UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

School of Psychology

NEURODEVELOPMENTAL FUNCTIONING IN INFANTS WITH CONGENITAL HEART DEFECTS

Volume I: Neurodevelopmental outcome in children with congenital heart defects

Volume II: Novelty processing in infants with acyanotic congenital heart defects

by

Amy Winterson, BSc (Hons)

17,846 words

Thesis for the degree of Doctor of Clinical Psychology

June 2006

Thesis Abstract

This thesis consists of two papers: the first is a literature review providing a summary of the existing research documenting neuropsychological outcome in infants and children with congenital heart defects; the second paper presents the findings from an empirical study of infants with acyanotic congenital heart defects, and represents the first attempt to study novelty processing using electrophysiological methods in this population.

List of tables

List of figures

List of pictures

Acknowledgements

I would like to acknowledge the assistance of the following individuals in the completion of this research study:

Dr Alexandra Hogan and Dr Cathy Hill for their unending advice and support throughout the duration of this project.

Dr Hilary Robinson for her assistance in the identification and recruitment of participants.

Dr Fenella Kirkham for her helpful comments on earlier drafts of both the literature review and the empirical paper.

Dr Tony Salmon and his colleagues in Paediatric Cardiology for the enthusiasm they demonstrated when the research proposal was presented, and for their helpful advice regarding the selection and recruitment of research participants.

Luke Phillips for providing technical support both at the University and at the Wellcome Trust Clinical Research Facility.

The Southampton branch of the National Childbirth Trust, for informing their members about this project, and assisting with the recruitment of healthy control infants to the study.

Carolyne Boyles, Jennifer Trewin, and Rosemary King, of the Wellcome Trust Clinical Research Facility at Southampton General Hospital, for helping to make research participation fun for all those involved.

I am extremely grateful to the parents of all infants who participated in this study for giving their time and effort to make this research possible.

Finally, I would like to sincerely thank my fiancé, Gareth Savage, for his constant encouragement and support throughout this project.

Volume I of II: Literature Review

UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

School of Psychology

Neurodevelopmental outcome in children with congenital heart defects

by

Amy Winterson BSc (Hons)

Thesis for the degree of Doctor of Clinical Psychology

June 2006

This review has been prepared for submission to Child Development.

Abstract

Congenital heart defects (CHD) are the most common birth defect, affecting approximately 1% of live births. In the last few decades, major advances in surgical and medical management have led to increased survival rates, and as a result, interest has instead begun to focus on morbidity. There is a growing body of evidence to suggest that children born with CHD are at increased risk of neurodevelopmental impairments, which appear to be multifactorial in origin, and may relate to pre-operative, intra-operative and post-operative factors.

This article will give a critical overview of the literature describing neurodevelopmental outcome in children with CHD. This is intended to provide a basis for consideration of the challenges that exist in attempting to identify infants who are at risk of later neurodevelopmental impairments, such as those born with CHD. The difficulties that are inherent in predicting cognitive outcomes, related to the poor predictive validity of standard infant developmental screening tests, will be discussed. Finally, novel assessment methods to predict later cognitive functioning will be explored, and recommendations will be made regarding future research.

Introduction

The term congenital heart defect (CHD) refers to a group of defects which are present at birth, and involve structural alterations to the heart itself or to the major blood vessels surrounding the heart (Figure 1 gives a structural diagram of the heart and coronary blood vessels). It is estimated that CHD affects approximately 1% of live births (and a higher percentage of those aborted spontaneously or stillborn), making CHD the most common birth defect (Hoffman, 1990). Although the aetiology of CHD is often unknown and is presumed to be due to a combination of genetic and environmental factors, specific types of CHD are found to show an increased prevalence in the presence of chromosomal abnormalities, such as Down's syndrome (e.g. Figueroa, Magana, Hach, Jimenez, & Urbina, 2003).

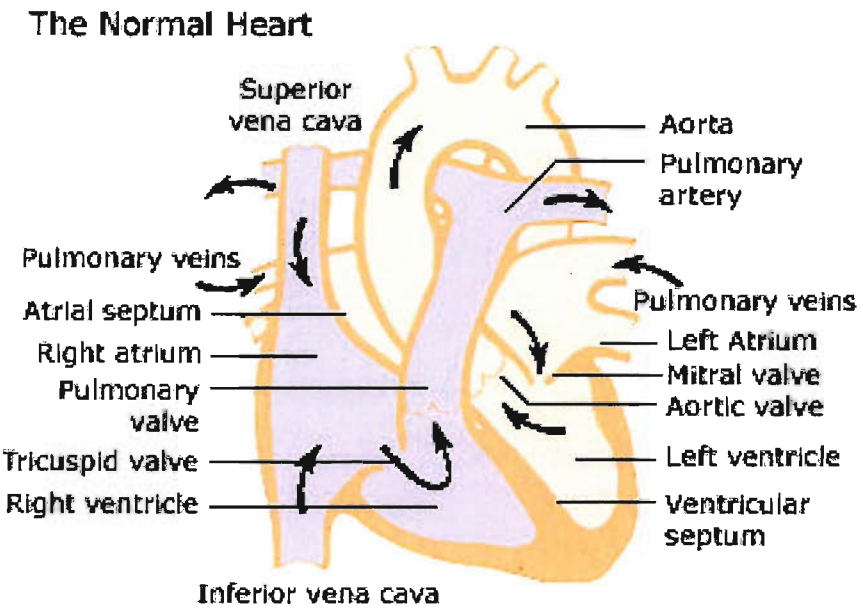


Figure 1: Structural diagram of the heart (retrieved 20.04.06 from http://www.bhf.org.uk/hearthealth/index.asp?secID=1&secondlevel=77&thirdlevel=361)

CHD are primarily divided into two classes, depending upon their effect on the circulation of oxygenated blood: cyanotic CHD refers to those defects where the lesion involves deoxygenated blood bypassing the lungs (a right to left shunt), and levels of oxygen in the circulation are reduced; acyanotic CHD is the term used to describe lesions in which the defect does not result in blood bypassing the pulmonary circulation, therefore levels of oxygen tend to be normal or near normal depending on the adequacy of gaseous exchange. The majority of patients with CHD have only mild lesions which do not require surgery and some of the most minor defects may correct themselves with time, such as a small ventricular septal defect. However, a significant minority of patients will require surgical and/or medical treatment in order to correct the lesion and/or to treat the effects of the lesion on the circulation, and with advances in medicine, surgical correction is now often undertaken during the neonatal period. A brief description of the most common types of CHD, their clinical implications, and their associated treatments is provided in table format in Appendix 1.

Neurodevelopmental outcome in children with CHD

In the past few decades, significant medical advances have resulted in dramatic improvements in survival rates for infants with CHD (Delamater, 2003); however, a growing body of evidence exists indicating that children born with congenital heart defects (CHD) are at increased risk of developmental and intellectual deficits (e.g. Griffin, Elkin & Smith, 2003). A recent review concluded that children with cyanotic lesions have more pronounced intellectual and cognitive impairment than those with acyanotic lesions, resulting in a full scale IQ score of

between 8 and 10 points lower (Bass et al., 2004). Children with acyanotic lesions typically perform better, but nevertheless show some impairments compared to healthy controls (e.g. Linde, Rasof, & Dunn, 1967), possibly due to reduced cerebral perfusion (Limperopoulos et al., 1999). Given the significant confound between chromosomal abnormalities and intellectual development, the vast majority of research in this field has excluded children with known chromosomal abnormalities or diagnosed genetic syndromes; in this review, the reader may assume that all studies discussed have excluded children with known chromosomal abnormalities or diagnosed genetic syndromes unless otherwise stated.

In studying neurodevelopmental outcome for children with CHD, researchers have often divided participants into two groups, and compared children with cyanotic CHD to those with acyanotic defects. Research has consistently found a significantly lower level of global intellectual functioning in children with cyanotic CHD compared to healthy children (e.g. DeMaso, Beardslee, Silbert & Fyler, 1990; Alden, Gilljam & Gilberg, 1998) and a higher incidence of learning disability (Feldt, Ewert, Stickler, & Weidman, 1969); this result may be explained by central nervous system vulnerability, which is more prominent in primary school aged children with corrected cyanotic CHD than in healthy children (DeMaso et al., 1990). It has been suggested that cyanosis may be the most significant factor responsible for the lower scores obtained by children with cyanotic CHD, given that significant differences in IQ scores between children with cyanotic CHD and children with acyanotic CHD have been demonstrated when the effects of age, social class, degree of sickness of the child at the time of

testing, and the type of test used have been taken into account (Aram, Ekelman, Ben-Shachar, & Levinsohn, 1985).

In a study of intellectual functioning and personality in children with CHD, Kramer, Awiszus, Sterzel, van Halteren and Claßen (1989) divided children into two groups according to the severity of their symptoms, irrespective of diagnostic group. The 'symptomatic' group, described as demonstrating limited physical capacity, consisted of 28 children who had undergone corrective surgery and 49 children who had either received palliation or did not require surgery. The asymptomatic group, whose physical capacity was described as "normal", contained 25 children who had already undergone corrective surgery and 26 who had not. A healthy control group was selected from children presenting at clinics with innocent heart murmurs, a common condition that does not appear to be associated with clinically significant symptoms (Smith, 1997). Significant group differences were found on German adaptations of the Wechsler intelligence tests, such that children who were described as symptomatic obtained results that were significantly lower than both the asymptomatic children and the healthy control children. This result has at least two possible explanations: the physical limitations of the symptomatic children may have a negative impact on cognitive development, or physical ability is simply a proxy measure of brain vulnerability. Either way, it appears that the functional implications of having a heart defect may be a more important factor in children's cognitive outcome than the type of CHD per se.

As can be seen from the literature already described, it appears that the presence of any type of CHD may be a risk factor for neurodevelopmental impairment. In attempting to understand the reasons why having CHD can result in adverse cognitive outcome, it is necessary to consider the many potentially negative influences on brain development that occur when a child has CHD.

Neurodevelopmental outcome in children with cyanotic CHD

In their pre-operative study of children with CHD Linde, Rasof, and Dunne (1967) found that children with cyanotic defects had marked impairments in gross motor functioning, and that in the younger children, the degree of physical incapacity was significantly associated with the level of developmental delay observed, indicating that being able to physically interact with one's environment may be crucial for normal development to occur. However, an alternative explanation for this result given by Linde and colleagues suggested that the reliance on sensory-motor items in early-years tests may have caused this association. Research using the Bayley Scales of Infant Development (BSID) with infants with CHD aged between 2 and 13 months who had not yet undergone any surgical intervention, found a strong independent relationship between the presence of congestive heart failure and developmental delay (Aisenberg, Rosenthal, Nadas, & Wolff, 1982). In addition, the presence of hypoxaemia (systemic arterial oxygen saturation <90%) was significantly related to motor functioning scores, perhaps related to a direct effect on processing speed as has been demonstrated at altitude. It is noted that Aisenberg and colleagues' study did not include any long-term follow up, and therefore it is not clear whether the developmental delays evident at the age of 2 months in these infants were

transient, or an early signal that their later cognitive functioning would be compromised.

In a study designed to evaluate the effects of chronic hypoxia in children with CHD, Silbert, Wolff, Mayer, Rosenthal, and Nadas (1969) evaluated three groups of children aged between 4 and 8 years, on tests of intellectual, perceptual and motor functioning. A sample of children with cyanotic CHD were compared with children with acyanotic CHD who had experienced congestive heart failure, and a further group of children with acyanotic CHD who had not experienced any episodes of heart failure and had not received any cardiac medications. Stanford Binet IQ scores were significantly lower in children with cyanotic CHD than in children with acyanotic CHD; in general, children with cyanotic CHD performed more poorly in tests of perceptual skills and intellectual functioning than children with acyanotic CHD who had experienced heart failure, and children with acyanotic CHD without a history of heart failure obtained the highest scores. Significant differences in gross (but not fine) motor functioning were also found between groups, with children with cyanotic CHD demonstrating specific difficulties on items requiring the use of lower limbs. In attempting to explain these findings, Silbert and colleagues analysed data concerning the activity levels of children in each of the three groups, and found that children in the cyanotic group were most likely to restrict their own activity, and were most likely to have their activities restricted by their parents, than children in other groups. When these data were divided based on the children's level of physical activity, significant differences still existed in intellectual and perceptual functioning between children with cyanotic CHD and children with acyanotic CHD,

suggesting that cyanosis has a significant effect on cognitive development irrespective of its effects on physical activity.

It has been suggested that prolonged cyanosis has an adverse effect on cognitive development due to the inadequate oxygenation of the brain during early critical periods of growth (Delamater, 2003); this finding indicates that early surgical intervention for children with cyanotic CHD should be prioritised. Indeed, children who underwent surgical correction for transposition of the great arteries before the age of 14 months obtained higher IQ scores at age 9 than those children whose surgery was conducted later (O'Dougherty, Wright, Loewenson, & Torres, 1985), suggesting that the duration of hypoxia may be critical in determining later neurodevelopmental outcome. Further supporting evidence of an inverse correlation between age at repair and WPPSI IQ scores in children with cyanotic CHD has also been reported (Newburger, Silbert, Buckley, & Fyler, 1984), supporting the proposal that increased duration of cyanosis (hypoxia) may cause a progressive impairment of cognitive functioning. However, in Newburger and colleagues' sample, there was a significant relative deficit in perceptual-motor functioning in children with CHD, which was present even among those children who underwent surgical correction during the first year of life, demonstrating the vulnerability of infant neurological development to the effects of hypoxia. More recent research has failed to find a correlation between age at repair and IQ scores in children with cyanotic CHD (e.g. Alden et al., 1998; Oates, Simpson, Cartmill, & Turnbull, 1995).

Clearly, specific factors related to CHD, such as acute hypoxic episodes related to cyanosis, or hypoxic-ischemic insults due to reduced cerebral perfusion, may be responsible for changes to children's neurodevelopmental trajectory, but it is also important to consider whether the general effects of the presence of a chronic illness may be responsible for the poorer cognitive outcomes documented in children with CHD. Wray and Sensky (1999) conducted a controlled prospective study of cognitive development in young children with CHD, and compared their performance on a range of developmental assessments with children requiring bone marrow transplants, in order to control for the effect of chronic illness on development. Their study found that prior to surgical interventions, children in the cyanotic CHD, acyanotic CHD, and bone marrow transplant groups all scored within the normal range on intellectual assessments, but scored significantly lower than a healthy control group, suggesting that factors related to the presence of a chronic illness may have influenced intellectual development. Following surgery and transplants, children with CHD still scored significantly lower than healthy controls, but results from children who had had bone marrow transplants were not significantly different from healthy children, suggesting that there may be specific effects related to the presence of CHD which have a detrimental influence on cognitive development. However, six of the children with cyanotic CHD were readmitted to hospital following surgery, an event that did not occur for children in any of the other groups, suggesting that absence from school may also have influenced the poorer results obtained by the children with cyanotic CHD.

Relatively few studies of developmental functioning in infants with congenital heart defects have investigated neurodevelopmental status prior to corrective

surgery. Techniques used during open-heart surgery in infants can often involve alterations to the blood supply (e.g. cardiopulmonary bypass), which have the potential to adversely influence neurological functioning (e.g. Robertson, Justo et al., 2004). The absence of information on baseline neurodevelopmental functioning prior to surgical intervention against which to compare post-operative assessment results makes it difficult to attribute observed abnormalities in this population directly to changes relating to CHD, as perioperative factors, prolonged hypoxia, restricted physical capacity, or a combination of all of these factors are often present in children with CHD (Hamrick et al., 2003).

Pre- and post-operative studies of infants with CHD

Neuroimaging studies

Dittrich et al. (2003) conducted prospective research on infants with CHD, and found that despite all infants having normal cranial ultrasound prior to surgery, 25 out of 68 infants were judged to have neurological abnormalities before surgery. The rate of neurological abnormalities was lower in those infants awaiting palliative surgery (6/10) compared to those awaiting corrective surgery (19/58), although interpretation of this finding is made difficult by the significant difference in group sizes. Magnetic resonance imaging (MRI) has also been used to investigate the morphologic features of the brain in infants and children before and after cardiac surgery. McConnell et al. (1990) found that one third (5/15) demonstrated abnormal MRI findings before surgery, and only 2/15 children had normal MRI post-surgery. A recent MRI study of infants before and after surgical correction of complex CHD (of both cyanotic and acyanotic types) revealed that approximately one quarter of infants' MRI scans prior to surgery either

demonstrated abnormality of the white matter near the ventricles or evidence of infarcts (Mahle et al., 2002). Early post-operative MRI scans showed that two-thirds of infants had new lesions or worsening of existing lesions, although on repeated scanning at 3 to 6 months of age many of these had resolved. Presently the literature suggests that a relationship exists between white matter lesions and subsequent cognitive deficits in children who were born preterm (e.g. Olsén et al., 1998), but no such evidence currently exists in infants with CHD, making it difficult to state conclusively what the clinical implications of these white matter abnormalities might be for later neuropsychological functioning.

A neuropathological study of 38 infants who died after cardiac surgery revealed that cerebral white matter damage (periventricular leukomalacia - PVL) was the most significant lesion in both severity and incidence (Kinney et al., 2005). Although no significant relationship was found between infant variables such as age at time of surgery and severity of brain damage or operative variables such as duration of deep hypothermic circulatory arrest and severity of brain damage, there was a tendency for neonates to be at greater risk for acute PVL, which the authors suggested reflected the greater vulnerability of the immature white matter to hypoxic-ischemic damage, which can occur pre-, intra- or post-operatively. Further research is required to establish whether the abnormalities uncovered on pre and post-operative MRI are permanent or whether they might reflect transient intracranial venous hypertension (Welch & Byrne, 1990). Even transient neuroimaging abnormalities might be indicative of a significant insult predictive of neurodevelopmental problems for infants and children with CHD.

Oxyhaemoglobin saturation

Research studying the oxygen saturation of neonates without pre-existing brain damage before, during, and after cardiac surgery concluded that the pre-operative neurological status of neonates had a significant impact on the post-operative neurological outcome (Toet et al., 2005). On the basis of the finding that infants with lower pre-operative regional cerebral oxygen saturation values tended to have lower developmental quotient scores at 30 to 36 months, Toet and colleagues proposed that lack of pre-operative brain damage may be a necessary requirement for normal neurodevelopmental outcome after cardiac surgery in infancy.

