UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

School of Psychology

Executive Functions and Behaviour in Prematurely Born Children

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Thesis for the degree of Doctor of Philosophy

October 2004

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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The thesis investigated Executive Functions (EF) and behaviour outcome in prematurely born children. Three aims were addressed: the first to assess the cognitive and behavioural outcome of prematurely born children, the second to identify which neonatal risk factors may be important in predicting cognitive outcome, and the third to explore the relationship between EF, IQ and behaviour.

Forty prematurely born children and 41 term born control children aged 6 - 12 years were assessed on a cognitive test battery including EF (working memory, inhibition and cognitive switching), IQ and their behaviour rated using parental report questionnaires. Neonatal data were obtained from hospital medical records.

The results showed that as expected, prematurely born children had an IQ in the low average range, and significant performance deficits on the inhibition and cognitive switching dimensions of EF. Contrary to predictions, prematurely born children did not present with an elevated level of externalizing behaviour problems. However, in an enlarged sample, prematurely born children were found to present with more emotional behaviour problems than their term born peers. The analysis of neonatal risk factors revealed that respiratory insufficiency, particularly the requirement for a prolonged period of neonatal oxygen therapy, was associated with poor inhibition and cognitive switching skills. Low IQ was associated with behaviour problems in the prematurely born group only.

The findings suggest that prematurely born children are at risk of poor cognitive outcome, specifically with respect to EF skills. Higher neonatal respiratory insufficiency represents the risk of poor cognitive outcome in middle childhood, specifically for inhibition and cognitive switching. It is suggested that subcortical brain damage mediates the relationship between neonatal risk and cognitive outcome, and a structural equation model is proposed for investigation in future research.

Acknowledgements

This is my chance to thank those involved in this thesis and to comment on the experience.

Prof. Jim Stevenson (or Uncle Jim as the PhD students like to think of him), has been a fantastic supervisor and mentor, with a gift of patience, great sense of humour (remember the first email exchange, ref. Santa) and an air of authority. Thanks for three years of happy work.

Dr. Ineke Pit-ten Cate is a terrific advisor, on matters concerning the PhD, life, the universe and everything. On top of that she bakes wonderful Dutch apple pies and grows the largest courgettes I have ever seen.

I would like to express my thanks to Dr. Mike Hall and his colleagues at the Princess Anne Hospital, the staff at Ludlow Junior and Infant Schools, as well as at the European School Karlsruhe, for their cooperation.

Just over 100 children gave up more than 2 hours of generally hot and sunny afternoons (it rarely rains when you have to collect data) to take part in this research, thank you all, and thanks to your parents for your willingness to participate, and the cups of tea, fruit squash and biscuits.

This studentship was jointly funded by the Economic and Social Research Council, and The Faculty of Medicine, Health and Life Sciences.

Last but definitely not least, Thank You to my family. Financial support throughout the years, moral support in times of "crisis" and above all laughter and happy times are invaluable contributions to this thesis. Ben - thanks for making dinner, dragging me away from work to go diving, and putting up with the "occasional" rotten moods.

Finally a research note:

I will admit to a fair bit of moaning during the course of the PhD. But in perspective it's been a fantastic three years. I have made great friends, had enough time off to visit three continents, learn what a "half out" is and that I am not likely to ever perform one, learn what a 203c is and that with enough determination I can perform one, realize that I am rubbish at playing the flute, that reverse dives are cool (feels like flying), learn some basic Greek, have a go in a glider (scariest-but real flying) and truck loads more. Would I do it again? Probably...

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CHAPTER 1
Thesis introduction and outline

Premature birth is acknowledged as a risk factor for childhood developmental delays and long term negative outcome and presents a source of stress to the parents, the wider family and the affected child. It is not surprising therefore, that developmental psychologists are interested in studying prematurely born children and their families. While there are many sombre messages surrounding premature birth and later developmental outcome, both behavioural and cognitive, a substantial proportion of children born prematurely develop adequately and only experience minor developmental problems and long-term difficulties. However, it is important to study morbidity and outcome of these children, to inform perinatal and neonatological practice, decisions surrounding medical ethics, national health services and, of course, the affected families of the risks and costs associated with premature birth.

