dr Audrey Kermode, and will be recorded by the Committee at their meeting in September.

This committee is fully compliant with the International Committee on Harmonisation/Good Clinical Practice (ICH) Guidelines for the Conduct of Trials involving the participation of human subjects as they relate to the responsibilities, composition, function, operations and records of an independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Constitution, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997.

Yours sincerely

A R Kermode

Mrs Clair Wright
Research Ethics Manager

APPENDIX 3

Data Protection correspondence

Southampton NHS
University Hospitals NHS Trust

Corporate Information Services Directorate
Data Protection Office
Old Nurses Home, Mailpoint 79
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

Tel: 023 8079 5079
Fax: 023 8079 4741

7 November 2002

DP Ref No: 082/02

Phillipa Young-Raybold

Dear Phillipa,

Ethics Committee Number: 223/02/t

Thank you for returning the Data Protection Guidance pack duly completed as part of your Ethics Committee submission and a copy of your Honorary Contract.

I am pleased to advise you that you comply with the principles of the Data Protection Act 1998 and your response will be held on file within this department. Will you ensure that data is anonymised, secure, password protected and cannot be accessed by any unauthorised person.

If I can be of any further assistance, please do not hesitate to contact me.

Yours sincerely,

Dannie Howe
Data Protection Officer
Corporate Information Services Directorate

Data Protection Notice:
Your response will be held in the Corporate Information Directorate. You have the right to apply for a copy of your information and to have any inaccuracies corrected.

APPENDIX 4

Research & Development correspondence

Southampton NHS
University Hospitals NHS Trust

Research & Development
2ND Floor
Trust Management Offices
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

Tel: 023 8079 5044
Fax: 023 8079 8678

Ref: PD1/02
15 October 2002

Dear Ms Young-Raybold

Re: Allocation of R&D Project ID Number

Local Ethics No. (LREC): **M223/02**
Project Title: **An investigation of neuropsychological outcome for paediatric heart surgery patients**

Thank you very much for returning the R&D database registration forms and a copy of your completed R&D Project Passport.

Your project is now registered on the R&D database and you may refer to it in correspondence by either its database identification number (RHM **CHI0266**) or by its LREC number.

This letter provides the formal SUHT approval required for your project to commence and confirms that SUHT indemnity for negligence is in place. **Please note: If this is a commercial research project, you must not start until our Director of R&D or his deputy has signed the ABPI-type indemnity provided by the sponsor.**

The conditions of this approval and indemnity require you as Principal Investigator to ensure the following:

- All staff involved in the project are familiar with the SUHT R&D policy, the Research Governance Framework for Health and Social Care and the SUHT Data Protection policy.
- All staff that will be involved with SUHT NHS patient's and/or have access to identifiable patient data has honorary SUHT contracts.
- All data must be collected and stored in accordance with ICH GCP and/or MRC Guidelines for GCP in clinical trials.
- All essential documents are to be stored and maintained in the Project files provided by R&D.
- All serious adverse events are to be reported in writing to the Ethics Committee and copied to the R&D directorate within 7 days.

Please note that this trust approval (and your ethics approval) only applies to the current protocol. Any changes to the protocol can only be initiated following further approval from the ethics committee via a protocol amendment. Please contact your R&D Coordinator who will advise you re the possible need for an additional Project Passport to be completed.

Should any of your team require training in the above policies and procedures please do not hesitate to contact us.

Any breaches of the above may constitute non-compliance with the Research Governance Framework and the project may need to be suspended until such issues are resolved.

Please do not hesitate to contact us should you require further information.

Kind regards

Di Sheridan-Foskett
Research Governance Manager

APPENDIX 5

Information sheets (parent and child)

Southampton NHS
University Hospitals NHS Trust

Information Sheet for Parents

Project Title: **An Investigation of Neuropsychological Outcome for Paediatric Heart Surgery Patients**

My name is Pip Young-Raybold and I am a Trainee Clinical Psychologist based at the University of Southampton. I am currently carrying out a research project aimed at finding out more about the memory and thinking skills of paediatric heart patients before and after heart surgery. I am writing to ask you if you would be willing for your child to participate in this study, but before you decide please take time to read the information below carefully and feel free to discuss it with others. Please contact me if you would like any further information.

What is the purpose of this study?
The aim of this study is to investigate some of the intellectual difficulties experienced by children with heart defects before and after they undergo heart surgery. It is anticipated that this research project could contribute to current understanding of the transient and permanent memory and thinking difficulties experienced by this group of children as a consequence of their heart problems. It is also hoped that this project may help to highlight ways in which these children could be supported within the educational setting.

Why have I been chosen?
You have been chosen because you have a child between the ages of 6 and 16, who has a heart problem that requires surgery.

What will happen if I take part?
If you agree to take part in this study, I will visit you and your family at home to conduct a series of tests which will assess your child's abilities in areas such as memory, attention, visual and verbal skills. Testing will be conducted on 3 occasions:

i) 1 to 2 weeks before the operation;
ii) 4 weeks after the operation;
iii) 4 months after their operation.