Neurodevelopmental assessments

In one of the few studies to evaluate neurological functioning in infants with CHD before open-heart surgery, Limperopoulos et al. (1999) completed a neurobehavioural assessment and a neurological examination in 56 infants awaiting surgical repair. Infants with hypoplastic left heart syndrome, extracardiac abnormalities involving the central nervous system (CNS), or known CNS insults were excluded. One fifth of the infants had an abnormal neurobehavioural assessment result, and 56% of the infants demonstrated one or more abnormal findings when examined by a neurologist. Interestingly, infants with *acyanotic* CHD were found to be at greater risk of having an abnormal neurological examination. Limperopoulos and colleagues suggested that this result may have occurred due to reduced cardiac output, resulting in decreased cerebral perfusion and increasing the potential for hypoxic-ischaemic brain damage. The authors concluded that neurobehavioural abnormalities, as measured using a standardised assessment, were common in children with CHD

pre-surgery, and argued that further investigation should be undertaken to focus on the causes of these neurological deficits as a priority.

Comparison of scores obtained on the Bayley Scales of Infant Development (BSID), recorded pre- and post-operatively in infants undergoing cardiac surgery with cardiopulmonary bypass, have shown significant changes in neurodevelopmental functioning (Robertson, Justo et al., 2004). The BSID is a standardised assessment tool designed to evaluate neurodevelopmental status in infancy and childhood, and yields two index scores, a Mental Development Index (MDI), and a Psychomotor Development Index (PDI); both index scores have a mean of 100 and a standard deviation of 15. Robertson, Justo, and colleagues found that for infants born with CHD, 5.7% of the sample had PDI scores below the normal range prior to surgery, whereas only 57% of infants had both MDI and PDI scores that were within the normal range at one-year follow-up. This finding suggests that infants with CHD are at a significant risk of abnormal neurodevelopmental outcome due to the vulnerability of the infant brain to hypoxic-ischaemic insults. Infants with CHD are often exposed to multiple potential causes of hypoxia during the neonatal period, such as pre-operative hypoxic periods due to cyanosis or reduced cerebral perfusion due to poor cardiac output, restricted blood flow, intra-operative insults due to CPB and other life-support methods, and hypoxic incidents during post-operative recovery.

Robertson, Joffe, et al. (2004) assessed neurodevelopmental functioning at 18 months in 67 survivors of neonatal heart surgery. Children with the lowest Bayley MDI and PDI scores tended to have chromosomal or other congenital

anomalies, such as chromosome 22q11 deletion syndrome or Down's syndrome. Outcomes for the 85 children studied were recorded at 18 months as in-hospital death, post-discharge death, motor or sensory disability, motor or mental delay, and intact survival. One quarter of the children studied were found to have motor or mental delay. A multivariate analysis model predicted 55% of variance in outcome: 23% was determined by pre-operative, 18% by intra-operative, and 14% by post-operative factors. Robertson and colleagues found that the duration of pre-operative ventilation contributed most to the likelihood of an adverse outcome, and concluded that infants requiring respiratory support represented the most vulnerable proportion of the sample. In contrast with previous research findings (e.g. Forbess, Visconti, Bellinger, Howe & Jonas, 2002), neither socio-economic status (SES) nor parental education profiles predicted outcome. The authors suggested that this lack of association may have occurred because environmental factors had perhaps not yet had a chance to exert a significant influence on neuropsychological functioning, or because the influence of having a major illness on neuropsychological functioning was much stronger at this young age.

The research findings presented thus far indicate that the neuropsychological development of infants with CHD may be adversely affected, with particularly compelling evidence for an association between cyanotic CHD and poorer neurodevelopmental outcome. However, few studies have systematically looked at whether children with acyanotic CHD have an entirely normal neurodevelopmental trajectory. Prospective studies using neuroimaging have indicated that neurological structures may be damaged by hypoxia-ischaemia even

before infants undergo surgery, and that the risk of these insults is present in infants with both cyanotic and acyanotic CHD. Results obtained on neurodevelopmental assessments pre and post-surgery have highlighted that infants with CHD are exposed to a variety of risk factors that may be responsible for neurodevelopmental impairments. The most significant risk factor would appear to be hypoxia-ischaemia, which may be caused by cyanosis, reduced cerebral perfusion due to poor cardiac output or restricted blood flow in the aorta, or hypoxic insults occurring during surgical procedures. It is also important to give consideration to factors related to the presence of any significant medical condition that may adversely affect development. These may include the effect of prolonged hospitalisation on the level of environmental and social stimulation an infant receives, and the ongoing restrictions placed on an infant's interactions with objects in its environment when physical capacity is limited by illness.

At present there has been limited research which has studied pre-operative baseline neuropsychological functioning in infants with CHD, and clearly neurological and neuropsychological morbidity may be significantly influenced when infants undergo open heart surgery. Many research projects have focused on evaluating the associations between surgery-related variables and cognitive outcomes for children with CHD, in order to improve morbidity, and some of the findings related to intra-operative risk factors will now be discussed.

Investigations of intra-operative variables

Haneda, Itoh, Togo, Ohmi, and Mohri (1996) conducted pre and post-operative assessments on 161 infants and children, in order to assess the impact of cardiac

surgery on intellectual functioning. Using the Gesell Developmental Schedule for Infants and the Binet Intelligence Test for Children in a repeated measures design, between one and two weeks before surgery, and two to four weeks afterwards, their results found that in general, post-operative scores showed a tendency to increase. Statistically significant increases were found in post-operative IQ scores for children who had undergone surgical correction of atrial or ventricular septal defects, Transposition of the Great Arteries (TGA), Tetralogy of Fallot (TOF), or complete atrioventricular canal. By contrast, infants who experienced an extended period of circulatory arrest during surgery (>50 minutes) demonstrated a significant decrease in developmental quotient scores. Haneda and colleagues concluded that cardiac surgery did not normally significantly impair intellectual function, but that the application of circulatory arrest for periods of more than 50 minutes increased the risk of cerebral dysfunction post-surgery. Comparable results were obtained by Forbess, Visconti, Bellinger et al. (2002) who found a trend towards lower full scale IQ scores in five year olds who had experienced periods of hypothermic circulatory arrest of longer than 39 minutes duration when undergoing cardiac surgery as infants, although the result was not statistically significant.

A comparison of 8-year neurodevelopmental outcomes for infants who received two different methods of vital organ support during cardiac surgery revealed that both groups showed IQ scores that were within the normal range and levels of academic achievement that were comparable (Bellinger et al., 2003). However, despite demonstrating overall intellectual functioning that was within normal limits on standardised testing, more than a third of children in both samples had

been identified as requiring additional educational support, and many showed relative deficits in specific areas of neuropsychological functioning, such as working memory, sustained attention and vigilance, and higher-order language skills. The comparison of vital organ support methods revealed that infants who underwent total circulatory arrest showed greater morbidity in the domain of motor functioning compared to those infants supported with low-flow cardiopulmonary bypass.

Sharma et al. (2000) evaluated a sample of 100 infants who underwent surgical correction of CHD using deep hypothermic bypass with and without circulatory arrest. Follow-up evaluations (carried out at approximately 4 years of age using a revised version of the Gesell Developmental Schedule) found that operated infants had a mean mental performance quotient that was significantly below the mean of a demographically matched control group, but that there was no significant difference in outcomes between infants who had total circulatory arrest and those who did not. Similar findings were reported by Bellinger et al. (2003), who found significantly greater morbidity in motor functioning in infants who had undergone total circulatory arrest during surgery, compared to those infants supported by low-flow cardiopulmonary bypass. These results suggest that despite the majority of research findings documenting non-significant differences in global measures of cognitive functioning post-surgery between children with CHD and healthy controls, there are clearly long-term effects of life support techniques on specific aspects of neuropsychological functioning.

Summary of research findings related to neurodevelopmental outcome in CHD

As can be seen from the research described so far, the weight of evidence indicates that neurodevelopmental outcomes for children born with CHD are different than those for healthy children. However, this is not to suggest that the situation regarding psychometric outcomes is clear-cut. Forbess, Visconti, Hancock-Friesen et al. (2002) found that children who had undergone surgical repair or palliation of CHD scored within one standard deviation of the normative population mean on tests of intellectual functioning. However, the authors concluded that despite apparently normal test results, children with CHD still demonstrated impairments in neurodevelopmental functioning, based on the finding that a significant proportion of the sample had received assistance from Speech and Language Therapists or Occupational Therapists. Similar results have been reported by Wright and Nolan (1994), whose study compared a sample of children with corrected cyanotic CHD (TGA or TOF) and a control sample of children with innocent heart murmurs. Wright and Nolan found a higher incidence of referral for additional educational support among children with corrected CHD, which is in concordance with Bellinger et al.'s (2003) report that one third of children who had undergone cardiac surgery as infants had been identified as needing additional educational support, despite scoring within the normal range on standardised intellectual assessments. These findings all suggest that children with CHD may be at a disadvantage in their learning compared to their healthy peers, despite apparently normal test results.

In Kramer and colleagues' (Kramer et al., 1989) study, symptomatic children with CHD scored below asymptomatic children with CHD (symptomatic mean IQ 102.6, s.d. 12.6; asymptomatic mean IQ 107.4, s.d. 19.6), who scored less than healthy control children (mean IQ 114.2, s.d. 13.9) on tests of intellectual functioning. Despite the significant difference in scores between symptomatic and healthy children, the mean score of the symptomatic group still fell within the normal range according to published test data. Kramer and colleagues concluded that the comparison with healthy control children reflected a true difference in intellectual functioning, and that the comparison with published test norms was no longer valid. Similar results have been reported by Wray and Sensky (1999), and by Aram and colleagues (Aram et al., 1985) who found significantly higher IQ scores in children with acyanotic CHD (mean IQ 112.81 ± 14.52) compared to children with cyanotic CHD (mean IQ 103.5 ±15.81), although both cardiac groups scored within the normal range according to test standardisation samples. The lack of a control group in Aram and colleagues' study makes it difficult to establish the significance of this finding for acyanotic children. However, in the context of convergent evidence where healthy control groups have been included (e.g. Kramer et al. 1989; Wray & Sensky, 1999) it is reasonable to conclude that children with cyanotic CHD have a reduced level of intellectual functioning.

Causal pathways explaining the association between CHD and neurodevelopmental problems remain under investigation. Relatively few studies have managed to observe infants pre-operatively, but studies using prospective neuroimaging have indicated that significant damage may have already occurred prior to surgery taking place. Studies examining the relationship between age at

corrective surgery (assumed to be a marker of the duration of chronic hypoxia) and neurodevelopmental outcome have not shown a clear benefit of earlier surgery, although there are many potential confounds to be considered. As cardiac surgical techniques have advanced, often the age at which such repairs are undertaken has reduced; in addition, there is a greater understanding of the potentially protective effects of specific life-support techniques in terms of neurodevelopment. In general, it may not be assumed that age of surgery is a good indicator of either severity of hypoxic exposure or of future cognitive capacity. Findings relating the duration of cardiopulmonary bypass (CPB) to outcome have suggested a trend towards longer bypass resulting in increased morbidity; however, statistics demonstrate that the largest proportion of variance in outcome for infants with CHD can be attributed to pre-operative factors. Taken together, these findings suggest that the severity of the defect may be confounded with the length of time on bypass, as more severe defects may require a greater period of time in order for the surgeon to complete the palliation or repair.

A further significant difficulty has been identified in assessing intellectual functioning in children with CHD, namely the selection of an appropriate control group, but an additional problem is the practicality of conducting pre-operative assessments when comparing groups longitudinally. As noted by Forbess and colleagues (Forbess, Visconti, Bellinger, et al., 2002), many of the heart defects are not conducive to the survival of the child without prompt surgical intervention, and with surgery now taking place in the neonatal period, this makes pre and post-operative testing (to allow children to act as their own controls) extremely difficult. In addition, children with CHD may have a significantly

different early infancy to healthy children; spending long periods of time in hospital potentially limits the level of stimulation they receive and restricts their social interactions, which may in turn adversely affect their social and language development. Perhaps unsurprisingly, there is also evidence to suggest that parents of children with CHD demonstrate higher anxiety levels than parents of healthy children, and thus restrict the activity level of their child (Kramer, et al., 1989) or limit their interactions with other children for fear of putting their child at risk of acquiring an infection (Wray & Sensky, 1999). This could potentially place further limitations on their child's cognitive and social development.

Outcomes for children with CHD are often reported using broad indicators of overall functioning, such as IQ scores. The research presented here suggests that these children perform statistically differently from healthy children; the IQ scores obtained by children with CHD may fall within the normal range, but are, on average, significantly lower than those obtained by healthy children. Some have suggested that this is due to the general increase in average test scores over time, and that comparisons with test norms are no longer valid (e.g. Fuggle, Tokar, Grant & Smith 1992), but this criticism is not upheld by those studies that have compared children with CHD to healthy controls using the same measures. Moreover, evidence to suggest that school-aged children with CHD are more likely to have been identified as experiencing problems with their learning than healthy children (e.g. Forbess, Visconti, Hancock-Friesen et al., 2002; Wright & Nolan, 1994), further highlights the significance of the reduction, albeit subtle, in intellectual functioning.

As yet, few research studies have determined which aspects of cognitive functioning are problematic for children with CHD as they grow up, nor have they been able to identify at an early age which children may later need additional educational support. Those few studies which have presented detailed neuropsychological profiles of older children with CHD have suggested that executive functioning, including working memory, sustained attention, and higher order language skills, may be an area of relative deficit for children with CHD (e.g. Bellinger et al., 2003), and is in concordance with findings from studies of the effects of hypoxia on intellectual functioning in adults (e.g. as a result of chronic obstructive pulmonary disease; Hynninen, Breitve, Wiborg, Pallesen, & Nordhus, 2005).

Recent prospective longitudinal research has attempted to investigate whether IQ scores at 8 years of age could be predicted from developmental test scores at 12 months in children who underwent surgical correction for cyanotic CHD (TGA) in the first 3 months of life (McGrath, Wypij, Rappaport, Newburger, & Bellinger, 2004). McGrath and colleagues assessed 135 infants using the BSID and the Fagan Test of Infant Intelligence (FTII – a measure of infant visual information processing), and completed a WISC-III IQ assessment with the children seven years later. Their analyses revealed that although children with poor neurodevelopmental scores at year 1 were at increased risk of achieving lower IQ scores at year 8, linear regression analyses demonstrated that all three indices of neurodevelopmental status at year 1 (Bayley MDI and PDI scores, and FTII) had low positive predictive values (35-42%) for year 8 scores. This result highlights that a substantial proportion of infants who scored within the normal

range at year 1 will go on to demonstrate deficits in intellectual functioning at 8 years of age, underscoring the need for more accurate assessments of infant cognitive functioning. If it is accepted that an important research direction is the prediction of those infants with CHD who are at greatest risk of later cognitive deficit, then new assessment tools should be developed. Such an assessment needs to be sensitive enough to identify the early precursors of the high prevalence/low severity neurodevelopmental impairments seen later on in children with CHD.

Predicting later cognitive functioning from infant assessments

Aylward (2002) has suggested that research on cognitive outcome in infants at risk of deficit has traditionally taken too broad a view on cognitive functioning. Specifically, such research has tended to use later IQ scores as a marker of overall intellectual functioning or as a measure of the success of early development. Aylward argues that this approach has a tendency to mask subtle deficits, or areas for potential remedial interventions, and that in practice, many children with scores at the lower end of the *normal* range of IQ may in fact struggle when competing with class mates who have a high average IQ; this has indeed been demonstrated in children with CHD (e.g. Forbess, Visconti, Hancock-Friesen et al., 2002; Wright & Nolan, 1994). Aylward proposed that evaluations should encompass a wide range of different cognitive and behavioural skills, and that care should be taken to report on the findings from each of these aspects, rather than reporting of an overall score. Others have suggested that a generalised rather than specific approach may have actually prevented researchers from accurately identifying domains of impairment in infants and children with CHD (Delamater,

Brady, & Blumberg, 1999). One of the primary difficulties in assessing developmental trajectories is that our ability to detect more subtle problems increases with age, as the range of potential assessment methods increases and the test materials become more sophisticated (in line with increasing maturity of cognitive function). This may result in previously 'silent' problems emerging at an older age, (Wernovsky, Shillingford, & Gaynor, 2005); i.e. children *growing-into* a deficit. For example, Karl and colleagues (Karl et al., 2004) found that significant differences between CHD and control children were evident in older groups (using the WISC-III for school-aged children), but not in a younger group (using the WPPSI – preschool version of the IQ test). Karl and colleagues concluded that this result had probably occurred due to the poor reliability of IQ tests in younger children, but did not provide evidence to substantiate this claim; perhaps a more likely explanation for this result is that the younger group contained a much smaller sample (n=32) to the older group (n=116) and that a lack of statistical power prevented a significant difference being demonstrated between groups, as both age groups showed a numerically similar discrepancy between healthy participants and those with CHD. It is also possible that the increasing complexity of test items for older children allowed specific deficits in higher-level cognitive processing to be highlighted.

The ability to predict neurodevelopmental outcome in children who have challenging medical problems early in life may inform decisions about the timing of intervention to minimise cognitive deficit (Aylward, 2004). Historically, however, significant difficulties have been encountered in predicting later intellectual functioning from measures completed during infancy and early

childhood; estimates indicate that only 1% to 6% of the variance in later IQ is explained by measures completed in infancy (Aylward, 2004). Recent prospective longitudinal research utilising the Bayley (BSID-II) MDI has called into question its use in predicting later functioning in infants-at-risk (Hack et al., 2005). Hack and colleagues assessed a large sample of 200 toddlers aged 20 months who were born at extremely low birth weight (mean 811g), and re-assessed them at age 8 years using the Kaufman Assessment Battery for Children (KABC) Mental Processing Composite (MPC) score. The MPC score comprises results obtained on four different subtests and is considered to be an equivalent of an IQ score, with a mean of 100 and a standard deviation of 15. The positive predictive value (i.e. probability) of having a significantly low MPC (< 70) at age 8 given a significantly low MDI score (< 70) at age 20 months was just 0.37. Among the group of children who were free of neurosensory abnormalities, 80% of those who obtained an MDI of <70 at 20 months had scores which were within the normal range at 8 years of age; however, further investigation revealed that these children did have poorer academic achievement and social functioning, and continued to score more poorly on the MPC than children whose MDI scores were >70. Hack and colleagues concluded that MDI scores at 20 months showed reasonable positive and negative predictive value among children with neurosensory abnormalities, but should not be used as an independent predictor of cognitive outcomes in children without neurosensory impairments. Finally, McCall (1989) also noted that scores obtained on the BSID during infancy are not usually related to later IQ scores.

The reasons for the poor predictive validity of infant tests are likely to be multifaceted. One interpretation is based on the differences in test items used to measure intelligence across discrete developmental stages (e.g. sensorimotor items in infants, and measures of verbal comprehension and expression in toddlers). Specifically, it has been suggested that many authors have failed to find strong evidence for predictive validity because they have focused on traditional neuropsychological tests, rather than investigating fundamental cognitive processes that reflect possible sources of continuity (e.g. Berg & Sternberg, 1985).