While this thesis does focus on the cognitive difficulties faced by prematurely born children compared to their term born peers, it seems necessary to stress that an absence of developmental difficulties should be considered reassuring. Advances in neonatal medicine mean that infants of ever lower gestational age survive, and that the prognosis for those of higher gestational age is improving. It is encouraging to consider that amongst infants born more than 8 weeks prematurely and at less than 1500g, 63% have no health status problems during middle childhood (Theunissen, den-Ouden, Meulman, Koopman, Verloove-Vanhorik, & Wit, 2000). Similar rates of Special Educational Needs requirements have been reported (Pinto-Martin et al., 2004).

This is an impressive outcome considering the potential gravity of the impact of premature birth on the premature infant and his / her physiological and psychological wellbeing. From a scientific point of view, studying the development and outcome of prematurely born children is important, not only in order to make prognoses, but also in terms of understanding plasticity and the capacity of the developing brain to compensate for early insult and adverse environment.

The thesis investigates the cognitive outcome of prematurely born children during middle childhood (6-12 years) with specific emphasis on Executive Functions (EF). The study of EF in a developmental context requires both the study of normally developing children, and special populations of children who are at risk of developmental delay. Prematurely born children are considered as such a population, because the potential brain damage occurs very early in the course of development, and therefore can inform the study of the brain's capacity to compensate for early injury. Furthermore, EF are considered by some developmental neuropsychologists (e.g. Duncan, 1995; Russell, 1999) to be closely associated with and to underlie general cognitive development. It therefore seems appropriate to study EF outcome in children who are at risk for brain insult and developmental difficulties. In addition EF have been given less consideration in the prematurity outcome literature. General cognitive outcome and EF of prematurely born children are investigated in Study 1.

Behavioural development after premature birth has been studied more extensively, with the view to identifying whether prematurely born children have a higher than expected rate of behavioural problems than their peers. This is the second objective of Study 1. Study 2 considers neonatal risk factors such as the duration of ventilation, and oxygen therapy as markers for infant illness. These neonatal factors are used to predict outcome within the premature group (Study 2). The relationship between IQ, EF and hyperactive behavioural style is investigated (Study 3). Finally the main findings are replicated with a second sample of prematurely born children, of slightly older age (Study 4).

The thesis is organized into 9 chapters. Chapters Two and Three provide a background on premature birth, the associated medical complications and the literature on cognitive and behavioural outcome. Chapter Four describes the methodological issues, the measures and the pilot study. Study 1 is reported in Chapter Five. Chapter Six describes Study 2 which investigates neonatal factors in relationship to cognitive and behavioural outcome. Chapter Seven considers the relationships between IQ, EF and behaviour (Study 3), and Chapter Eight revisits the issues of Studies 1-3 using the extended sample. Chapter Nine serves as a thesis summary and discussion and includes directions for future work.

CHAPTER 2

Review of the Literature on Premature Birth and Development

2.1 Premature birth – implications for development

Premature birth has become a central area of research in neonatal medicine and paediatric psychology over the last 30 years. It is considered a major clinical problem associated with perinatal and neonatal mortality, as well as various degrees of childhood disability. An infant is classified as premature if s/he is born before 37 of the normal 40 weeks of gestation. Between 6-10% of infants are born prematurely in Western countries (Lumley, 2003). The majority (about 80%) of premature infants are born between 32 and 36 weeks of gestational age (GA), 10% between 28 and 31 weeks, and approximately 6% at less than 28 weeks GA.