It should take about 3 hours for all tests to be completed with your child the first and last time I visit, but this depends on a number of factors such as concentration, speed of completing tasks, fatigue, motivation, etc. Regular breaks will be allocated to try to reduce the effects of fatigue upon performance. At the second time point, testing will take less than an hour and I will ask you some questions about your child's progress since the operation. I would also like to test another of your children in the same way as described above, to gather assessment information that would contribute to comparison data for a control group.

I will be assessing a small number of children and their siblings for this study. Once all assessments have been completed, the results for your child can be made available to you at your request. All information related to your child will be made anonymous.

What are the possible risks of taking part?
Occasionally, some children find some of the tasks more difficult than they had expected and this can be disappointing for them. I do not expect your child to know the correct solutions for every question or problem and I will try to allay any of their worries regarding test performance.

Will I benefit from taking part?
Neither you nor your child(ren) will benefit directly from taking part in this study. However, you would be participating in research that could contribute to the way in which both health professionals and families like yours understand some of the difficulties experienced by children with heart problems.

Do I have to take part?
It is your decision as to whether you would like your children to take part in this study. If you decide to participate but then change your mind, you can withdraw your consent at any time and do not have to provide a reason for this decision. Your decision will not affect any current or future medical care.

Will my taking part in the study be kept confidential?
All information collected for this study will be kept strictly confidential. Although there will only be a small number of participants, each child's identity will be kept anonymous when the final report is written.

What will happen to the results of the study?
All participants will be provided with a summary report, which will detail the overall results for the group of children that took part. Individual feedback of your child's results can be provided on request, but only once all results have been collected and the study has been completed.

Who is organising and funding the research?
The project is being conducted in collaboration with Dr Gnanapragasam (Consultant Paediatric Cardiologist and Susan Knight (Consultant Clinical Child Psychologist), both based at Southampton General Hospital and is a requirement of my training on the Doctoral Programme in Clinical Psychology at Southampton University.

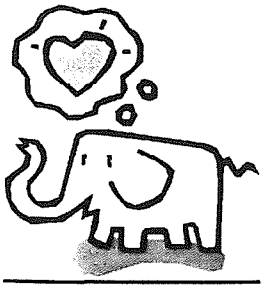
Who has reviewed the study?
The Southampton and South West Hants Local Research Ethics Committee has reviewed this study. If you have any questions about your rights as a participant or feel you have been placed at risk, Dr Gnanapragasam or I would be happy to discuss this with you.

How can I find out more?
If you have any questions or would like more details about this project, please feel free to contact me. My contact details are as follows:

Pip Young-Raybold (Trainee Clinical Psychologist)
Doctoral Programme in Clinical Psychology
University of Southampton
Shackleton Building (No. 44)
Highfield SO17 1BJ Tel: 023 8059 5321

Thank you for reading this information sheet.

Southampton NHS
University Hospitals NHS Trust



Information Sheet for Children

Project Title: **Does a heart operation change your memory and thinking?**

My name is Pip Young-Raybold and I am a Trainee Clinical Psychologist based at the University of Southampton. I am carrying out a research project to find out more about the memory and thinking abilities of children who have heart problems. I am writing to ask you if you would like to help me with my project. Before you make up your mind, please read this information sheet and then talk to your parents about it.

Why is this project being done?
This project is being done to find out how children who have heart problems think and remember things. To do this I would need to meet with you before and after your heart operation. It is hoped that this would tell people who work with children like you (such as doctors, nurses and teachers) more about the sorts of things that you are good at, and the things that might be a bit more difficult, so that they know how best to help children like you after a heart operation.

Why have I been chosen?
You have been chosen because you are between the age of 6 and 16, and have a heart problem that needs an operation.

What will happen if I take part?
If you agree to help, I will meet with you and your family at home. I will ask you to carry out some memory and thinking tasks for me. I will come to your house 3 times, which will be:

i) 1 to 2 weeks before your operation;
ii) 4 weeks after your operation;
iii) 4 months after your operation.

It will take a little while to do all the tasks with me each time I visit you, but you can have some time to rest if you get tired. I would also like to do the same sorts of tasks with your brother or sister (if you have one).

When I have collected all the information I need for this project, I will write to you and your parents to let you know what I found out. All information about you will be kept anonymous.

Are there any problems for me if I do help?
Sometimes, some children find some of the tasks more difficult than they had thought they would and this can be a bit annoying for them. However, I do not expect you to know the answers to every question I ask you, but I would like you just to do your best.

Will I benefit from taking part?
This study will not help you or your family directly, but it could help health professionals to better understand children like you, who have problems with their heart.

Do I have to take part?
It is up to you and your parents to choose whether you would like to help me with this project. If you think you would like to help but then change your mind, that is okay and you do not have to tell me why you changed your mind. Whether you decide to help in this project or not, this will not make any difference to the medical help that you are getting now or any medical help you might need in the future.

Will my taking part in the study be kept confidential?
All information collected for this study will be kept strictly confidential, and details about you, such as your name and address will not be written in my final report.

What will happen to the results of the study?
All children and their families who help with this project will be given a report to let you know what I found. I will also write up the results in a report for the University, the hospital and my colleagues.