Berg and Sternberg (1985) argued that response to novelty is a continuous feature and as such provides a means for understanding the nature of intellectual and cognitive development throughout childhood. Importantly, this view concurs with many conceptual theories of the nature of intelligence. For example, Piaget (1966) theorised that the processes of assimilation and accommodation (e.g. the capacity to adapt to new situations) underpin intellectual development, and longitudinal research has demonstrated the ability of measures of infant novelty processing to predict full scale IQ at age 11 (e.g. Rose & Feldman, 1995). Rose and Feldman (1995) found that visual recognition memory assessed in 7 month old infants was significantly correlated with full scale IQ at 11 years of age ($r=0.41$, $p<.05$). In addition, research in adults has found that the ability to cope with novelty in a problem-solving task was significantly correlated with intelligence test scores (Neubauer, 1990), supporting the position that novel problem solving is a particularly robust measure of fluid intelligence (Duncan, Elmslie, Williams, Johnson & Freer, 1996).

A concordant theoretical position has been taken by Fagan (2000), who proposed that intelligence should be defined as the ability to process information; traditional measures of intelligence, such as IQ scores, are therefore measuring a combination of information processing ability and acquired knowledge. Fagan suggested that the ability to process information has a significant effect on development, such that an individual who begins life with poor processing abilities may be expected to know less later in life than an individual who has more efficient processing skills. Kail (2000) similarly argues that processing speed is a basic parameter of cognitive functioning, and that processing speed is causally linked to other elements of intelligence: "more rapid processing enhances memory, which, in turn, enhances reasoning" (p.59). Kail also suggests that developmental changes in processing speed can be attributed to biological causes. However, the extent to which 'faster' is consistent with 'better' across all stages of child development has not been confirmed; at some points in infant and child development it may actually be adaptive to have longer processing time to ensure that all stimulus features are encoded. These theories nevertheless provide a basis for examining continuity in development, and suggest that assessment of infant information processing abilities may provide a basis for more accurate prediction of developmental outcomes later in life, as the ability to process new information efficiently will predict how successfully learning will take place.

The search for continuity: research assessing information processing in infants

This section of the literature review will consider in greater detail the research evidence relating infant information processing and later cognitive functioning.

While the main aim is to demonstrate the existence of continuities in development, it is inevitable that attention will also be drawn to the methodological complexities associated with this line of research.

Rose and Wallace (1985) studied 35 pre-term infants longitudinally during the first 6 years of life, in order to evaluate the predictive validity of infant visual recognition memory in estimating later cognitive outcome. Visual recognition memory was assessed at the age of 6 months, and was indexed as the relative amount of time infants spent looking at the novel compared to the familiar stimulus. Infants were also assessed using the BSID, which was administered at one and two years of age. Further assessment using the Stanford Binet Intelligence Test was conducted at the ages of 2 years 10 months and 3 years 4 months, and a final assessment using the WISC-R was conducted at 6 years of age. Visual recognition memory at 6 months of age was found to be significantly related to MDI scores at 24 months ($r=0.53$, $p<.01$), and IQ scores at 34 months ($r=0.66$, $p<.01$), 40 months ($r=0.45$, $p<.05$), and 6 years of age ($r=0.56$, $p<.01$). In contrast, MDI scores at 6 and 12 months were not significantly related to any measures of cognitive outcome between 1 and 6 years of age. The MDI score obtained at 2 years of age predicted later IQ scores, perhaps because the BSID at this age incorporates more language items. This study suggests that items on the earlier BSID (<1 year) are not specifically related to competencies that are central to later cognitive functioning, supporting Berg and Sternberg's (1985) argument that early infant assessments rely on sensori-motor performance which is related to but does not equate with later cognitive function.

A recent study of information processing in 7-month-old infants used structural equation modelling to more directly test the pathways between infant and child cognitive function (Rose, Feldman, Jankowski, & Van Rossem, 2005). Rose and colleagues studied four cognitive domains in 7-month-old pre-term and full-term infants: (i) memory was assessed using a paired-comparison paradigm, in which time spent looking at the novel stimulus was recorded, (ii) encoding speed was assessed using a continuous familiarisation task, in which the number of trials required by the infant to demonstrate a consistent preference for the novel stimulus was recorded, (iii) representational competence was assessed using a cross-modal transfer task in which the familiarisation phase occurred in the tactile modality and was tested in the visual modality and (iv) infant attention was assessed by the mean look duration and number of gaze shifts between paired targets per second. Later cognitive outcome was assessed by the administration of the Bayley MDI at age 2 and 3 years. Rose and colleagues argued that "if indeed individual differences in these abilities are maintained over age, it is anticipated that early abilities will predict later ones. Such findings would have implications for the identification of the roots of later cognition and for the early identification of children at risk" (p.1173). In support of this hypothesis, the results demonstrated that infant information-processing is related to later cognitive competence. Moreover, prematurity had a detrimental effect on attention, speed, and memory functioning as assessed at 7 months of age, and these impairments in cognitive functioning accounted for deficits on the MDI at 2 and 3 years. Rose and colleagues concluded that simple cognitive processes, such as attention, speed, and memory, are critical to the development of more complex cognitive processing abilities. These findings also confirmed that deficits in processing

abilities can be detected in the first year of life using experimental measures; the potential clinical relevance for the development of tests of infant behaviour was demonstrated.

An earlier longitudinal study by the same authors followed a group of children whose information processing abilities were assessed at the ages of 7 months and 1 year, and demonstrated significant correlations between two measures of infant information processing (visual recognition memory and cross-modal transfer) and full scale WISC-R IQ at the age of 11 years (Rose & Feldman, 1995). This study included 50 pre-term babies, considered to be medically 'at risk', and 40 full-term babies; both samples were from families in low socio-economic groups. In reviewing these results, Rose and Feldman concluded that cognitive abilities assessed in childhood are present in some form in infancy. This was supported by correlations between infant measures and specific cognitive abilities at age 11, independent of motor speed (infants may be expected to be slower than children) and IQ (which would require a degree of language competency not present in the infants). The authors proposed that a common thread of continuity in cognitive functioning, best conceptualised as perceptual speed, was present across ages and had contributed to these correlations. This study also provided further evidence for the differences in cognitive functioning between children born pre-term and full-term, with the pre-terms obtaining IQ scores that were on average 10 points lower at age 11. However, the correlations between infant measures and outcomes at 11 years were similar across groups, indicating that the continuity demonstrated in intellectual functioning over the first 11 years of life occurs even

in the context of significant medical and social risk factors, such as prematurity and low socio-economic status.

Thompson, Fagan, and Fulker (1991) found significant correlations between infant novelty preference scores (averaged from two assessments at 5 and 7 months of age) and IQ scores from a Stanford Binet IQ assessment completed at 3 years of age ($r=0.58$, $p<.01$). Using partial correlations, novelty preference score was found to predict receptive language scores at 36 months independent of the contribution of general intelligence ($r=0.24$, $p<.05$), suggesting that individual differences in infant novelty processing may reflect a specific cognitive ability that significantly influences later intelligence and language acquisition. Later repeated assessments of these same children found that the correlations between infant novelty preference scores and WISC-R IQ scores at age 7 were positive but not statistically significant ($r=0.13$, $p>.05$; Thompson & Petrill, 1994). Thompson and Petrill (1994) suggested that the lack of a statistically significant relationship between infant novelty processing and later cognitive outcome in older children in this study may have occurred due to the small sample size and the low reliability of earlier measures, which have since been updated.

Indeed, research conducted by Smith, Fagan, and Ulvund (2002) attempted to clarify the relationship between novelty processing in infancy, parental SES and later intellectual functioning in a longitudinal study of 69 low birth weight babies. Visual Recognition Memory (VRM) score obtained from two assessments using the FTII during the first 13 months of life was a significant predictor of the children's KABC MPC scores at 8 years of age. The contribution of the VRM

score to the prediction of 8 year outcome was independent of the significant contribution made by parental SES. "An infant who readily sorts out familiar stimuli will more often turn its attention to novel and more informative aspects of the environment, and in so doing gets a head start over its age peers who are in need of longer time to choose between the familiar and the novel" (Smith et al., p.257). In other words, Smith and colleagues suggested that infants whose visual recognition memory functions in a more efficient manner, will be able to spend more time exploring other aspects of their visual environment and learning more about novel stimuli that surround them. This indicates therefore that faster processing speed may well be an adaptive feature at any age. Similar longitudinal research conducted with pre-term infants showed a negative association between fixation duration in infancy and IQ scores at 18 years of age ($r=-.36$, $p<0.001$; Sigman, Cohen, & Beckwith, 1997), again suggesting that infant attention measures may be useful as a predictive tool. Sigman and colleagues' (1997) research also highlighted the role of the environment in moderating the effect of information processing ability, as maternal vocalisations only had a significant effect on outcome among infants with shorter fixation durations. Thus, while SES may have only a limited impact on the appearance of these early developing behaviours, other environmental factors may be influential.

Tasbihsazan, Nettelbeck, and Kirby (2003) conducted a study of 78 healthy infants tested at 27, 29, 39 or 52 weeks using the FTII. Scores obtained at 27, 29 and 39 weeks did not reliably predict later intellectual functioning (MDI and Stanford-Binet scores at 2 years), although there was one exception of a significant correlation between FTII score at 52 weeks and MDI at 2 years

($r=0.49$, $p<0.017$). However, there are two criticisms that may be made of this study to explain the lack of consistent findings. Firstly, the babies recruited into this study were all healthy and taken from a population of middle class families, thereby restricting the range of scores that may have been obtained in assessments. Secondly the FTII has been accused of poor internal consistency (Lavoie & Desrochers, 2002) which may have prevented accurate prediction of later intellectual functioning. The former criticism may be unjustified considering the larger number of infants assessed in this study, and in view of the significant predictive validity of other studies that have controlled for SES (Smith et al., 2002). The latter criticism is not supported by other studies that have demonstrated the sensitivity of similar infant visual processing measures to the presence of neurodevelopmental vulnerability (e.g. Rose et al., 2005).

Lavoie and Desrochers (2002) used applied regression analysis to study visual habituation in infants, evaluating the short-term reliability of a series of measures in twenty-one 5 month old infants. A number of measures of infant visual processing were recorded on two occasions separated by 24 hours. Six of the eight variables based on the duration of habituation showed moderate test-retest reliability, in addition to a variable labelled "reaction to novelty" which was derived from the difference between the mean of the test trials for the novel stimulus and the last habituation trial. Interestingly, Lavoie and Desrochers found that the measure of the infants' *preference* for the novel stimulus (considered to be similar to the FTII novelty preference score) was not reliable over time. Conversely, the degree of an infant's *interest* in the stimuli, recorded as the

percentage of time that an infant spent looking at the stimuli over the course of the whole session, showed the highest reliability ($r=.67$, $p<.0001$).

Ruff (1986a) conducted research on response to novelty in infants aged 7 months, by examining similar behavioural responses, and found that pre-term infants showed delayed latency to examine a novel object, and spent less time overall examining such objects than did full-term infants. This indicated that infants at greater risk of later intellectual and cognitive impairments could be differentiated from control infants using behavioural measures of attention to novel objects. This hypothesis was given empirical support by a longitudinal study of normally developing infants reported in the same year. Ruff (1986b) found that two measures of response to novelty in 6 month old infants were significantly related to two behavioural measures of cognitive functioning at 3½ years of age: the first significant correlation was demonstrated between latency to examine a novel object at 6 months and reaction time at 3½ years of age; the second significant correlation was found between the duration of examining novel objects at 6 months and the number of times that 3½ year old children got out of their seat during a formal assessment. Ruff concluded that the latency measure may be related to arousal, alerting, and orienting of cognitive processing. Specifically, this measure is suggested to represent the time taken for a change in attentional state to occur when a change occurs in the environment, and that this attentional state change prompts further information processing. The duration of examining is presumed to be related to behaviour that is associated with learning about the stimulus. These findings indicate that stability exists in individual differences in novelty processing over time despite significant developmental changes, and

suggests that behavioural indices of novelty processing may potentially provide an alternative method designed to assess infant cognitive functioning.

In summary, the adoption of a continuity theory of intellectual development, such as Berg and Sternberg's (1985) novelty processing theory, has allowed researchers to move away from using traditional sensori-motor infant developmental assessments in search of alternative measures of infant cognitive functioning. It is fair to conclude that the research described herein is generally supportive of a continuity theory of intellectual development. Measures of infant novelty processing have demonstrated predictive validity for later cognitive functioning that has exceeded the predictive validity of traditional infant assessments. Moreover, infant novelty processing measures may have particular value in predicting outcome for infants at risk. Notwithstanding the potential clinical importance, there is clearly a need for further research to improve the reliability of such assessments, and room for improving the sensitivity of such assessments. Perhaps most importantly, the brain processes underpinning novelty processing are not considered in the infant and child literature, despite an increase in understanding that conditions such as prematurity are associated with subtle brain pathology (e.g. Olsén et al., 1998). This means that brain-behavioural relationships are inferred rather than confirmed. In recent times, attention has turned to using electrophysiological measures of cognitive processing, which may be considered to be more objective than traditional assessments. The following section will describe the research pertaining to the use of event-related potentials (ERPs) in studying cognitive processing, and its potential application to the study of infant novelty processing.

Using electrophysiological measures to study cognitive functioning in infants

ERPs are extracted from the electroencephalogram (EEG) which is recorded non-invasively by placing electrodes at specific locations on the infant's scalp. The electrodes record electrical activity of the brain. This signal is amplified and appears as positive/negative deviations in the EEG trace. In an ERP paradigm, stimuli are presented while the EEG is recorded. Off-line, the EEG is then segmented into epochs which are time-locked to the different types of stimuli (e.g. tones or pictures). The epochs associated with each category of stimuli are averaged together (e.g. low and high tones). This allows for the identification of positive or negative components at specific time points (in milliseconds - ms) post stimulus presentation. For example, the P300 component is a positive deflection at approximately 300ms, typically elicited by oddball stimuli. There is considerable development of ERP components across the first 12 months of life, typically with latencies decreasing and amplitudes increasing over time (Kushnerenko et al., 2002); Kushnerenko and colleagues (2002) found that peaks observed in auditory ERPs from infants of 12 months of age were also observable from ERPs recorded at birth, suggesting that despite changes in amplitude and latency, component morphology may be similar. The basic principle is that it is possible to identify specific ERP components associated with specific stimuli, and compare these waveforms between groups.

Thomas (2003) and DeRegnier (2005) have argued that ERPs have advantages over other methods of assessing cognitive functioning, as they can be used to evaluate early cognitive development in infants, before the infants have acquired

language skills and at a time when they have limited behavioural repertoires. In addition, traditional developmental tests require that an infant has adequate mobility, but ERPs may be used in infants whose mobility has been restricted by medical problems or surgery. ERPs could also be used to evaluate changes in brain functioning that have occurred following interventions designed to improve developmental outcomes in infants at risk. DeRegnier argues that ERP techniques show great promise for providing longitudinal assessments of infant development over time, but as yet no sensitivity and specificity data have been agreed that would allow results obtained from individual infants to be clinically evaluated.

ERP research with infants at risk

A recent study of auditory ERPs found significant differences in the mismatch-negativity response (MMN) between pre-term infants and a healthy term control group (Fellman et al., 2004). The MMN is elicited by subtracting average ERP for standard stimuli from average ERP for oddball (deviant) stimuli; the MMN is thus a 'difference' waveform. Fellman and colleagues compared auditory ERPs using an oddball paradigm at three time points during the first year of life in three groups of infants: small for gestational age (SGA) pre-term infants, appropriate for gestational age (AGA) pre-term infants, and a healthy term control sample. Their results demonstrated that no distinct MMN response was recorded in either of the pre-term samples, and they concluded that this potentially might represent poorer sound discrimination ability in these infants. Additionally, significant correlations were found between specific ERP components and scores obtained on the BSID at 2 years of age: in pre-term infants, the positive peak to standard

stimuli at the parietal electrodes correlated with the BSID index score at 2 years, both during the 150-250ms window (p150; $r=0.6$, $p<.048$) and the 250-350ms window (p350; $r=0.64$, $p<.032$). Fellman and colleagues suggested that this may indicate that certain ERP components may be of value as a measure of cognitive functioning in infants. Further studies of auditory ERPs in premature and term babies have similarly revealed significant differences in ERP components between groups (e.g. Therien, Worwa, Mattia, and deRegnier, 2004). Therien and colleagues studied ERP recordings to speech sounds and to two different voices in 75 babies (40 term controls and 35 pre-terms) with normal cranial ultrasonography, and found altered discrimination of speech sounds and deficits in auditory recognition memory in pre-term infants at 40 weeks post-menstrual age.

Longitudinal studies of children at risk of developing dyslexia have used ERPs in infancy and correlated specific indices from the ERP recordings (such as peak amplitudes or latencies) with measures of language functioning in later childhood (e.g. Molfese, 2000; Guttorm et al., 2005). Molfese (2000) found that specific ERP components recorded within 36 hours of birth had the ability to discriminate with an accuracy of 81.25% between children who at age 8 were assessed as normal readers, poor readers, or dyslexic. Significant differences were found between groups in latency to the first negative peak to the speech syllable /gi/, and in three amplitude measures recorded in the right hemisphere to speech and non-speech syllables, suggesting that these differences are associated with later difficulties in language processing.

As part of a wider longitudinal investigation investigating dyslexia in children of parents with and without reading difficulties, Guttorm et al. (2005) collected ERP data from 49 healthy newborns: 26 at-risk infants (one or both parents had dyslexia) and 23 control infants (neither parent had dyslexia, and parental IQ was matched to at-risk group). ERPs were recorded to three different consonant-vowel syllables (/ba/, /da/ and /ga/); an earlier investigation had revealed that the greatest differences between groups were found in right-hemispheric responses to /ga/ at the latency of 540 to 630 milliseconds. In this study, the mean amplitude of responses during this timeframe was used in a correlation analysis with scores obtained from testing of the children at ages 2.5, 3.5 and 5 years using a battery of neuropsychological tests. The results obtained demonstrated that a larger and more positive ERP response in the right hemisphere had a significant association with poorer receptive language at 2.5 years, and that more positive ERP responses in the left hemisphere were associated with poorer verbal memory skills at 5 years of age. Guttorm and colleagues concluded that ERPs may provide a measure of the origins of children's later language and verbal memory functioning. These studies suggest that ERPs could potentially have great utility in identifying children who may be at risk of later developmental language problems and therefore may benefit from receiving early interventions targeted at improving their language abilities. The ability of infant ERPs to speech sounds to predict specific language difficulties up to 8 years later permits optimism that this method may potentially improve the prediction of specific cognitive outcomes from infant assessments, and suggests that further longitudinal research using ERP would be a worthwhile venture.