Through technological and medical advances the survival of premature babies as young as 22 and 23 weeks GA is considered possible. Infants born at 24 weeks GA are routinely resuscitated, while for those born earlier it is the decision of paediatric consultants and parents. Extremely premature infants are clearly at the greatest risk for survival and for lasting disability. Infants may develop cerebral palsy, hydrocephalus, chronic lung disease and often suffer cardiac difficulties. Prematurely born children are slow to develop, and even in the absence of major neurological difficulties there is greater than normal rate of learning disability in this population. Early neonatal care of the infant is thought to have important effects on later outcome (Allen, 2002; Jacobs, O'Brien, Inwood, Kelly, & Whyte, 2000)

2.2 Causes of premature birth

The onset of premature labour is generally related to the mother's medical condition. Pre-existing conditions such as high blood pressure, obesity and diabetes, as well as maternal age (above 35 years), smoking, poor diet and general health are considered risk factors (Mifflin, 2003). Gynaecological infections, for example, chorioamnionitis, which is an infection of the membranes surrounding the foetus are a common cause of premature birth. Conditions such as pre-eclampsia (raised maternal blood pressure causing fluid retention, proteinuria, and interruption of placental blood supply), placenta previa (placenta detaches early due to poor location and causes blood loss and early labour), polyhydramnios (an excess of amniotic fluid surrounding the baby, which stretches the uterus), and early rupture of membranes are further common causes of premature birth (Mifflin, 2003). Furthermore, multiple pregnancies are less likely to be carried to term, due to lack of space in the uterus. Prevention of premature birth involves identifying early signs of medical complications as well as taking sensible health precautions during the course of pregnancy. Research into the causes and potential preventative measures of prematurity are ongoing. However, a substantial body of research addresses the outcome for mother and child after premature birth.

2.3 Predictors of child outcome

2.3.1. Birthweight and gestational age

The two most commonly cited predictors of outcome are gestational age and birthweight, both of which are positively associated with later child development. Birthweight (BW) is more commonly reported, as it is routinely recorded. Gestational age (GA) on the other hand can be difficult to ascertain, and may be less reliable, especially if the mother is uncertain of her dates. Gestational age of the infant is estimated using ultrasound prior to birth and postnatal assessment of the maturation of different body features (e.g. cartilage of the ear, fingernails). Infants born between the 32nd

and 37th week of gestation are considered *premature*, those born between 28 and 32 weeks are *very premature*, and infants born before the 28th week of gestation are considered *extremely premature* (Mifflin, 2003). Similar descriptions are given for birthweight categories *low birthweight* (2500g – 1500g), *very low birthweight* (1000g – 1499g), and *extremely low birthweight* (<999g) (e.g. Bohm, Katz-Salamon, Smedler, Lagercrantz, & Fossberg, 2002).

While gestational age and birthweight are closely correlated in most cases, some infants are born at a birthweight which is inadequate for their gestational age. This may occur both for preterm and term born infants. These infants are considered small for gestational age (SGA) and often suffer from intrauterine growth retardation (IUGR), which typically results from malnutrition or placental insufficiency. To determine whether an infant is SGA the Lubchenco classification is used (Battaglia & Lubchenco, 1967). Infants whose birthweight is below the tenth percentile for their gestational age are considered SGA. Being born small for gestational age is considered an additional risk factor to premature birth (see Robson and Cline, 1998), as these children are under-developed as well as being subjected to the demands of extrauterine life too early. IUGR is associated with a disruption of the normal developmental processes especially affecting the Central Nervous System (CNS; Leitner et al., 2000). Prematurely Born (PB) children on the other hand are not delayed in their development according to their gestational age but born too soon, and consequently not prepared for life outside the womb. Not all studies that use gestational age or birthweight as inclusion criteria specify whether children who were small for gestational age are included. Wherever available, the distinction will be made within this thesis.

2.3.2. Medical complications

In addition to birthweight and gestational age, neonatal medical complications are also considered risk factors for outcome. These include complications of the respiratory and pulmonary system, neurological risks resulting from Intraventricular Haemorrhage (IVH, brain bleed in the area between the lateral ventricles) as well as the secondary consequences of various treatments. These predictors of outcome will be discussed in detail in the following sections.