Who is organising and funding the research?
The project is being carried out with Dr Gnanapragasam (your doctor) and Susan Knight (a Psychologist who works with children), and is being done as part of my training at Southampton University.

How can I find out more?
If you have any questions or want to know more, you and your parents can contact me by sending me a letter or telephoning me. My address and telephone number are:

Pip Young-Raybold
Trainee Clinical Psychologist
Doctoral Programme in Clinical Psychology
University of Southampton
Shackleton Building No. 44
Highfield
Southampton SO17 1BJ Tel: 023 8059 5321

Thank you for reading this information sheet.

APPENDIX 6

Consent forms (parent and child)

Version 1 15.03.02
Ref: 223/02/T

Southampton NHS
University Hospitals NHS Trust

CONSENT FORM

Researcher: Pip Young-Raybold (Trainee Clinical Psychologist)
Doctoral Programme in Clinical Psychology
Shackleton Building (No. 44)
University of Southampton
Highfield
Southampton SO17 1BJ

Tel: 023 8059 5321

Title of Project: An Investigation of Neuropsychological Outcome for Paediatric Heart Surgery Patients

Please respond to the following statements: **(Please initial box)**

1. I confirm that I have read and understood the information sheet dated 20.7.02 (Version 2) for the above study, have had the opportunity to ask questions and on this basis, agree for my child(ren) to participate. ☐

2. I understand that participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my child's medical care and legal rights being affected. ☐

3. I understand that my child's medical notes may be looked at by responsible individuals from Southampton General Hospital or the University of Southampton or from regulatory authorities, where it is relevant to participation in this research study. I give permission for these individuals to have access to my child's records. ☐

4. I understand that I will be provided with my child's results if I request this information, otherwise only a summary sheet containing brief details for the whole group of children tested, will be provided. ☐

Name of child requiring surgery	Name of child's brother/ sister*

Name of Parent (Father/ Mother)*	Date	Signature
Researcher	Date	Signature

(* please delete as appropriate)

Southampton NHS
University Hospitals NHS Trust

CONSENT FORM FOR CHILDREN

Researcher: Pip Young-Raybold (Trainee Clinical Psychologist)
Doctoral Programme in Clinical Psychology
Shackleton Building (No. 44)
University of Southampton
Highfield
Southampton SO17 1BJ **Tel:** 023 8059 5321

Title of Project: Does a Heart Operation Change your Memory and Thinking?

Please answer each of the following statements: (Please tick boxes)

1. I have read and understood the information sheet dated 20.7.02 (version 2) for this project and I am willing to take part. ☐

2. I know that I am free to choose whether I would like to help in this project and can change my mind about taking part at any time. ☐

3. I know that the people carrying out this project may need to look at some of my hospital notes. ☐

4. I understand that my parents and I will be given the results from my tests if we ask for them. ☐

Name of child (Patient or Brother/ Sister/Friend)*	Date	Signature
Researcher	Date	Signature

(* please delete as appropriate)

APPENDIX 7

Testing protocol

TESTING PROTOCOL

First home visit, introduction to parents and child:

Hello, as I mentioned on the telephone, my name is Pip Young-Raybold and I am a Trainee Clinical Psychologist. I am conducting this research project as part of the requirement of the Doctoral Programme in Clinical Psychology at Southampton University, where I am currently a student.

Discussion with child prior to testing in the presence of the parents:

Thank you for agreeing to take part in my study. I will need to visit you three times altogether and each time we will do a variety of games and puzzles. As it will take some time to finish all of the tests, we will take breaks to stop you from getting too tired. Do you have any questions?

Tests were administered in the following order at the first and last time point:

1. VMI
2. RAVLT
3. CFT
4. WISC
5. TEA-Ch
6. WIAT
7. RBMT (RBMT-C)
8. WMTB-C
9. Nepsy

APPENDIX 8

Semi-structured interview (patient and control)

NAME:.....
DATE:.....

SEMI-STRUCTURED INTERVIEW FOR PARENTS

(Heart Patient Version)

1. How has (name) been over the last month, following his/ her operation?

2. Have you noticed any changes in (name)'s abilities in any particular area(s) since the operation?

    a. In what ways do you feel their abilities have changed?

    b. Have these problems improved or worsened over the last month?

3. When are you planning for (name) to return to school?

4. How long will (name) have been off school by that time?

5. How was (name) getting on at school before the operation?

6. Do you feel that there are any specific factors that will affect their performance at school when they return?

7. Is (name)'s pattern of recovery as you expected?
    a. In what way is it different?

8. Do you have any particular concerns about (name)'s progress so far?

NAME:.....
DATE:.....

SEMI-STRUCTURED INTERVIEW FOR PARENTS

(Control version)

1. How has (name) been over the last month?

2. Have you noticed any changes in (name)'s abilities in any particular area(s)?

    a. In what ways do you feel their abilities have changed?

    b. Have these problems improved or worsened over the last month?

3. How has (name) been getting on at school?

4. Do you feel that there are any specific factors that affect their performance at school?

5. Do you have any particular concerns about (name)'s progress?