More recently, responses to novel sounds in biologically at risk infants have been studied using ERP; Hogan (2003) investigated auditory ERP responses to novel sounds longitudinally in 3, 9, and 12-month-old healthy infants and in a similar size group of infants with sickle cell anaemia (who are also at increased risk of hypoxia and neurodevelopmental delay; Hogan et al., 2006) and found differences between waveforms in these two groups. Specifically, by 12 months the early positive component morphology was different (single peak) in sickle cell infants compared to controls (bifurcated peak). These findings suggest that electrophysiological measures of response to novelty can be sensitive to mild perturbations in systemic physiology, e.g. anaemia, abnormal heart function. However, long term follow-up data are required to be able to determine the predictive validity of early ERP findings.

Conclusions: implications for future research with infants with CHD

The research findings discussed here have underlined the increased risk of high prevalence/low severity neurodevelopmental impairments faced by children with CHD, and have highlighted the difficulties inherent in teasing apart the multi-factorial causes of these difficulties. It appears that children with CHD are at increased risk of neurodevelopmental delay, but that these problems often are not identified until later in childhood. At present the research literature has tended to focus upon overall cognitive functioning in the form of IQ scores, a method which may result in deficits being masked by apparently "normal" scores. Broader assessment of multiple cognitive domains is needed in order to explore possible dissociations in neuropsychological performance. There is already evidence to

indicate that children with CHD are vulnerable to deficits in the domain of executive functioning (e.g. sustained attention and working memory). It is of interest that impaired executive function has also been demonstrated in studies of children who have experienced chronic and intermittent hypoxia (see Bass et al., 2004, for review). A consistent pattern across different diagnostic groups (but with vulnerability to hypoxia in common) may eventually be found.

This review has discussed the critical issue of being able to identify during infancy those individuals whose neuropsychological development has been (or will be) compromised. The evidence described herein has provided a reminder of the significant concerns regarding the reliability of traditional assessments, and the relative lack of predictive validity of standard infant tests in predicting later cognitive outcome. This issue clearly warrants further attention, as the identification of such problems early in life may potentially allow for intervention. Thus, it may be possible to maximise the child's functional learning outcome.

More recent theorising about the nature of intelligence has encouraged researchers to move away from the traditional infant sensori-motor tests, and instead focus on designing innovative methods to assess early behaviour. Contemporary theories of intelligence highlight the efficiency of information processing, and have introduced response to novelty as a continuous feature of intellectual functioning. Longitudinal research conducted with samples of infants at risk has offered a tantalising glimpse into the potential of this line of research, indicating the ability of measures of infant novelty-processing to predict cognitive outcome into later childhood with greater accuracy than some traditional tests. More recently,

electrophysiological methods have shown some promise in being able to distinguish vulnerable infants, and have the added advantage of being independent of the quality of an infant's physical and motor development.

In conclusion, it is suggested that further research efforts might usefully concentrate on studying electrophysiological and behavioural measures of novelty processing in infants with CHD, and comparing the results obtained with those of an age-matched control group. Ideally, such research would use a prospective longitudinal design, following these infants up as their development progresses, utilising concurrent standardised neuropsychological assessments at regular intervals, in order to evaluate the clinical significance of ERP findings; however, before such large-scale studies of this nature are possible, preliminary investigations will be necessary to discover whether ERP paradigms and behavioural indices of novelty processing have the potential to differentiate between groups of healthy children and those with CHD. This in itself represents an important first step in the development of more sensitive assessments of infants with CHD.

References

Aisenberg, R.B., Rosenthal, A., Nadas, A.S., & Wolff, P.H. (1982). Developmental delay in infants with congenital heart disease: correlation with hypoxemia and congestive heart failure. *Pediatric Cardiology, 3,* 133-137

Alden, B., Gilljam, T., & Gilberg, C. (1998). Long-term psychological outcome of children after surgery for transposition of the great arteries. *Acta Paediatrica, 87,* 405-410

Aram, D.M., Ekelman, B.L., Ben-Shachar, G., & Levinsohn, M.W. (1985). Intelligence and hypoxemia in children with congenital heart disease: fact or artifact? *Journal of the American College of Cardiology, 9,* 889-893

Aylward, G.P. (2002). Cognitive and neuropsychological outcomes: more than IQ scores. *Mental Retardation and Developmental Disabilities Research Reviews, 8,* 234-240

Aylward, G.P. (2004). Prediction of function from infancy to early childhood: implications for pediatric psychology. *Journal of Pediatric Psychology, 29 (7),* 555-564

Bass, J.L., Corwin, M., Gozal, D., Moore, C., Nishida, H., Parler, S., Schonwald, A., Wilker, R.E., Stehle, S., & Kinane, T.B. (2004). The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics, 114,* 805-816

Bellinger, D.C., Wypij, D., duPlessis, A.J., Rappaport, L.A., Jonas, R.A., Wernovsky, G., & Newburger, J.W. (2003). Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. *The Journal of Thoracic and Cardiovascular Surgery, 126 (5),* 1385-1396

Berg, C.A. & Sternberg, R.J. (1985). Response to novelty: continuity versus discontinuity in the developmental course of intelligence. *Advances in Child Development and Behavior, 19,* 1-47

Delamatar, A, (2003). Cardiovascular Disease. In M.C. Roberts (Ed). *Handbook of Pediatric Psychology* (3rd edition). London: The Guilford Press.

Delamater, A.M., Brady, E.U., & Blumberg, M.J. (1999). Cardiac conditions. In Brown, R.T. (Ed.). *Cognitive aspects of chronic illness.* New York: Guilford Press.

DeMaso, D.R., Beardslee, W.R., Silbert, A.R., & Fyler, D.C. (1990). Psychological functioning in children with congenital heart defects. *Journal of Developmental and Behavioral Pediatrics, 11,* 289-294

DeRegnier, R.O. (2005). Neurophysiologic evaluation of early cognitive development in high-risk infants and toddlers. *Mental Retardation and Developmental Disabilities Research Reviews, 11,* 317-324

Dittrich, H., Buhrer, C., Grimmer, I., Dittrich, S., Abdul-Khaliq, H., & Lange, P.E. (2003). Neurodevelopment at 1 year of age in infants with congenital heart disease. *Heart, 89,* 436-441

Duncan, J., Emslie, H., Williams, P., Johnson, R., & Freer, C. (1996). Intelligence and the frontal lobe: the organisation of goal-directed behaviour. *Cognitive Psychology, 30,* 257-303

Fagan, J.F. (2000). A theory of intelligence as processing: implications for society. *Psychology, Public Policy and Law, 6 (1),* 168-179

Feldt, R.H., Ewert, J.C., Stickler, G.B., & Weidman, W.H., (1969). Children with CHD: motor development and intelligence. *American Journal of Diseases in Childhood, 117,* 281-287

Fellman, V., Kushnerenko, E., Mikkola, K., Ceponiene, R., Leipälä, J., & Näätänen, R. (2004). Atypical auditory event-related potentials in preterm infants during the first year of life: a possible sign of cognitive dysfunction? *Pediatric Research, 56 (2),* 291-297

Figueroa, J.D., Magana, B.D., Hach, J.L.P., Jimenez, C.C., & Urbina, R.C. (2003). Heart malformations in children with Down syndrome. *Revista Espanola de Cardiologica, 56 (9),* 894-899. Abstract retrieved 01.05.06 from http://portal.isiknowledge.com/portal.cgi?DestApp=WOS&Func=Frame

Forbess, J.M., Visconti, K.J., Bellinger, D.C., Howe, R.J., & Jonas, R.A. (2002). Neurodevelopmental outcomes after biventricular repair of congenital heart defects. *Journal of Thoracic and Cardiovascular Surgery, 123 (4),* 631-639

Forbess, J.M., Visconti, K.J., Hancock-Friesen, C., Howe, R.C., Bellinger, D.C., & Jonas, R.A. (2002). Neurodevelopmental Outcome After Congenital Heart Surgery: Results From an Institutional Registry. *Circulation, 106[suppl I]* 95-102

Fuggle, P.W., Tokar, S., Grant, D.B., & Smith, I. (1992). Rising IQ scores in British children – recent evidence. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 33 (7),* 1241-1247

Griffin, K.J., Elkin, T.D., & Smith, C.J. (2003). Academic outcomes in children with congenital heart disease. *Clinical Paediatrics, 42 (5),* 401-409

Guttorm, T.K., Leppänen, P.H.T., Poikkeus, A-M., Eklund, K.M., Lyytinen, P., & Lyytinen, H. (2005). Brain event-related potentials (ERPs) measured at birth predict later language development in children with and without familial risk for dyslexia. *Cortex, 41,* 291-303

Hack, M., Taylor, G., Drotar, D., Schluchter, M., Cartar, L., Wilson-Costello, D., Klein, N., Friedman, H., Mercuri-Minich, N., & Morrow, M. (2005). Poor predictive validity of the BSID for cognitive function.....*Pediatrics, 116,* 333-341

Hamrick, S.E.G., Gremmels, D.B., Keet, C.A., Leonard, C.H., Connell, J.K., Hawgood, S., & Piecuch, R.E. (2003). Neurodevelopmental outcome of infants supported with extracorporeal membrane oxygenation after cardiac surgery. *Pediatrics, 111 (6),* 671-675

Haneda, K., Itoh, T., Togo, T., Ohmi, M., & Mohri. H. (1996). Effects of cardiac surgery on intellectual function in infants and children. *Cardiovascular Surgery, 4 (3),* 303-307

Hoffman, J.I.E. (1990). Congenital heart disease: incidence and inheritance. *Pediatric Clinics of North America, 37 (1),* 25-43

Hogan, A.M. (2003). A longitudinal study of auditory ERP response to novelty in infants with and without sickle cell anaemia. Unpublished doctoral dissertation, University College London.

Hogan, A.M., Kirkham, F.J., Prengler, M., Telfer, P., Lane, R., Vargha-Khadem, F., & de Haan, M. (2006). An exploratory study of physiological correlates of neurodevelopmental delay in infants with Sickle Cell Anaemia. *British Journal of Haematology, 132,* 99-107

Hynninen, K.M.J., Breitve, M.H., Wiborg, A.B., Pallesen, S., & Nordhus, I.H. (2005). Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. *Journal of Psychosomatic Research, 59,* 429-443

Kail, R. (2000). Speed of information processing: developmental change and links to intelligence. *Journal of School Psychology, 38 (1),* 51-61

Karl, T.R., Hall, S., Ford, G., Kelly, E.A., Brizard, C.P.R., Mee, R.B.B., Weintraub, R.G., Cochrane, A.D., & Glidden, D, (2004). Arterial switch with full-flow cardiopulmonary bypass and limited circulatory arrest: neurodevelopmental outcome. *Journal of Thoracic and Cardiovascular Surgery, 127 (1),* 213-222

Kinney, H.C., Panigrahy, A., Newburger, J.W., Jonas, R.A., & Sleeper, L.A. (2005). Hypoxic-ischemic brain injury in infants with congenital heart disease dying after cardiac surgery. *Acta Neuropathologica, 110,* 563-578

Kramer, H.H., Awiszus, D., Sterzel, U., van Halteren, A., & Claßen, R. (1989). Development of personality and intelligence in children with congenital heart disease. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 30 (2),* 299-308

Kushnerenko, E., Čeponiené, R., Balan, P., Fellman, V., Huotilainen, M., & Näätänen, R. (2002). Maturation of the auditory event-related potentials during the first year of life. *NeuroReport, 13 (1),* 47-51

Lavoie, C., & Desrochers, S. (2002). Visual habituation at five months: short term reliability of measures obtained with a new polynomial regression criterion. *Journal of Genetic Psychology, 163 (3),* 261-271

Limperopoulos, C., Majnemer, A., Shevell, M.I., Rosenblatt, B., Rohlicek, C., & Tchervenkov, C. (1999). Neurologic status of newborns with congenital heart defects before open heart surgery. *Pediatrics, 103 (2),* 402-408

Linde, L.M., Rasof, B., & Dunn, O.J. (1967). Mental development in congenital heart disease. *Journal of Pediatrics, 71 (2),* 198-203

McCall, R.B. (1989). Commentary. *Human Development, 32,* 177-186

McConnell, J.R., Fleming, W.H., Chu, W., Hahn, F.J., Sarafian, L.B., Hofschire, P.J., & Kugler, J.D. (1990). Magnetic resonance imaging of the brain in infants and children before and after cardiac surgery: a prospective study. *American Journal of Diseases of Children, 144,* 374-378

McGrath, E., Wypij, D., Rappaport, L.A., Newburger, J.A., & Bellinger, D.C. (2004). Prediction of IQ and achievement at age 8 years from neurodevelopmental status at age 1 year in children with D transposition of the great arteries. *Pediatrics, 114,* 572-576

Mahle, W.T., Tavani, F., Zimmerman, R.A., Nicolson, S.C., Galli, K.K., Gaynor, J.W., Clancy, R.R., Montenegro, L.M., Spray, T.L., Chiavacci, R.M., Wernovsky, G., & Kurth, D. (2002). An MRI study of neurological injury before and after congenital heart surgery. *Circulation, 106 (suppl. I),* 109-114

Molfese, D.L. (2000). Predicting dyslexia at 8 years of age using neonatal brain responses. *Brain and Language, 72,* 238-245

Neubauer, A. C. (1990). Coping with novelty and automatization of information processing: an empirical test of sternberg's two-facet subtheory of intelligence. *Personality and Individual Differences, 11 (10),* 1045-1052

Newburger, J.W., Silbert, A.R., Buckley, L.P., & Fyler, D.C. (1984). Cognitive function and age at repair of transposition of the great arteries. *New England Journal of Medicine, 310,* 1495-1499

O'Dougherty, M., Wright, F.S., Loewenson, R.B., & Torres, F. (1985). Cerebral dysfunction after chronic hypoxia in children. *Neurology, 35,* 42-46

Oates, R.K., Simpson, J.M., Cartmill, T.B., & Turnbull, J.A.B. (1995). Intellectual function and age of repair in cyanotic congenital heart disease. *Archives of Disease in Childhood, 72,* 298-301

Olsén, P., Vainionpää, L., Pääkkö, E., Korkman, M., Pyhtinen, J., & Järvelin, M.R. (1998). Psychological findings in preterm children related to neurologic status and magnetic resonance imaging. *Pediatrics, 102,* 329-336

Piaget, J. (1966). *The origins of intelligence in children.* Routledge and Kegan Paul.

Robertson, C.M.T., Joffe, A.R., Sauve, R.S., Rebeyka, I.M., Phillipos, E.Z., Dyck, J.D., Harder, J.R., & The Western Canadian Complex Pediatric Therapies Project Follow Up Group (2004). Outcomes from an interprovincial program of newborn open heart surgery. *Journal of Pediatrics, 144,* 86-92

Robertson, D.R., Justo, R.N., Burke, C.J., Pohiner, P.G., Graham, P.L., & Colditz, P.B. (2004). Perioperative predictors of developmental outcome following cardiac surgery in infancy. *Cardiology in the Young, 14 (4),* 389-395

Rose, S.A., & Feldman, J.F. (1995). Prediction of IQ and specific cognitive abilities at 11 years from infancy measures. *Developmental Psychology, 31 (4),* 685-696

Rose, S.A., Feldman, J.F., Jankowski, J.J., & Van Rossem, R. (2005). Pathways from prematurity and infant abilities to later cognition. *Child Development, 76 (6),* 1172-1184

Rose, S.A., & Wallace, I.F. (1985). Visual recognition memory: a predictor of later cognitive functioning in preterms. *Child Development, 56,* 843-852

Ruff, H.A. (1986a). Attention and organisation of behaviour in high risk infants. *Journal of Developmental and Behavioral Pediatrics, 7 (5),* 298-301

Ruff, H.A. (1986b). Components of attention during infants' manipulative exploration. *Child Development, 57,* 105-114

Sharma, R., Choudhary, S.K., Mohan, M.R., Padma, M.V., Jain, S., Bhardwaj, M., Bhan, A., Kiran, U., Saxena, N., & Venugopal, P. (2000). Neurological evaluation and intelligence testing in the child with operated congenital heart disease. *American Journal of Thoracic Surgery, 70,* 575-581

Sigman, M. & Cohen, S.E., & Beckwith, L. (1997). Why does infant attention predict adolescent intelligence? *Infant Behavior and Development, 20 (2),* 133-140

Silbert, A., Wolff, P.H., Mayer, B., Rosenthal, A., & Nadas, A.S. (1969). Cyanotic heart disease and psychological development. *Pediatrics, 43,* 192-200

Smith, K.M. (1997). The innocent heart murmur in children. *Journal of Pediatric Health Care, 11 (5),* 207-214

Smith, L., Fagan, J.F., & Ulvund, S.E. (2002). The relation of recognition memory in infancy and parental soioeconomic status to later intellectual competence. *Intelligence, 30,* 247-259

Tasbihsazan, R., Nettelbeck, T., & Kirby, N. (2003). Predictive validity of the Fagan Test of Infant Intelligence. *British Journal of Developmental Psychology, 21,* 585-597

Therien, J.M., Worwa, C.T., Mattia, F.R., & deRegnier, R.O. (2004). Altered pathways for auditory discrimination and recognition memory in preterm infants. *Developmental Medicine and Child Neurology, 46,* 816-824

Thomas, K.M. (2003). Assessing brain development using neurophysiologic and behavioural measures. *Journal of Pediatrics, 143,* S46-53

Thompson, L.A., Fagan, J.F., & Fulker, D.W. (1991). Longitudinal prediction of specific cognitive abilities from infant novelty preference. *Child-Development, 62 (3)* 530-538

Thompson, L.A., & Petrill, S.A. (1994). Longitudinal predictions of school-age cognitive abilities from infant novelty preference. In J.C. DeFries, R. Plomin, & D.W. Fulker (Eds.). *Nature and nurture during middle childhood.* Malden, MA: Blackwell Publishers.

Toet, M.C., Flintermann, A., van de Laar, I., de Vries, J.P., Bennink, G.B.W.E., Uiterwaal, C.S.P.M., & van Bel, F., (2005). Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 hours after arterial switch procedure in neonates without pre-existing brain damage: its relationship to neurodevelopmental outcome. *Experimental Brain Research, 165,* 343-350

Welch, R.R., & Byrne, P. (1990). Transient changes in neuroimaging appearances of the brain following cardiopulmonary bypass. *American Journal of Diseases of Children, 144,* 1184

Wernovsky, G., Shillingford, A.J., & Gaynor, J.W. (2005). Central nervous system outcomes in children with complex congenital heart disease. *Current Opinion in Cardiology, 20,* 94-99

Wray, J., & Sensky, T. (1999). Controlled study of preschool development after surgery for congenital heart disease. *Archives of Disease in Childhood, 80,* 511-516

Wright, M., & Nolan, T. (1994). Impact of cyanotic heart disease on school performance. *Archives of Disease in Childhood, 71 (1),* 64-70

Volume II of II: Empirical Paper

UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

School of Psychology

Novelty processing in infants with acyanotic congenital heart defects

by

Amy Winterson BSc (Hons)

Thesis for the degree of Doctor of Clinical Psychology

June 2006

This paper has been prepared for submission to Child Development.