2.3.2.1 An Immature Pulmonary System

Premature infants born before 32 weeks GA are at risk of developing Respiratory Distress Syndrome (RDS), also known as Hyaline Membrane Disease (HMD). In RDS the lungs are insufficiently expanded, due to the lack of surfactant, a substance normally secreted by the lungs but insufficient in PB infants. Surfactant reduces surface tension within the lungs thereby preventing the alveoli (air sacs) from collapsing. In infants born before 35 weeks GA insufficient surfactant has developed, as a result of which infants may suffer from inefficient and "stiff" lungs, and may exhibit shallow, laboured and rapid breathing (Mifflin, 2003). This condition is usually treated using continuous positive airway pressure (CPAP) from a respirator. In addition infants are medicated using a synthetic surfactant. Several randomised control trials have shown that the administration of surfactant significantly reduces infant mortality and morbidity (Courtney, Durand, Asselin, Hudak, Aschner, & Shoemaker, 1995; Horbar et al., 1993; Sauve et al., 1995).

Treatment using mechanical ventilation may lead to longer term lung disease. Bronchopulmonary Displasia (BPD) is a chronic lung disease caused by trauma resulting from mechanical ventilation. Infants may develop fluid in the lungs, scarring as well as lung damage which is apparent on x-ray examination. Recovery usually takes place over a period of about 2 years; however, some severely affected patients may develop longer term lung diseases such as asthma (Anand, Stevenson, West, & Pharoah, 2003).

In order to improve lung maturation, corticosteroid drugs (e.g. Dexamethasone) may be administered prenatally to the mother, or postnatally to the infant. Dexamethasone is a commonly administered corticosteroid drug, which is thought to decrease the risk of BPD; however, it carries the risk of various side effects. Generally treatment outcome is favourable. Cummings, D'Eugenio and Ross (1989) reported that 42 day treatment of PB infants (<30 weeks GA) who were ventilator and oxygen dependent resulted in earlier weaning from both respiratory aids than for infants who received only an 18 day treatment, or a placebo. Furthermore, clinical complications of steroid therapy were not observed. The infants in the 42 day trial showed better outcome at 6 and 18 months than did the infants in the other two groups. More recently, Saarela, Ristela and Koivisto (2003) reported on the suppressive effects of corticosteroids on growth. In particular they were interested in the effects of corticosteroids on collagen, an important matrix protein, and found that dexamethasone has a fast and deep acting suppressive effect on two types of collagen synthesis in treated preterm infants. The authors suggest that this has implications both for the general growth of the infant, and for the increased risk of Intraventricular Haemorrhage (IVH, a brain bleed), which occurs as a result of weak tissue matrix in the intraventricular space.

Some studies have suggested that Dexamethasone increases the risk of cerebral palsy and developmental delay. Rennie, Wheater and Cole (1996) studied the effect of antenatal steroid administration on infant morbidity, and found a three fold improvement of normal survival in the Dexamethasone treated versus placebo treated group. However, Shinwell et al. (2000) report the results of a randomised controlled trial of neonatal Dexamethasone. Amongst the infants who received Dexamethasone, 55% suffered developmental delay. Forty-nine percent had a diagnosis of cerebral palsy, compared to 29% and 15% respectively in the placebo control group. The 3 day treatment of infants who had already been treated with surfactants and required respiratory support resulted in an elevated rate of cerebral palsy and other complications. There may be an indirect association between increased survival through therapy and an increase of disability in this sample of children. In other words, treatment with Dexamethasone will increase chances of survival for extremely premature infants, who are at the greatest risk of the effects of Intraventricular Haemorrhage (IVH) and the subsequent development of cerebral palsy common to extremely PB infants.

2.3.2.2 Neurological Risk Factors

Brain damage is one of the most serious medical risks for prematurely born infants. There are multiple causes of brain damage which can be broadly classified as those of a brain insult origin (such as stroke) and those that result from the disruption of developmental processes and affect predominantly the white matter (Damman & Leviton, 1999). Brain insult includes Intraventricular Haemorrhage (IVH), hypoxia (lack of oxygen)/ischemia (stroke) and infection. IVH occurs as a result of ruptures in the fragile blood vessels of the infant brain. The resulting blood clot may prevent cerebrospinal fluid from draining from the cerebral ventricles, which in turn causes ventricular dilation and may result in Hydrocephalus. Hypoxic and ischemic damage is related to both the risk for oxygen insufficiency in prematurely born infants, as well as an unstable circulation which may not consistently supply the brain with the necessary nutrients. The immature regulatory mechanisms of the preterm infant's brain may not adequately control blood pressure, therefore damage may also occur as a result of reperfusion of the blood vessels (Volpe 1997). Indirect effects of prematurity on brain damage and development affect the myelination process which takes place during the third trimester of pregnancy, a time which is concurrent with premature birth. A second indirect cause of brain damage is the lack of neurotrophic protective factors which, during the course of normal gestation, are derived from maternal sources. Such neurotrophic protective factors are not available to the preterm infant, who as a result is more vulnerable to brain insult. Disrupted neural migration is a further disruption to development (Damman & Leviton 1998).