Abstract

Congenital heart defects (CHD) are the most common birth defect, occurring in approximately 8 in 1000 live births. There is a growing body of evidence to suggest that children born with CHD are at increased risk of neurodevelopmental impairments, although at present the ability to predict cognitive outcome in infants at risk is severely limited by the poor reliability of traditional infant assessments and their reliance on intact motor development. Recent theorising about the nature of intelligence has proposed that novelty processing demonstrates continuity across development, and may provide an alternative method for assessing cognitive function in infants. Infants with acyanotic CHD (n=9) and a matched control sample (n=15) aged between 6 and 9 months were recruited in order to study novelty processing using behavioural and electrophysiological techniques. No significant differences were found between groups in anthropometric data, or in results obtained on both a standardised neurodevelopmental screening assessment and a measure of socio-emotional development. In support of the hypothesis that novelty processing is abnormal in infants with CHD, significant differences were found between groups on ERP indices: infants with CHD had an attenuated later negativity associated with novel stimuli over the parietal cortex compared to control infants. The results are discussed in light of the possible causative mechanisms for this impairment, and with regards to the potential utility of ERP paradigms in assessing infant cognition.

Introduction

Congenital heart defects (CHD) are the most common birth defect, affecting approximately 8 in 1000 live births (Hoffman, 1990). In the last few decades, major advances in surgical and medical management have led to increased survival rates, and as a result, interest has instead begun to focus on morbidity (Delamater, 2003). There is a growing body of evidence to suggest that children born with CHD are at increased risk of neurodevelopmental impairments (e.g. Griffin, Elkin & Smith, 2003), which appear to be multifactorial in origin, and may relate to pre-operative, intra-operative and/or post-operative factors.

CHDs are classified into two main types: cyanotic CHD refers to those defects where the lesion involves deoxygenated blood bypassing the lungs (a right to left shunt), and levels of oxygen in the circulation are reduced; acyanotic CHD is the term used to describe lesions in which the defect does not result in blood bypassing the pulmonary circulation, therefore levels of oxygen tend to be normal or near normal depending on the adequacy of gaseous exchange. The majority of patients with CHD have only mild lesions which do not require surgery and some of the most minor defects may correct themselves with time, such as a small ventricular septal defect (Delamater, 2003). However, a significant minority of patients will require surgical or medical treatment in order to correct the lesion and/or treat the effects of it (e.g. congestive heart failure), and with advances in medicine, such correction is now often undertaken during the neonatal period.

In one of the few studies to evaluate pre-surgical neurological functioning, Limperopoulos et al. (1999) completed a neurobehavioural assessment (Einstein Neonatal Neurobehavioural Assessment Scale - ENNAS) and a neurological examination in 56 infants with CHD who were less than one month of age. Infants with hypoplastic left heart syndrome, extracardiac abnormalities involving the central nervous system (CNS), or known CNS insults were excluded. According to established cut-off scores, 20% of the infants with CHD had an abnormal ENNAS score, and 56% of the babies demonstrated one or more abnormal findings (e.g. hypotonia or motor asymmetries) when examined by a neurologist. Interestingly, infants with acyanotic CHD were found to be at greater risk of having an abnormal neurological examination than infants with cyanotic CHD. Limperopoulos and colleagues attributed this result to the fact that some acyanotic defects result in reduced cardiac output or changes to the blood flow in the aorta, potentially leading to decreased cerebral perfusion and increasing brain vulnerability to hypoxic-ischaemic damage.

A later study by the same authors provided further evidence to suggest that early neurodevelopment in acyanotic infants is not without risk. Specifically, developmental assessments (Peabody Developmental Motor Scale and Griffiths Mental Development Scale) carried out on 61 children at age 20.7 months (± 8.3 months) who had undergone open heart surgery in the neonatal or early infancy period, found that infants with acyanotic CHD were more likely to have developmental delay than infants with cyanotic CHD (Limperopoulos et al., 2002). There is also conflicting evidence suggesting that cyanotic and acyanotic defects do not result in different degrees of cognitive deficit. Wray and Sensky

(1999) found significant impairments in cognitive and developmental functioning in a group of young children (aged 0 to 3.5 years), including those with cyanotic (n=11) and acyanotic CHD (n=14), compared to healthy controls (n=15), but no significant difference was found between acyanotic and cyanotic subtypes. Similarly, Majnemer and colleagues (Majnemer et al., 2006) found no significant predictive relationship between the type of heart defect (cyanotic or acyanotic) and developmental and neurological status at school entry in a sample of 94 children with CHD. It is nevertheless indicated that although children with acyanotic CHD may be expected to have fewer problems than infants with cyanotic CHD, they are vulnerable to neurodevelopmental deficit. In support, studies from the era when cardiac surgery was rarely performed in infancy have observed lower pre-surgical IQ and gross motor scores, and later age of walking in children with acyanotic CHD (mean age 4.9 years) than in age-matched healthy children (Linde, Rasof & Dunn, 1967). Lower IQ scores were also found by Yang and colleagues in two age-groups of acyanotic children (5-8 years: 93.3 ± 13.5; 9-14 years 83.3 ± 8.6) compared to age-matched controls, who obtained IQ scores of 103.7 and 99.3 respectively, with additional impairments in higher-order executive functions (Yang, Liu, & Townes, 1994).

Despite the implication that there may be brain abnormality in infants with acyanotic CHD, there are few published neuroimaging data, in part due to the difficulties involved with scanning young children. In a sample of nine infants and children with acyanotic CHD requiring surgical intervention, evidence of brain abnormality (e.g. ventriculomegaly, subdural haematoma) on magnetic resonance imaging (MRI) was found in one five month old infant pre-operatively,

and in seven infants post-surgery (McConnell et al., 1990). A retrospective review of cranial ultrasound studies obtained from 49 full-term infants with CHD and 42 controls found a significantly higher incidence of abnormality in infants with CHD (59% vs. 14%, $p<.001$; van Houten, Rothman, & Bejar, 1996). van Houten and colleagues reported that cerebral atrophy and linear echodensities in the basal ganglia and thalamus were the most prevalent abnormalities, and were particularly common in infants with two specific types of acyanotic CHD, namely coarctation of the aorta and ventricular septal defects. In addition, intraventricular haemorrhage occurred more often in infants with acyanotic CHD than in infants with cyanotic CHD.

Consistent with this result, a later study of 11 pre-operative infants with coarctation of the aorta found that only four had normal cranial ultrasound findings, with the remaining seven infants demonstrating evidence of ventriculomegaly, widened subarachnoid spaces, cerebral oedema, or intraventricular haemorrhage (Te Pas, van Wezel-Meijler, Bőkenkamp-Gramann, & Walther, 2005). Te Pas and colleagues concluded that reduced cerebral perfusion may have caused ischaemia and/or decreased brain growth. While such abnormalities may be expected to contribute to those cognitive deficits described above, a direct relationship has not yet been established. This highlights an important limitation of the literature. Without longitudinal data it is not possible to determine the extent to which such delay is transient, or whether it predisposes the infant to more overt cognitive deficit later in childhood.

In any condition that manifests from early infancy it is of interest to determine whether there are early precursors of later cognitive competence. Historically, however, significant difficulties have been encountered in predicting later intellectual functioning from measures completed during infancy and early childhood; estimates indicate that only 1% to 6% of the variance in later IQ is explained by measures of infant behaviour (Aylward, 2004). Differences in test items used to measure intelligence across seemingly discrete developmental stages (e.g. sensorimotor items in infants, and measures of verbal comprehension and expression in childhood as language skill progresses) indicate that such associations may be futile. However, others have suggested that there are fundamental aspects of intellectual function that represent a source of continuity in development. Berg and Sternberg (1985) have argued that response to novelty represents one such source of continuity in intellectual development. Indeed, the assimilation and accommodation of new information into existing schemas is a basic tenet of Piaget's theory of intellectual development (Piaget's 1966), and research with adult samples has found that the ability to cope with novelty in a problem-solving task was significantly correlated with intelligence test scores (Neubauer, 1990), suggesting that novelty processing is an integral component of intellectual functioning.

Particularly relevant to the novelty hypothesis are two studies by Ruff (1986a, b). In the first study, it was found that infants born prematurely showed delayed latency to examine a novel object at the age of 7 months, and spent less time overall examining novel objects compared to full-term infants (Ruff, 1986a). The second study was longitudinal, revealing that latency to examine a novel object at

7 months was related to reaction time (speed to press a button on hearing an auditory signal) at 3.5 years, and that duration of examining a novel object at 7 months was related to a measure of sustained attention at 3.5 years (a tally of the number of times the child got out of their seat during administration of the Stanford Binet test; Ruff, 1986b). These findings suggest that behavioural measures of infant novelty processing may provide a complementary method for assessing cognitive processing in infants, and that such measures may be of value in predicting later cognitive functioning. One problem with this approach however, is the large numbers of infants typically required to demonstrate significant group differences on behavioural measures, particularly when data derived from such measures are qualitative and when the neuropathology is subtle. It is important therefore to contemporaneously develop assessment techniques that yield greater level of sensitivity to variations in infant novelty processing.

Converging evidence for abnormal novelty processing may be provided by electrophysiological measures. Event-related potentials (ERPs) may be acquired in even very young infants who may be expected to have only limited behavioural repertoires (DeRegnier, 2005). The auditory novelty oddball paradigm has been used to study the waveforms of typically developing infants, and an infant analogue of the adult P3 response (originally described by Courchesne, Hillyard & Galambos, 1975) has been described (Kushnerenko et al., 2002a). Kushnerenko and colleagues called the components of this positive-negative complex in infants the 'P3a' and 'late negativity' respectively[1]. In a second study

[1] As it is not confirmed that this infant 'P3a' is the same as the widely replicated adult 'P3a', this term is not adopted in the present study.

(Kushnerenko et al., 2002b), six newborn infants and six toddlers aged two years were administered an oddball paradigm consisting of frequent tones and infrequent novel stimuli (environmental sounds such as bird noises). Novel stimuli were found to elicit a clearly identifiable fronto-central positive component at approximately 300ms in both infants and toddlers, followed by a bifurcated negative wave (late negativity). However, as this study presented only one type of infrequent (novel) stimulus, it is not confirmed that infants were responding to stimulus novelty rather than stimulus probability. The novelty auditory oddball has not been widely used with infants developing atypically. However, using other ERP paradigms, such as different speech sounds, the usefulness of ERP indices in distinguishing between typically and atypically developing infants has been demonstrated. For example, the mismatch negativity response has been found to be abnormal in preterm infants (Fellman et al., 2004), and a late negative waveform elicited by an auditory recognition memory task (differentiating the mother's voice from a stranger's voice) was absent in infants born to diabetic mothers (Siddappa et al., 2004).

The aim of the present study was to test the hypothesis that novelty processing is abnormal in infants with acyanotic CHD. This was assessed by administering behavioural and ERP measures of novelty processing to nine infants with CHD (6-9 months) and a group of 15 controls of a similar age and socio-economic status.

Method

Ethical permission for the study was granted by the Local Research & Ethics Committee, Hampshire, UK. The study design was cross-sectional: all infants attended for one session of approximately 1½ hours duration.

Participants

Parents of infants known to the Paediatric Cardiology service at Southampton University Hospital Trust were approached by one of the Cardiologists and asked if they were interested in receiving more information about the study. Healthy control infants were recruited by the same Cardiologist from the paediatric cardiology database (e.g. infants referred for further investigations but subsequently diagnosed with innocent heart murmurs) and from local post-natal and nursery groups. Further information about recruitment is provided in the 'Procedure' section below.

Table 1 provides details of each of the infants recruited to the CHD group. Infants with known chromosomal abnormalities, other significant congenital anomalies, visual or hearing impairments, having undergone cardiopulmonary bypass, born significantly pre-term (>34 weeks), Apgar score at 5 minutes of less than 5, evidence of significant birth asphyxia, and at very low birth weight (below 2nd centile) were excluded. The CHD group was heterogeneous with regard to diagnosis, but in this respect this study does not differ from similar studies already published (e.g. Limperopoulos et al., 1999; Robertson et al., 2004). Table 2 provides information regarding the age, birthweight, gender and socio-economic status of infants recruited to the study. There were no significant differences between groups on any of these variables (all $p>.1$).

Table 1: Diagnostic classifications of infants recruited to the acyanotic CHD group

Infant	Gender	Gestational Age (weeks)	APGAR score at 1/5 mins	Admitted to SCBU	Previous SpO_2 (age in days)	Diagnosis
1	F	39	-/-	No	99 (91)	Coarctation of the aorta
2	F	41	9/9	7 days	94 (193)	Ebstein's anomaly
3	F	35	-/-	9 days	-	Ventricular septal defect
4	F	40	9/9	No	99 (10)	Supra-ventricular tachycardia
5	F	40	-/-	No	96 (9)	Coarctation of the aorta
6	M	34	9/9	-	100 (1)	Ventricular septal defect
7	F	41	-/-	No	98 (28)	Supra-ventricular tachycardia
8	F	38	5/8	1 day	98 (1)	Coarctation of the aorta, VSD and bicuspid aortic valve
9	F	38	9/9	No	-	Patent foramen ovale

Note. '-' denotes information absent from the infant's medical file.

Table 2: Median and range of age and birthweight, and gender / paternal occupation composition of the study groups.

	Controls (n=15)	CHD (n=9)
Gestational age (weeks)	40 (35.0-41.3)	39.0 (34.0-41.4)
Corrected age at testing (weeks)	30 (25.3-39.0)	27.85 (24.7-38.0)
Birthweight (kg)	3.43 (2.36-3.97)	2.85 (2.32-3.77)
Gender (% males)[a]	46.7	11.1
Paternal occupation score	2 (1.2-7)	4 (1.2-6)

Note. All Mann Whitney test (except [a] Fisher's exact test). Paternal occupation is reported as most mothers were full-time carers, and had been so for a number of years. The National Statistics Socio-Economic Classification (Office for National Statistics, 2005) scale was used to determine occupation score. This scale ranges from 1.1 to 8, with lower numbers representing higher managerial and higher professional occupations, and higher values representing routine occupations and the long-term unemployed. A median score of 2 indicates that most fathers of infants in the control group were employed in lower professional and higher technical operations; a median score of 4 indicates that most fathers of infants with CHD were employed in small organisations or were own-account workers.

Measures

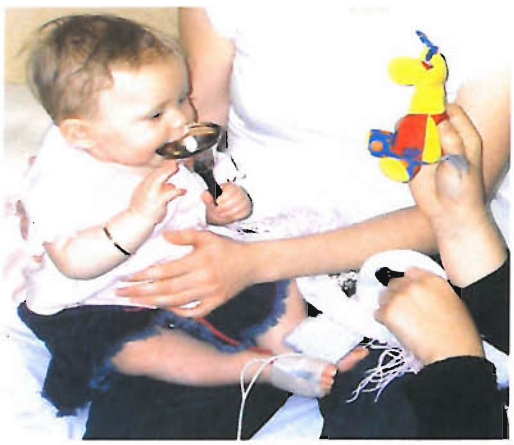
(i) Pathophysiology

These measures were performed by an experienced operator (transcranial doppler: Dr Alexandra Hogan, Principal Supervisor) or by a Paediatric Research Nurse (length, weight, oxygen saturation, heart rate). Both were blinded to CHD status, and to neurodevelopmental test scores. All measures were acquired while the infant was awake and/or while they were being fed.

Anthropometric Measures: Length, weight and head circumference was recorded and converted to centiles using the revised British Growth reference (Child Growth Foundation, 1996).

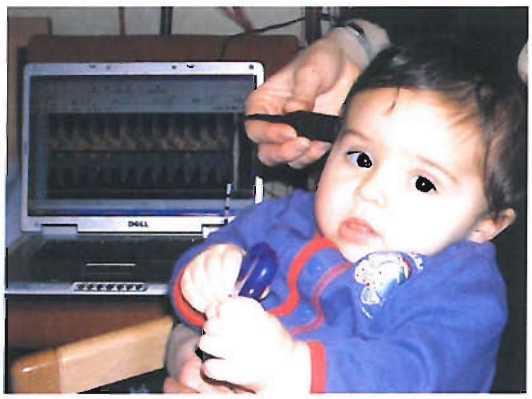
Oxygen Saturation and Heart Rate: Measured by pulse oximetry using a Masimo Radical^{TM}. A sensor was taped to the infant's foot (see Picture 1). The percentage SpO_2 (normal values are 95-100%) and pulse (normal range for 6-9 month infants is between 100 and 160 beats per minute; Medline Plus, 2006) were recorded every 10 seconds over a three-minute period and the mean value is reported (Hogan et al., 2006).

Picture 1: Collection of oxygen saturation and heart rate data



Transcranial Doppler Sonography: The middle cerebral artery (MCA) was tracked through shallow (~38mm), mid (~44mm) and deep (~50mm – bifurcation of the middle and anterior cerebral arteries) depths on the left and right side of the infants head, through the temporal ultrasound 'acoustic window' above the zygomatic arch and anterior to the ear (see Picture 2), using a (2MHz pulsed doppler) Doppler Box^{TM} (DWL, UK). Each reading produced a mean measure of cerebral blood flow velocity (CBFV), and the maximum MCA value (cm/sec) across depths and sides is reported (Bode & Wais, 1988). Increased CBFV can indicate narrowing of the blood vessel (cerebrovascular disease), or increased cerebral blood flow, in either case this may indicate a brain at risk of abnormal oxygen delivery (hypoxia) (see Hogan et al., 2006).

Picture 2: Transcranial Doppler Sonography of the middle cerebral artery



(ii) General neurocognitive and socio-emotional development

These measures were administered by the researcher Ms Amy Winterson, who was blinded to CHD status and to TCD scores.

Bayley Infant Neurodevelopmental Screener (BINS; Aylward, 1995): The BINS is a screening test designed to identify infants aged 3-24 months who are developmentally delayed or who have neurological impairment. The BINS

consists of 11-13 items, dependent upon the age of the infant, and takes approximately 10 minutes to administer. Items were derived from the Bayley Scale of Infant Development, and include ratings of muscle tone, quality of movements, early language development (e.g. babbling), and intellectual development (e.g. object permanence). At each age the BINS gives a raw score, ranging from 1-13 depending on the age of the infant, and a category score classifying infants into one of three groups: low, moderate, or high risk for neurodevelopmental delay. High and moderate risk groups may be combined for analysis and compared to infants scoring within the low risk range (Hogan et al., 2006). Comparisons of BINS risk scores with the Bayley Scales of Infant Development-II (BSID-II) have reported that the BINS demonstrates acceptable concurrent validity; agreement rates between the two measures for high risk status classifications were between 68 and 96% (Aylward, 2004).

Greenspan Social-Emotional Growth Chart: The Greenspan is a norm-referenced screening measure of the key social and emotional milestones to be mastered in infants and children, from birth to 42 months of age (Greenspan, 2004). The questionnaire consists of up to 35 items (dependent upon age) and can be completed by parents or caregivers in approximately 10 minutes. The first group of items is designed to screen for difficulties in sensory processing, which may potentially contribute to the infant's failure to master emotional milestones. A total score is also obtained.

(iii) Behavioural Measure of Novelty Processing – Novel Object Exploration

Based on Ruff's (1986a,b) investigation of infants' attention to novel objects, infants were video-recorded interacting with and exploring up to 7 novel objects. The objects were modified household objects (see Picture 3); it was important to use objects that none of the infants would have been previously exposed to. The objects were chosen to be similar in size, but to differ in colour and shape.

Picture 3: Novel objects used for behavioural exploration measure

Infants were seated on the floor, with their mother sat behind them to support their positioning where necessary. The mother was told that she was allowed to rest her hands on her infant's waist to provide support and reassurance, but that she must not try to verbally or physically engage her infant. Objects were presented to the infant in pseudo-random order. A trial started as the experimenter put the object down in front of the infant, and lasted for 60 seconds. Objects that rolled or were pushed out of reach by the infant were retrieved by the researcher and placed in their starting position. Data were analysed off-line.

The number of trials successfully completed was recorded for each infant. Trials were not started until the infant was sitting quietly and attentively. Those trials in which the infant briefly looked at or touched the object (i.e. showed only passing

interest ~ <5 seconds) but then attempted to crawl away, or started to fuss or cry, and/or wanted to be picked-up by their mother were recorded as fail (a score of 0). In this case attempts were made to administer further trials once the infant had settled. Latency to examine the objects (see Ruff 1986a) was not recorded as in the majority of cases the infants reached for the object as soon as it was in sight and there was no discernable delay. During each trial, the duration of examining or exploratory behaviours (defined as any of the following: looking at the object with an intent expression on the face, manipulating the object, mouthing the object, or banging it against another surface) was recorded. Pictures 4a and 4b give examples of infants engaged in examining or exploratory behaviours. Any periods where the infant disengaged from the toy were not included (for example, dropping the toy and looking elsewhere). Pictures 4c and 4d give examples of infants' disengagement with the toys. For the novelty exploration duration measure it was decided a priori to include only those infants who had completed a minimum of two full trials in the statistical analysis. The mean duration of novel object exploration was calculated across trials. As this task demonstrated a high level of inter-rater reliability in the original study by Ruff (1986a), and in the present study the rater was blinded to CHD status, it was not considered necessary to perform an inter-rater reliability check.

Pictures 4a and 4b:
Infants engaged in
exploratory behaviours

(a) (b)

Pictures 4c and 4d: Infants disengaged from the novel objects

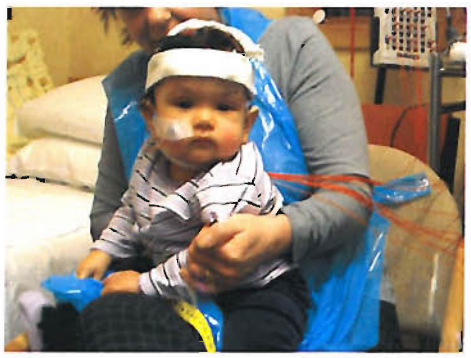
(c) (d)

(iv) Event-Related Potential (ERP) Measure of Novelty Processing: Auditory Novelty Oddball Paradigm

The ERP paradigm was administered by Dr Alexandra Hogan (Principal Supervisor), and the offline scoring and data analysis was performed by Ms. Amy Winterson.

Auditory Novelty Oddball Paradigm: A series of tones and novel sounds was presented to all subjects: (i) frequent standard tone (1kHz, 80% probability); (ii) infrequent high tone (1.5kHz, 10% probability); (iii) novel environmental sounds (e.g. dog bark, car horn; 10% probability). Stimulus-onset-asynchrony (SOA) was 900ms and each tone/novel sound was of 200ms duration. In total, the task took approximately ten minutes to complete, during which time the infant was seated on their mother's lap. All infants were awake throughout the duration of this task and watched the experimenter (Ms Winterson) blow bubbles in order to keep them calm. A short break was given if the infant started to fuss or cry.

EEG Recording: Electrodes were individually positioned at midline sites of the 10-20 system (Jasper, 1958): midline frontal (FZ); central (CZ); parietal (PZ), and were held in place by an elastic bandage wrapped around the head (see Picture 5). Two electrodes were placed directly behind the ears (linked mastoids) and served as reference, and the ground electrode was placed on the forehead above the left eye (FP1). Eye-blinks were recorded from bipolar channels above and below the right eye (blinks), and at the outer canthi of each eye (lateral eye movements). This enabled EEG activity contaminated by eye movement to be identified and removed off-line. Continuous EEG data were recorded at a sampling rate of 500Hz (band-pass 0.05 to 70Hz). For all infants impedance was maintained at less than 5kΩ indicating that in each case the recording was of good quality.



Picture 5: Infant prepared for ERP recording

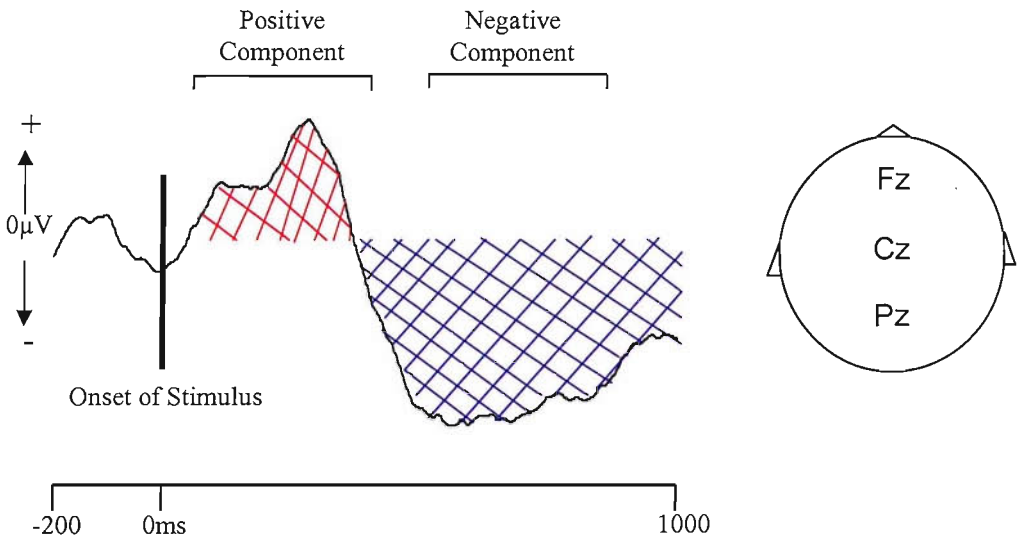
ERP Processing: EEG data were analysed off-line. First, those parts of the EEG recording that were contaminated by a blink or a large lateral eye movement (apparent in the ocular channels) were highlighted, such that any stimuli occurring during this time were not included in the analyses. Secondly, the EEG was low-pass filtered at 20Hz, and divided into epochs (-200 to 1000ms), whereby 0ms

represented the time of occurrence of the various types of stimuli (low, high tones, or novel noises)[2]. Epochs were aligned across scalp sites (baseline corrected) and automatically excluded if they exceeded 250μV in either direction. All automatically accepted epochs were also visually examined and excluded if there was persisting eye-blink or movement artefact. The remaining epochs were then averaged together according to stimulus type (Low Tones, High Tones, Novel Noises). In contrast to adults and older children, infants have long-latency waveforms that do not necessarily appear as a 'sharp' component. It was therefore considered of greater interest to measure the area score rather than the peak amplitude and latency.

Figure 2 illustrates how for each infant an early positive and later negative area score was determined automatically for each infant at each site (i.e. Fz, Cz. Pz); this is intended as a schematic rather than an actual representation of data. As it was of interest to investigate group effects in two ways, namely across stimuli and across site, it was also decided a priori to include in the ERP analysis only those infants for whom a sufficient number of trials (>10 for each stimulus type) were obtained for each stimulus at each location.

[2] During the EEG recording stimulus codes appear at the bottom of the screen, e.g. 1 for a low tone, etc. This information is saved with the EEG trace to allow the extraction of ERP components off-line.

Figure 2. Schematic diagram to illustrate how the positive (red hatch) and negative (blue hatch) component area scores were determined on the basis of the group averages for novel stimuli. Note that in individual infants both scores incorporate positive and negative values, particularly if the component is attenuated (i.e. close to 0μV for the duration of the area score time-window), and/or if the component changes (i.e. from positive to negative) earlier or later than indicated in the group



Procedure

The research proposal was approved by the Local Research Ethics Committee, and approval was also obtained from the local NHS Trust Research and Development and Data Protection Departments (see Appendices 2,3, & 4). Parents of infants known to the Paediatric Cardiology Service who met the inclusion criteria were identified and approached by a Specialist Registrar in Paediatrics (Dr Hilary Robinson) by telephone or letter. Consent was sought by the Specialist Registrar for the researcher to make contact with interested parents to provide further information about the study. Information sheets (Appendix 5) were provided and a consent form (Appendix 6) was completed on attendance at the research appointment. At that time consent was also obtained to video-tape /

photograph the infant and to use images in publications and for teaching purposes. Parents were also offered a copy of any photographs taken.

The infants attended one appointment lasting approximately one and a half hours at the Wellcome Trust Clinical Research Facility at Southampton General Hospital. The order of the procedures during the appointment was varied according to the infants needs; for example, during periods when infants were settled, the TCD reading was attempted, the weighing and measuring of infants took place when a nappy change was required, and ERP equipment was set up while infants were being fed. File data was collected from hospital or parent-held records (where possible) concerning infants' birthweight, Apgar scores at 1 and 5 minutes, whether the infant spent any time in Special Care Baby Unit, and any previous oxyhaemoglobin saturation readings. All infants were accompanied by their mothers. Data were collected from mothers regarding paternal occupation, in order to classify the infant's socioeconomic position according to the National Statistics Socio-Economic Classification (Office for National Statistics, 2005).

Data analysis

Although data for all variables of interest resembled a normal distribution (as assessed by one-sample Kolmogorov-Smirnov tests), due to the small sample size, categorical nature of some measures (e.g. number of trials completed for novelty exploration task), and the fact that the control group had a larger number of infants compared to the CHD group, it was considered circumspect to perform non-parametric comparisons for the majority of measures.

For the ERP measures, data were obtained from a reduced number of control infants making the groups more equal (n= 12 vs. 9). In addition it was of interest to explore significant interactions between site, stimulus, and group. For this reason, a parametric mixed-factor ANOVA model was applied, once for the positive area scores and once for the negative area scores. For each model the within-subjects factors were stimulus (x3: Low Tones, High Tones, Novel Noises) and site (x3: Fz, Cz, Pz), and the between-subjects factor was group (Control vs. CHD). Significant main effects and interactions were explored using t-tests. For all analyses, the threshold for statistical significance was .05, with trends <.09 reported; the Greenhouse-Geisser (GG) statistic is reported for the ANOVA models when indicated.

Results

Although the CHD group weighed less, were shorter in stature, and had smaller head circumferences compared to controls (see Table 3), the groups were comparable with respect to these variables (all $p>.1$). The CHD group had a significantly slower heart rate, but there was no group difference for measures of oxygen saturation or CBFV. The subtle reduction in heart rate may reflect mild cardiac dysfunction.

Table 3. Median (range) centile scores for weight, length, and head circumference, heart rate, SpO_2 and CBFV in the Control and CHD groups.

		Controls (n=15)	CHD (n=9)
Anthropometric Measures	Weight	48.75 (0.66-91.84)	12.51 (0.64-89.78)
	Length	73.77 (14.26-97.93)	64.46 (0.33-98.79)
	Head circumference	57.35 (4.51-99.33)	29.14 (0.21-94.06)
Pathophysiological Measures	Heart Rate *	140.7 (112.61-155.05)	130.47 (119.7-141.00)
	SpO_2 (%)	99.0 (97.17-100.00)	99.14 (97.20-99.58)
	CBFV (cm/sec)	70 (55-117)	72.0 (61-92)

Note. For the measure of SpO_2 and heart rate there were 8 infants in the CHD group; one infant did not tolerate the sensor on her foot. CBFV – cerebral blood flow velocity in the middle cerebral artery. * Mann-Whitney U = 24, $p = .02$

The groups also performed similarly on measures of neurocognitive and socio-emotional development (see Table 4). Moreover, the number of infants scoring in

the moderate-high risk range on the BINS was not significantly elevated in the CHD group (Fisher's Exact: p = .130). In summary, the infants with acyanotic CHD appeared to be growing normally, and did not demonstrate any evidence of physiological abnormality (i.e. the CHD infants were not hypoxic at the time of assessment).

Table 4. Standardised developmental assessments median scores (ranges) for the Control and CHD groups.

	Controls (n=15)	CHD (n=9)
BINS (raw score)	10 (8-13)	10 (5-12)
Greenspan Total Growth Score	63 (49-73)	62 (55-74)
Greenspan Sensory Processing Score	34.5 (29-40)	35 (28-40)

Note. For the Greenspan measure, there were 14 infants in the control group and 8 in the CHD group – the parents of one control and one CHD infant did not complete the questionnaire. For all measures, higher scores equate to better performance. BINS – Bayley Infant Neurodevelopmental Screener.

Novel Object Exploration

A significantly larger number of trials were completed by control infants (n=15: median 6, range 0-7) compared to infants with CHD (n=9: 0, 0-5) (Mann-Whitney U=34.5, p=.042). Zero scores were obtained by infants in both groups. In younger infants poorer motor coordination appeared to sometimes prevent them from being able to manually engage with the toys satisfactorily (although it is noted that engagement was scored by looking as well as reaching behaviour).

Older infants, who were mobile, sometimes crawled away from the toy and the range of the video equipment. In other cases, it was not possible to prevent infants interacting socially with their caregivers. However, for the purposes of this study such activity in older infants was graded as disengaged from the task at hand. A total of 11 control infants and 4 infants with CHD completed at least two uninterrupted trials. The remaining infants' video footage had to be excluded, due to crying, fussiness, or because the infant was unable to sufficiently engage with the task in order to complete the minimum number of trials. A Mann Whitney test revealed a non-significant trend towards control infants spending longer examining and exploring novel objects in each trial ($U=11.5$, $p=.069$). (Controls: median 58.5 seconds (range = 54.7-60); CHD: median 56.4 seconds (range 47.5-59.7)).

Novelty Processing Assessed by Event-Related Potentials

Table 5 shows the mean number of acceptable trials for each stimulus type across groups; there were no significant differences between groups in the number of acceptable trials included in ERP analyses (all $p>.1$).

Table 5: Mean (standard deviation) number of acceptable trials for each stimulus type included in the grand averages for each group.

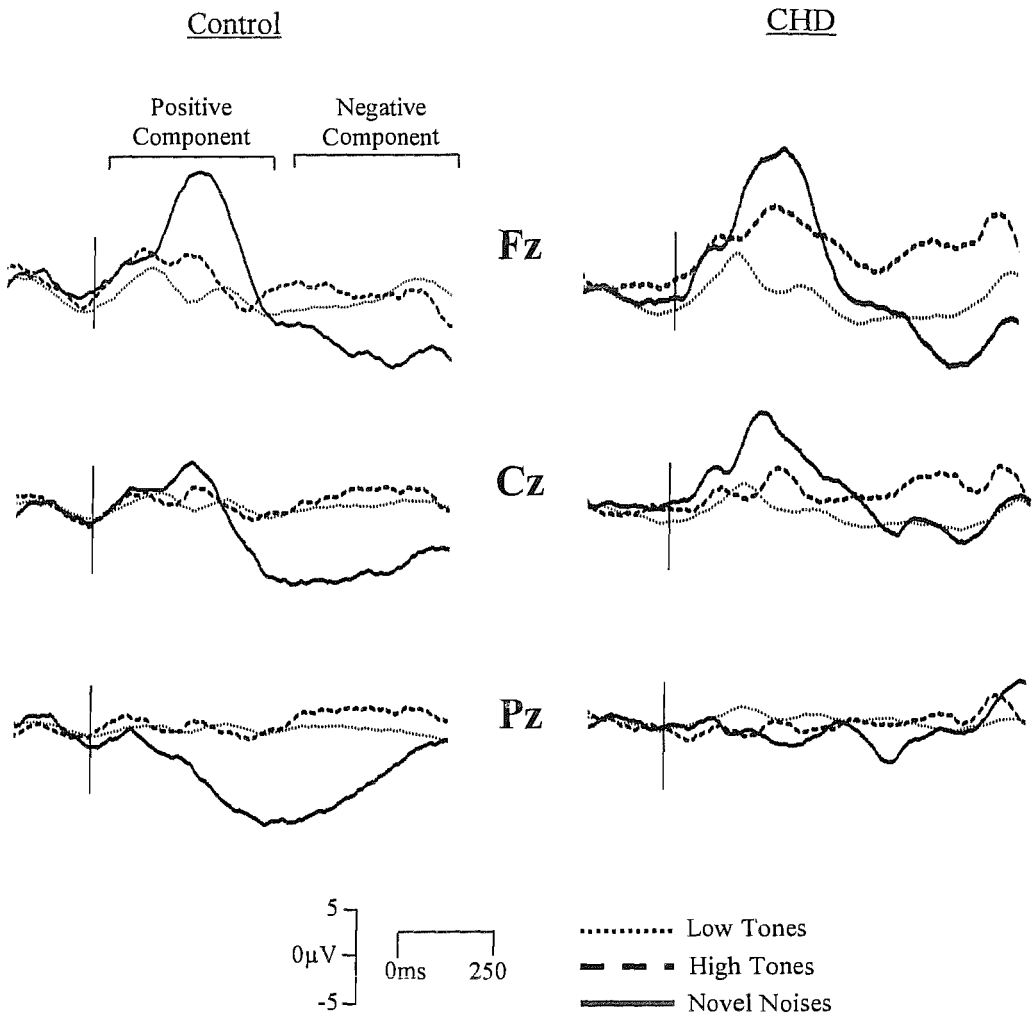
	Controls (n=12)	CHD (n=9)
Low Tones	189.92 (92.52)	195.13 (91.95)
High Tones	27.67 (11.79)	28.88 (14.27)
Novel Noises	28.67 (11.48)	32.50 (12.14)

Figure 3 presents the waveforms associated with each of the stimuli, and at each midline site, in both groups. There was a trend towards a larger early positivity in infants with CHD compared to control infants ($F(1,19) = 3.629$, $p=.072$). There was also a main effect of site indicating that the positive component was more prominent over the frontal lobes ($F(2,38) = 22.711$, $p < .001$), and an interaction between site and stimulus ($F_{GG}(2.0, 38.3) = 14.292$, $p < .001$). The area scores for all stimuli were greatest over the frontal lobes (Fz), lowest over the parietal lobes (Pz), and interim over the midline (Cz). However, this anterior-posterior decline in area scores was prominent for novel stimuli ($F_{GG}(1.5, 32.1) = 23.915$, $p<.001$), but not for low or high tone stimuli (both $p > .1$).

Table 6. Mean (standard deviation) area scores for the positive and negative components for each stimulus at each site in Control and CHD groups.

			Controls (n=12)	CHD (n=9)
Positive component	Low tones	Fz	-47.30 (1286.09)	799.39 (1308.09)
		Cz	224.92 (1049.17)	630.65 (1743.29)
		Pz	-210.93 (1250.14)	697.95 (1482.69)
	High tones	Fz	412.49 (3210.21)	2968.73 (2177.74)
		Cz	337.08 (4049.38)	1253.53 (1995.89)
		Pz	263.93 (3162.60)	-522.55 (3875.42)
	Novel sounds	Fz	2639.98 (3209.61)	4770.60 (4665.70)
		Cz	508.90 (4862.92)	3226.16 (3223.11)
		Pz	-3618.59 (4153.23)	-803.32 (4474.94)
Negative component	Low tones	Fz	-691.33 (1573.93)	-518.28 (2675.04)
		Cz	25.10 (1336.58)	-394.15 (3367.87)
		Pz	-463.18 (1207.28)	162.12 (2311.28)
	High tones	Fz	-892.68 (4753.14)	2688.54 (4310.53)
		Cz	825.25 (3903.65)	2085.89 (3468.36)
		Pz	1537.53 (4036.65)	503.08 (3009.52)
	Novel sounds	Fz	-4249.88 (5415.04)	-2441.14 (4227.05)
		Cz	-5402.43 (5639.60)	-1088.79 (3847.13)
		Pz	-5416.13 (4986.15)	-597.03 (3660.39)

Figure 3. Average waveforms for low tone, high tone and novel noise stimuli for control (n=12) and CHD (n=9) groups. The waveforms are similar over the frontal cortex (Fz), but the novel negative waveform becomes attenuated in the CHD group with progression to posterior sites (Pz).



For the later negative waveform, there was a main effect of stimulus (F_{GG} (1.5, 29.3) = 10.439, p =.001), reflecting greater negativity associated with novel stimuli compared to low and high tone stimuli, and a main effect of group (F (1,19) = 5.04, p = .0037) indicating generally greater negativity in controls compared to infants with CHD. A stimulus x site x group interaction was also

found (F (4,76) = 2.665, p = .039). Post-hoc testing revealed a significant interaction between stimulus and group over the parietal cortex (Pz) only (F_{GG} (1.4, 27.1) =3.386, p=0.044), and a trend towards a main effect of group (p=0.066). T-tests were performed to investigate group differences for the three types of stimuli: an independent samples t test confirmed a significant difference at the parietal cortex between infants with CHD and control infants for novel stimuli only (t (19) = -2.442, p=0.025). Interestingly, those infants with the lowest heart rates, indicative of mild cardiac dysfunction, had the smallest area scores at this location (n=21, across groups: Rho -.523, one-tailed, p = .007).

In summary, the control and CHD groups were comparable with respect to length, weight, head circumference, oxyhaemoglobin saturation and cerebral blood flow velocity measures. Infants with CHD had a lower heart rate than control infants. There were no significant differences between groups on standardised developmental assessments, or in measures of the duration of the infants' exploration of novel objects (although control infants were able to complete significantly more trials than infants with CHD). However, a significant difference was demonstrated between groups on ERP measures of novelty processing; infants with CHD had an attenuated later negativity associated with novel stimuli over the parietal cortex compared to control infants.

Discussion

Based on published evidence that infants with acyanotic CHD are susceptible to subtle neurological abnormality (e.g. Limperopoulos et al., 1999; Mahle et al., 2002), and developmental delay (e.g. Limperopoulos et al., 1999), this study aimed to investigate behavioural and ERP measures of novelty processing in nine infants with acyanotic CHD. In support of the hypothesis, significant differences between groups were found for measures of novelty processing. Infants with acyanotic CHD had an attenuated later negativity over the parietal cortex compared to control infants in response to novel noises.

The significant differences between groups for measures of novelty processing were found in the absence of group differences on demographic, anthropometric, or concurrent physiologic data, and in the absence of significant differences on a standardised infant developmental screening test, suggesting that all other variables indicated that these infants are developing normally. This is in contrast to earlier evidence (e.g. Limperopoulos et al., 1999) suggesting that infants with acyanotic CHD may be vulnerable to such deficit. Further inspection of the range of raw scores obtained by infants on the BINS indicated that the CHD group included some infants who were scoring lower than those in the control group. The lack of a statistically significant difference between groups may therefore have occurred due to a lack of statistical power.

Despite the small number of CHD infants in whom we could obtain a valid measure of novelty exploration (a potentially interesting fact in itself), the results

obtained from the infants' interactions with novel objects showed a trend towards healthy infants spending longer engaged in examining and exploratory behaviours than infants with CHD. A difference between groups was expected as observations by Ruff (1986a) reported that infants born prematurely (who, like children with acyanotic CHD, are at greater risk of later cognitive problems) spent less time examining novel objects than did full-term infants; numerically, if not statistically, the results of the present study are in the same direction. The lack of a consistent significant difference between groups in this experimental measure may be explained by the difficulties encountered in infants completing more than two uninterrupted trials. In this study, infants with acyanotic CHD managed to complete significantly fewer trials than healthy control infants. This result could perhaps be explained by deficits in sustained attention, a finding that has been reported in older children with acyanotic CHD (e.g. Bellinger et al., 2003), although further longitudinal research is required with a larger sample in order to firmly establish this hypothesis.

This is the first study to utilise ERP techniques with infants with acyanotic CHD, and importantly, the predicted group differences were observed in response to novel stimuli, further indicating a possible abnormality in the way in which infants with CHD process novelty. It has been suggested that the early positivity recorded in auditory novelty oddball paradigms relates to the infant responding to the frequency of the stimulus, and the later negativity (the negative slow wave) reflects "the detection of novel events against a background of familiar events", such as enables the updating of memory (Nelson & Monk, 2001; p.129). Research conducted with infants born to diabetic mothers (who, like children with

acyanotic CHD, have been shown to have lower scores on cognitive testing in later childhood) has found a similar attenuation of the negative slow wave, indicating to the authors an abnormality in the pathways involved in recognition memory (Siddappa, et al., 2004). The explanation of this ERP finding as an abnormality of memory processing in infants with acyanotic CHD would appear to fit with theories such as Berg and Sternberg's (1985), that novelty processing is an aspect of cognitive functioning that underpins intellectual development. This theory may potentially help to explain why children with acyanotic CHD appear to be at risk of obtaining lower scores on tests of intellectual functioning later in life. Long-term follow up including concurrent ERP and intellectual assessments in later childhood are required to determine whether the abnormalities seen in this infant group are transient or if they will persist, and whether they have clinically significant implications for later cognitive functioning.

There are a number of possible explanations for these findings. Perhaps the most critical factor in explaining cognitive deficit in children with CHD is the supply of oxygenated blood to the brain. At the time of testing, there were no significant differences between groups for measures of cerebral blood flow velocity or oxyhaemoglobin saturation, suggesting that abnormality in *current* oxygen delivery to the brain was not responsible for the significant findings. However, longitudinal studies are clearly necessary to determine whether fluctuations in oxygenation of the brain, particularly during the early months of life, may be sufficient to result in cognitive deficit later in infancy and childhood. Attempts were made to obtain earlier oxyhaemoglobin saturation data for all infants from the neonatal period, but these data were not available for the majority of infants.

Evidence exists to suggest that even mild hypoxia may have an effect on behaviour in other conditions, such as sleep-related breathing disorders (e.g. Kennedy et al., 2004); however, the present study did not find evidence for such an association.

Another possible explanation for these results relates to the effect of cardiac function on neuropsychological functioning. A study of infants aged 2 to 13 months with CHD observed an independent relationship between the presence of congestive heart failure and developmental delay (Aisenberg, Rosenthal, Nadas & Wolff, 1982), and research with older children with CHD (aged between 4 and 8 years) found that children with acyanotic defects who had not experienced heart failure obtained higher IQ scores than children who had experienced at least one episode (Silbert, Wolff, Mayer, Rosenthal & Nadas, 1969). More recently, when commenting on the increased likelihood of an abnormal neurological examination among infants with acyanotic as compared to cyanotic lesions, Limperopoulos and colleagues concluded that reduced cardiac output or restricted blood flow in the aorta resulting in decreased cerebral perfusion may have been responsible for the increased risk of neurological impairment (Limperopoulos et al., 1999). In this sample, mild pathophysiology was indicated by a slightly decreased heart rate, which was in turn significantly associated with lower magnitude of the ERP response to novel stimuli. It may be tentatively concluded that as yet unconfirmed mechanisms mediate the relationship between cardiac function and brain response to external stimuli.

In reviewing the significant findings reported here, it is important to give consideration to the limitations of this investigation. In common with many previous studies conducted with this population (e.g. Limperopoulos et al., 1999; Robertson et al., 2004), the acyanotic CHD group was heterogeneous in terms of diagnosis, and also potentially in terms of their early experiences and degree of pathophysiology. As heart rate was slower in the infants with cardiac disease, future studies might incorporate more detailed measures of cardiac function e.g. blood pressure or ventricular function documented at echocardiography.

This research represents a first step in using ERP techniques with infants with CHD. However, it may be important for future studies to attempt to restrict the inclusion of participants to those with a specific diagnosis, or instead to include other measures of the degree of sickness of the infant, such as the length of time spent in hospital. In common with many other infant studies, difficulties were experienced in recording a full data set from all participants. The option of extending the age range of infants included in this study in order to significantly increase the sample size was rejected. This decision was taken to avoid the potential confound of developmental changes in ERP waveforms among infants; the restricted age range of participants in this study is considered to be a methodological strength.

The cross-sectional nature of this research does not enable any predictions to be made with regard to long-term cognitive deficit in these infants, nor is it possible to state conclusively what the functional implications of such a deficit in novelty processing might be. Despite this import caveat, there is a theoretical basis for

predicting that differences in novelty processing may underpin later cognitive deficit, and the present study now lends some empirical support. Thus, the hypothesised link (cf. Berg & Sternberg, 1985) between novelty processing and later cognitive functioning has validity, and would appear to be supported in infants with acyanotic CHD by the conjunction of the research findings reported here and the literature regarding the difficulties experienced by older children with acyanotic defects. It is anticipated that the significant group differences observed in this study of infant novelty processing will inspire further research efforts to establish the clinical significance of these findings. This may ultimately enable the prompt identification of infants at risk and perhaps provide opportunities to implement interventions to address impairments before irreversible cognitive deficits occur.

References

Aisenberg, R.B., Rosenthal, A., Nadas, A.S., & Wolff, P.H. (1982). Developmental delay in infants with congenital heart disease: correlation with hypoxemia and congestive heart failure. *Pediatric Cardiology, 3,* 133-137

Aylward, G.P. (1995). *Bayley Infant Neurodevelopmental Screener. Second Edition.* San Antonio, TX: The Psychological Corporation.

Aylward, G.P. (2004). Prediction of function from infancy to early childhood: implications for pediatric psychology. *Journal of Pediatric Psychology, 29 (7),* 555-564

Bellinger, D.C., Wypij, D., duPlessis, A.J., Rappaport, L.A., Jonas, R.A., Wernovsky, G., & Newburger, J.W. (2003). Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. *The Journal of Thoracic and Cardiovascular Surgery, 126 (5),* 1385-1396

Berg, C.A. & Sternberg, R.J. (1985). Response to novelty: continuity versus discontinuity in the developmental course of intelligence. *Advances in Child Development and Behavior, 19,* 1-47

Bode, H., & Wais. U., (1988). Age dependence of flow velocities in basal cerebral arteries. *Archives of Disease in Childhood, 63(6),* 606-611

Child Growth Foundation (1996). *British 1990 growth reference – revised.* London: Child Growth Foundation.

Courchesne, E., Hillyard, S.A., Galambos, R., (1975). Stimulus novelty, task relevance and evoked-potential in man. *Electroencephalography and Clinical Neurophysiology, 39(2),* 131-143

Delamatar, A, (2003). Cardiovascular Disease. In M.C. Roberts (Ed). *Handbook of Pediatric Psychology* (3rd edition). London: The Guilford Press.

DeRegnier, R.O. (2005). Neurophysiologic evaluation of early cognitive development in high-risk infants and toddlers. *Mental Retardation and Developmental Disabilities Research Reviews, 11,* 317-324

Fellman, V., Kushnerenko, E., Mikkola, K., Ceponiene, R., Leipälä, J., & Näätänen, R. (2004). Atypical auditory event-related potentials in preterm infants during the first year of life: a possible sign of cognitive dysfunction? *Pediatric Research, 56 (2),* 291-297

Griffin, K.J., Elkin, T.D., & Smith, C.J. (2003). Academic outcomes in children with congenital heart disease. *Clinical Paediatrics, 42 (5),* 401-409

Greenspan, S.I. (2004). *Greenspan Social-Emotional Growth Chart.* San Antonio, TX: Harcourt Assessment, Inc..

Hoffman, J.I.E. (1990). Congenital Heart Disease: incidence and inheritance. *Pediatric Clinics of North America, 37,* 25-43

Hogan, A.M., Kirkham, F.J., Prengler, M., Telfer, P., Lane, R., Vargha-Khadem, F., & de Haan, M. (2006). An exploratory study of physiological correlates of neurodevelopmental delay in infants with Sickle Cell Anaemia. *British Journal of Haematology, 132,* 99-107

Jasper, H.H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology, 10,* 371-375

Kennedy, J.D., Blunden, S., Hirte, C., Parsons, D.W., Martin, A.J., Crowe, E., Williams, D., Pamula, Y., & Lushington, K. (2004). Reduced neurocognition in children who snore. *Pediatric Pulmonology, 37(4)*, 330-337

Kushnerenko, E., Ceponiene, R., Balan, P., Fellman, V., Huotilainen, M., & Näätänen, R. (2002a). Maturation of the auditory event-related potentials during the first year of life. *Neuroreport, 13,* 47-51

Kushnerenko, E., Ceponiene, R., Balan, P., Fellman, V., & Näätänen, R. (2002b). Maturation of the auditory change detection response in infants: a longitudinal ERP study. *Neuroreport, 13,* 1843-1848

Limperopoulos, C., Majnemer, A., Shevell, M.I., Rohlicek, C., Rosenblatt, B., Tchervenkov, C., & Darwish, H.Z. (2002). Predictors of developmental

disabilities after open heart surgery in young children with congenital heart defects. *Journal of Pediatrics, 141,* 51-58

Limperopoulos, C., Majnemer, A., Shevell, M.I., Rosenblatt, B., Rohlicek, C., & Tchervenkov, C. (1999). Neurologic status of newborns with congenital heart defects before open heart surgery. *Pediatrics, 103 (2),* 402-408

Linde, L.M., Rasof, B., & Dunn, O.J. (1967). Mental development in congenital heart disease. *Journal of Pediatrics, 71 (2),* 198-203

McConnell, J.R., Fleming, W.H., Chu, W., Hahn, F.J., Sarafian, L.B., Hofschire, P.J., & Kugler, J.D. (1990). Magnetic resonance imaging of the brain in infants and children before and after cardiac surgery: a prospective study. *American Journal of Diseases of Children, 144,* 374-378

Mahle, W.T., Tavani, F., Zimmerman, R.A., Nicolson, S.C., Galli, K.K., Gaynor, J.W., Clancy, R.R., Montenegro, L.M., Spray, T.L., Chiavacci, R.M., Wernovsky, G., & Kurth, D. (2002). An MRI study of neurological injury before and after congenital heart surgery. *Circulation, 106 (suppl. I),* 109-114

Majnemer, A., Limperopoulos, C., Shevell, M., Rosenblatt, B., Rohlicek, C., & Tchervenkov, C. (2006). Long-term neuromotor outcome at school entry of infants with congenital heart defects requiring open-heart surgery. *Journal of Pediatrics, 148,* 72-77

Medline Plus (2006). *Pulse.* Retrieved 01.03.2006 from http://www.nlm.nih.gov/medlineplus/ency/article/003399.htm

Nelson, C.A. & Monk, C.S. (2001). The use of event-related potentials in the study of cognitive development. In C.A. Nelson & M. Luciana (Eds.). *Developmental cognitive neuroscience (pp.125-136).* Cambridge, MA: MIT Press.

Neubauer, A. C. (1990). Coping with novelty and automatization of information processing: an empirical test of Sternberg's two-facet subtheory of intelligence. *Personality and Individual Differences, 11 (10),* 1045-1052

Office for National Statistics (2005). *The National Statistics Socio-economic Classification User Manual.* Basingstoke: Palgrave Macmillan.

Piaget, J. (1966). *The origins of intelligence in children.* Routledge and Kegan Paul.

Robertson, D.R., Justo, R.N., Burke, C.J., Pohiner, P.G., Graham, P.L., & Colditz, P.B. (2004). Perioperative predictors of developmental outcome following cardiac surgery in infancy. *Cardiology in the Young, 14 (4),* 389-395

Ruff, H.A. (1986a). Attention and organisation of behaviour in high risk infants. *Journal of Developmental and Behavioral Pediatrics, 7 (5),* 298-301

Ruff, H.A. (1986b). Components of attention during infants' manipulative exploration. *Child Development, 57,* 105-114

Siddappa, A., Georgieff, M.K., Wewerka, S., Worwa, C., Nelson, C.A., & DeRegnier, R. (2004). Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. *Pediatric Research, 55(6),* 1034-1041

Silbert, A., Wolff, P.H., Mayer, B., Rosenthal, A., & Nadas, A.S. (1969). Cyanotic heart disease and psychological development. *Pediatrics, 43,* 192-200

Te Pas, A.B., van Wezel-Meijler, G., Bökenkamp-Gramann, R., & Walther, F.J. (2005). Preoperative cranial ultrasound findings in infants with major congenital heart disease. *Acta Paediatrica, 94,* 1597-1603

van Houten, J.P., Rothman, A., & Bejar, R. (1996). High incidence of cranial ultrasound abnormalities in full-term infants with congenital heart disease. *American Journal of Perinatology, 13(1),* 47-53

Wray, J., & Sensky, T. (1999). Controlled study of preschool development after surgery for congenital heart disease. *Archives of Disease in Childhood, 80,* 511-516

Yang, L.L., Liu, M.L., Townes, B.D. (1994). Neuropsychological and behavioural status of Chinese children with acyanotic congenital heart defects. *International Journal of Neuroscience, 74 (1-4),* 109-115

Appendices

Appendix 1: Common types of CHD

	Name	Clinical description and treatment
Acyanotic subtypes	Pulmonary stenosis or aortic stenosis	The pulmonary valve (which allows blood to flow from the right ventricle to the lungs) is defective, causing the heart to pump harder than normal to overcome the obstruction. In severe cases some cyanosis can occur. Surgery serves to open the valve satisfactorily, and can be a relatively routine procedure (balloon valvuloplasty) or require open heart surgery.
	Aortic stenosis	The aortic valve (which allows blood to flow from the left ventricle and the aorta) is defective, causing the heart difficulty in pumping blood around the body. Surgery serves to open the valve satisfactorily, and can be a relatively routine procedure (balloon valvuloplasty) or require open heart surgery.
	Coarctation of the aorta	The aorta is constricted, which obstructs blood flow to the body, and causes high blood pressure or poor circulation to the limbs. In severe cases congestive heart failure may occur. Surgery can usually be delayed until later in childhood, unless the symptoms are particularly severe. The surgical procedure is called balloon angioplasty.
	Atrial septal defects (ASD)	An opening exists between the two atria that allows some blood that has already been to the lungs back into the right atrium, instead of flowing out of the aorta and to the body. Many children with ASD have few symptoms and the hole often closes spontaneously, although open heart surgery is required in some cases.
	Ventricular septal defects (VSD)	An opening exists between the two ventricles, causing blood from the lungs to leak back into the right ventricle instead of being pumped around the body. This means that the heart has to work harder, and may enlarge. Surgery is required when the hole is too large, causing high blood pressure in the lungs or failure to thrive.
	Atroventricular canal (also called atrioventricular septal defect)	A large hole exists where the four chambers of the heart join, and often there are malformations of the tricuspid and mitral valves, causing blood to leak back into the right side of the heart. The heart must pump more blood than normal, and may enlarge. Babies with this condition may become undernourished and have damaged blood vessels in the lungs due to high blood pressure. Surgery must usually be carried out in infancy; the hole is closed and the valve is

		reconstructed. A band may also be placed around the pulmonary artery to reduce the blood flow to the lungs.
Cyanotic subtypes	Tetralogy of Fallot (TOF)	The major defect in TOF is a VSD, and a narrowing near the pulmonary valve. In addition, the right ventricle is more muscular than usual, and the aorta lies directly over the VSD. These defects allow blood to pass from the right to the left ventricle without going through the lungs, causing severe cyanosis or even unconsciousness. Surgery begins with positioning a shunt between the aorta and the pulmonary artery to increase blood flow to the lungs. Later open heart surgery involves closing the VSD and removing obstructing muscle.
	Transposition of the Great Arteries (TGA)	The positions of the aorta and pulmonary artery are reversed, causing blood returning to the heart from the body to be pumped back out to the body without being reoxygenated in the lungs. Infants born with TGA only survive if they have another defect allowing oxygenated blood to reach the body, such as an ASD or VSD. Surgery is always necessary and involves balloon atrial septostomy to improve the body's oxygen supply. An arterial switch or venous switch is used to create a tunnel inside the atria.
	Tricuspid atresia	The infant is born without a tricuspid valve, meaning that no blood can flow from the right atrium to the right ventricle. Infants only survive if they have another defect such as a VSD or ASD. Often a surgical shunting procedure is used to increase blood flow to the lungs; others need a pulmonary artery banding to reduce the blood flow to the lungs.
	Pulmonary atresia	The infant is born without a pulmonary valve, meaning that blood does not flow into the lungs. Survival is based on the presence of a defect in the heart walls, allowing some oxygenated blood to be pumped around the body. Early treatment often involves medication to keep this defect open, and is followed by surgery to increase blood flow to the lungs. Open heart surgery is most successful when the pulmonary artery and right ventricle are of normal size. Otherwise, a compensatory surgical procedure (Fontan procedure) is used to connect the right atrium directly to the pulmonary artery.

Total anomalous pulmonary venous connection	The pulmonary veins are abnormally connected to the right atrium, causing oxygenated blood to be mixed with deoxygenated blood from the body. An ASD allows this mixture to pass through into the left side of the heart, from where it is pumped around the body. Due to the high degree of cyanosis, surgical repair must be carried in early infancy.
Hypoplastic left heart syndrome	The left side of the heart is dramatically underdeveloped. The condition becomes evident when the ductus arteriosus (a normal hole in the heart in the foetus) closes a few hours after birth, because this closure prevents blood from reaching the aorta. The defect isn't correctable; some infants undergo a series of operations and others require a heart transplant.

Appendix 2: LREC approval

STA

07 November 2005

NORTH AND & MID HAMPSHIRE LOCAL
RESEARCH ETHICS COMMITTEE
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
SO16 4RJ

Tel: 023 8036 2863
Fax: 023 8036 4110

Email: GM.E.hio-au.NMHREC@nhs.net

Miss Amy C Winterson
Trainee Clinical Psychologist
Taunton & Somerset NHS Trust
Musgrove Park Hospital
Taunton
Somerset
TA1 5DA

Dear Miss Winterson

Full title of study: **An exploratory study of novelty processing in infants with congenital heart defects**
REC reference number: **05/Q1703/55**

Thank you for your letter of 31 October 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form. Confirmation of approval for other sites listed in the application will be issued as soon as local assessors have confirmed they have no objection.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		31 October 2005
Investigator CV	1	12 September 2005
Protocol	2	31 October 2005
Covering Letter		12 September 2005
Letter from Sponsor		13 June 2005
Peer Review		01 March 2005
Participant Information Sheet - Parents	2	31 October 2005

Participant Information Sheet - Post-participation information for parents	2	31 October 2005
Participant Consent Form	2	31 October 2005
Response to Request for Further Information		31 October 2005
Researcher CV	1	13 September 2005
Memo of indemnity		20 June 2005
School of Psychology ethical approval		26 May 2005
Employment indemnity		15 July 2005
DPA compliance		22 August 2005
Trainee research governance	1	13 September 2005
Validated assessment		13 September 2005

Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q1703/55 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Mrs Jane Ogden-Swift
Chair

Email: GM.E.hio-au.SEHREC@nhs.net

Enclosures:

Standard approval conditions SL-AC2
Site approval form

Copy to:

Mr Peter Hooper
University of Southampton
Highfield
SOUTHAMPTON
Hampshire
SO17 1BJ

SF1 list of approved sites

An advisory committee to Hampshire and Isle of Wight Strategic Health Authority

Appendix 3: NHS Research and Development approval

Southampton University Hospital NHS Trust

Please reply to: Research and Development
Trust Management Offices
Mailpoint 18
Southampton General Hospital

Telephone: 02380 794752
Fax: 02380 798678
E-mail: wmr@soton.ac.uk

Ms Amy Winterson
Clinical Psychology Room 3003
Shackleton Building (44)
University of Southampton
Highfield
Southampton
SO17 1BJ

15 November 2005

Dear Ms Winterson

ID: RHM CAR0306 An exploratory study of novelty processing in infants with congenital heart defects

Thank you for submitting all the required documentation to complete registration. Your project is now fully approved and this letter provides the formal SUHT approval required for your project to commence.

Please find attached a summary of the conditions of approval which you are obliged to adhere to.

Your project is subject to R&D monitoring, and you will be contacted by our office to arrange this. We will require access to the project folder sent to you with initial registration, or any equivalent, and appropriate supporting documentation.

A condition of approval is that any changes, whether or not they require ethical approval, need to be timeously notified to the R&D office. This includes a copy of the ethics annual update report and close out letter when the study is completed.

In conducting this research activity should there be any issues relating to the management of this project R&D are to be contacted immediately

Should you, or any of your team, require training in any of the policies and procedures required to ensure compliance with the conditions of approval, please do not hesitate to contact us. Any breaches of the conditions of approval 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.

With kind regards

Yours sincerely

Angela Jackson

R&D Ethics & Information Manager

Appendix 4: Data protection approval

Southampton NHS
University Hospitals NHS Trust

REC reference number 05/Q1703/55

Information Management & Technology 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
e-mail address: Danni.Howe@suht.swest.nhs.uk

22 August 2005

Data Protection Reference No: DP 0139/05

Amy Winterson
Doctoral Programme in Clincal Psychology
Room 3003
Shackleton Building (44)
University of Southampton
Highfield
Southampton SO17 1BJ

Dear Amy,

Research & Development Number: RHM CAR 0306 – An exploratory study of novelty processing in infants with congenital heart defects

Thank you for returning the Data Protection Guidance pack duly completed as part of the Ethics Committee submission.

I am pleased to advise you that you comply with the principles of the Data Protection Act 1998 and the response will be held on file within this department. Please 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

Dannie Howe
Data Protection Officer
Information Management & Technology Directorate

copy to: Research & Development Department

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.

University of Southampton

Southampton University Hospitals NHS Trust

Appendix 5: Information sheet

Novelty Processing in Infants with Congenital Heart Defects
Information sheet for Parents

Your baby is invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you want your baby to take part.

Who is running the study?

- Amy Winterson, Trainee Clinical Psychologist,

Supervised by:

- Dr Alexandra Hogan, Lecturer in Developmental Neuroscience
- Dr Catherine Hill, Senior Lecturer in Child Health
- Dr Tony Salmon, Consultant Paediatric Cardiologist
- Dr Hilary Robinson, Specialist Registrar

What is the purpose of the study?

There is evidence that some children who are born with congenital heart defects can have educational difficulties later in life, but the age at which these difficulties start to show is not certain. It is possible that these problems may be detectable very early during infancy. We wish to investigate this issue in greater detail. The purpose of this study is to see whether there are any differences in the way that babies who are born with congenital heart defects process novel objects and sounds compared to healthy infants. Studies have shown that they way babies respond to novelty may be related to intellectual ability in childhood.

Why has my baby been chosen?

We aim to study 60 babies aged between 6 and 8 months. 20 babies with one type of congenital heart defect (cyanotic – where the defect causes oxygen-rich blood and deoxygenated blood to be mixed together), 20 babies with another type of congenital heart defect (acyanotic – where the defect does not alter the circulation of deoxygenated blood) and 20 healthy control babies. Cyanotic and acyanotic are terms used to describe differences in the severity of heart defect. In the case of babies with congenital heart defects, we would like to see your baby before his-her operation.

Does my baby have to take part?

Your baby's participation in this study is entirely voluntary. It is up to you to decide whether or not you wish your baby to take part in this study. If you would like your baby to take part you will be asked to sign a consent form. You should be aware that even though you may sign this consent form you are still free to

withdraw your baby from the study at any time without giving a reason. A decision not to take part in the study or a decision to withdraw your baby from the study at a later date, will not in any way affect the standard of care you and your baby are currently receiving or may receive in the future.

What will happen to me and my baby if I take part?
If you decide that you are interested to find out more about this study you may contact us on the telephone number at the foot of this form. At this time you may ask to speak to Amy Winterson, Dr Robinson, Dr Hogan or Dr Hill if you have any further questions about the study. If you decide to allow your baby to participate we will arrange an appointment at a time to suit you. We will try to arrange this time to coincide with a routine clinic appointment, so that you can participate in the study on the same day that you would be attending the hospital. We will ask you to bring the signed consent form to your baby's appointment.

The study will involve six types of assessment, which will last no longer than one hour, and you will be present throughout this time.

1. Questionnaires: We will ask you some questions about your baby, such as how they were born (normal delivery or caesarean section), how they are growing and feeding.
2. A ten-minute assessment of your child's sensory and motor skills.
3. Novel Object Exploration: Your baby will be presented with 6 different objects for one minute each. We will video-tape their response to each object.
4. Brain Response to Novel Sounds: We would like to look at how your baby's brain processes sounds. This is done by placing little sensors on your baby's scalp and forehead. The sensors are held in place with a vaseline-type gel, plasters and an elastic bandage. The sensors record brain waves while your baby listens to noises. This procedure is painless, routinely used with babies from birth, and does not involve needles. In the unlikely event that your baby is unhappy with this procedure, the sensors can be removed within one minute. Your baby will need to sit on your lap for about 10 minutes. During this time they may have a bottle and/or we will blow bubbles to keep them entertained.
5. Blood flow to the brain: A sensor is place at the side of your baby's head – by the temples – in order to see the speed at which blood is flowing to their brain. Blood carries oxygen (fuel) to the brain. Thus this study gives us some idea about how the brain is being fuelled. This 'doppler' study is similar to the type use to look at babies in the womb, and is painless. During the five minute study your baby may have a bottle or may sleep in your arms.
6. Blood oxygen level: A small peg is placed on your baby's finger or toe for three minutes. This will be done at the same time as the assessment of blood flow to the brain and is also painless, so your baby may have a bottle or may sleep in your arms.

What do I have to do?
You do not have to make any changes to your baby's routine or your normal family life if you decide to take part in this study. All we ask is that you contact us

as soon as possible if you are unable to attend an appointment or decide not to take part so that we may offer the appointment to another child.

What are the side effects or risks to my baby if he/she takes part?
This study will not administer any treatments (medicines) and none of the procedures are likely to cause any harm or discomfort. In the unlikely event that you or your infant finds any part of the study distressing, you will have an opportunity to talk through your concerns with the researcher.

What are the possible benefits to my baby if he/she takes part?
There are no direct benefits to you or your baby from participation in this research study. However, we are hopeful that the information we get from this study may help to further our understanding of educational development in children with congenital heart defects.

What happens when the research study stops?
The information obtained from your baby and from the other babies will be put together and carefully analysed. The findings will be reported in scientific journals and presented at conferences to enable other doctors to learn from our study. Your baby will not be identified by name in any publication, and we will not show the video we make of your baby to anyone outside the research team (named above) unless you give us permission to do so.

Feedback about individual babies will not be given in this study. This is for three reasons:

1. The screening assessment (Bayley's Infant Neurodevelopmental Screener) that was completed does not provide the level of information necessary for any formal diagnosis of learning disorder. In addition, it does not have the power to indicate whether or not your baby will go on to develop a learning disorder. Clinical and Educational Psychologists administer this measure, but only as part of a more in-depth assessment. In addition, they typically interpret the results alongside the results of other measures administered repeatedly as the baby progresses through toddler and pre-school stages. This enables them to determine if an individual child has a specific problem, if these problems are transient or if they are more long-term, and what to do to help.

2. One of the games involved your baby looking at novel objects. This game is being developed as a new way to investigate how babies interact with their environment. At this stage we do not have a clear understanding of what to expect, and are therefore unable to interpret individual results in any meaningful way.

3. Similarly, data from individual baby's brain waves or from the Doppler study does not show anything of interest. It is only when we average information together from all the children in each group that we can detect differences. Please note that although our brain wave study is similar to a clinical EEG study (e.g. for epilepsy), it does not provide the level of information necessary for a clinical diagnosis.

As you can see, the procedures used in this study do not provide the level of information necessary for a clinical diagnosis of developmental abnormality, nor do they enable us to predict with any certainty which babies will go on to develop learning difficulties. The information obtained is relevant only for the research questions of this study.

What if something goes wrong?
If you are concerned about any part of the study we advise you in the first instance to talk to the researchers (telephone number at the bottom of this sheet). If you would like to take your concerns further you may speak to your doctor and/or ask about the standard hospital complaints procedure.

Will the information obtained from my baby be confidential?
If you consent to allow your child to take part in the study, a member of Dr Tony Salmon's team at Southampton General Hospital may inspect your baby's medical records, and possibly those relating to your obstetric history (e.g. APGAR score at birth). All information about your baby (and yourself) that is collected during this study will be kept strictly confidential.

Who is organising the research?
Amy Winterson is a Trainee Clinical Psychologist completing a Doctoral Programme at the University of Southampton, and this research is being conducted as part of her training. The study is being closely supervised by Dr Alexandra Hogan, Lecturer in Developmental Neuroscience, Dr Catherine Hill, Senior Lecturer in Child Health, and Dr Hilary Robinson, Specialist Registrar. The research is also being supported by Dr Tony Salmon, Consultant Paediatric Cardiologist at Southampton General Hospital.

Who has reviewed the study?
The study has been reviewed and approved by the North and Mid Hampshire NHS Local Research Ethics Committee that includes members of the general public.

Contact for Further Information:
In the first instance, please contact Amy Winterson:
C/O University Child Health, Mailpoint CB803, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD
Telephone: 02380 796420

Dr Alexandra Hogan
Developmental Brain-Behaviour Unit, School of Psychology, University of Southampton, Highfield, Southampton, SO17 1BJ
Telephone: 02380 594603

Dr Cathy Hill
University Child Health, Mailpoint CB803, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD
Telephone: 02380 796091

University of Southampton

Southampton University Hospitals NHS Trust

Appendix 6: Consent form

NOVELTY PROCESSING IN INFANTS WITH CONGENITAL HEART DEFECTS

CONSENT FORM

Name of Researcher: _____

Name of Baby: _____
Please initial box:

1.	I confirm that I have read and understand the information sheet dated 31st October 2005 (version 2) for the above study, and have had the opportunity to ask questions.	
2.	I understand that my baby's participation is voluntary, and that I am free to withdraw my baby at any time, without giving any reason, without my baby's medical care or legal rights being affected.	
3.	I understand that my baby's medical records and my obstetric records may be looked at by Dr Tony Salmon, who is a Consultant Paediatric Cardiologist at Southampton General Hospital, or another doctor in his clinical service. I give permission for Dr Salmon and/or a doctor in his team to have access to my baby's medical records, and my obstetric records.	
4.	I give permission for the researchers to video-tape my baby during the assessment.	
5.	I agree to allow the researchers named on the information sheet to store anonymised results (including videos) obtained from my baby on a CD disc, hospital or university computer for up to 15 years after the study has finished.	
6.	I agree to let my baby take part in this study.	

Name of Parent	Date	Parent's signature

Name of Researcher	Date	Signature

The study has been described to me by the researchers, and I am willing at this time for my baby to take part. I understand, however, that I may withdraw my baby from the study at any time if I am unhappy.

Name of Parent	Date	Parent's signature

At this time we would also like to ask your permission to use the video we make of your baby for purposes of education and to support presentation of our findings. **The video will contain full-face pictures of your baby but they will not be identified by name. Your baby can still participate in the study if you would rather we did not use the video for this purpose.** Please indicate if we may use the videos in this way and how:

I give permission for the named researchers to show the video of my baby to students in higher education (e.g. psychology and medical students) for purposes of training.

YES / NO _____ (if yes - your initials)

I give permission for the named researchers to show the video of my baby at national (UK) and international conferences to demonstrate our findings.

YES / NO _____ (if yes - your initials)

I give permission for the named researchers to use stills (pictures) taken from the video to include in any publications (e.g. journal articles, book chapters) that they may write about this study.

YES / NO _____ (if yes - your initials)

(1 copy for parent, 1 copy for researcher)