While intrauterine infection and the associated foetal inflammatory response are a cause for premature birth, there is also evidence to suggest that intrauterine infection is a cause of white matter damage and abnormalities (Damman, Kuban, & Leviton, 2002). Metabolic disturbances resulting from nutritional complications are also thought to contribute to brain damage. Comparable to the physiological effects of immature regulatory systems, nutritional deficits and associated metabolic disturbances may equally increase risk of insult or abnormal development. These risk factors contribute to white matter damage which results in poor developmental outcome.

Prematurely born infants are routinely screened for abnormalities on ultrasound during the neonatal period. While only around 10% of infants have abnormal findings on perinatal ultrasound (Aziz, Vickar, Sauve, Etches, Pain, & Robertson, 1995), a higher rate of white matter abnormalities is detected in older children. Periventricular leukomalacia (PVL) is white matter damage occurring in the tissues between the two lateral ventricles. It is the most common form of brain damage in the premature infant and is thought to be caused by infection and ischemia or a combination of the two. PVL occurs in approximately 4-10% of infants born at less than 33-35 weeks of GA (Rezai and Dean, 2002). Neuroimaging studies have associated PVL with motor and cognitive deficits observed in prematurely born children later in life and have been associated with the development of cerebral palsy (Dammann et al., 2002;_Maalouff et al., 1999). Inder et al. (1998) have presented evidence for a relationship between PVL and the development of cerebral cortical grey matter. The group studied three cohorts of infants using magnetic resonance imaging techniques. A group of PB infants with ultrasonographic evidence of PVL, a group of PB infants without any evidence of PVL and a term born (TB) control group. Brain images were obtained at the age of 40 weeks GA. In addition to the expected reduction of total myelinated white matter, the infants with PVL also showed a reduction in the cortical grey matter. The authors suggest that this reduction in grey matter can be considered an anatomical correlate of intellectual deficits observed later in life.

While as yet there is no follow-up data available for the children enrolled in the Inder et al. (1998) study (to investigate these children's cognitive outcome), association of PVL to later cognitive impairments in PB children have been reported in other studies. A recent follow-up study (Stewart et al., 1999) of very prematurely born (VPB) children assessed brain structure at ages 14 /15 years. The authors' cohort of children had been assessed using ultrasonography after birth and at regular intervals during childhood. The researchers predicted that the children with abnormal ultrasound scans would be at a greater risk of abnormal MRI scans during adolescence. This was predicted to be associated with cognitive or behavioural difficulties.

The results generally confirmed this hypothesis. While the ultrasonography scans at birth only predicted abnormal MRI scans in some cases (22%), the scans of the PB group showed abnormalities significantly more often than those of the control group. Thinning of the corpus callosum and ventricular dilation were most commonly associated with each other and with other white matter lesions. The authors suggested that these abnormalities are markers of hypoxic-ischaemic damage. These results confirm previous work to show that brain damage in VPB infants most commonly results in lesions to the white matter (see Paneth et al., 1994). The observed lesions did not manifest themselves as neurological impairments as might be expected, but rather as a cognitive-behavioural deficit. The authors concluded that VPB children are likely to have abnormal MRI scans and related behavioural problems during adolescence. Such behavioural problems often include attentional deficits, as well as externalising and internalising problems.

Huppi et al. (1996) compared the MRI scans of PB infants two weeks postpartum, and again at term (a mean of 8 weeks later). Maturational changes were observed during this period, with normal developmental changes in the grey and white matter as well as increased myelination. However, compared to a group of term born (TB) infants, these children showed less brain differentiation at 40 weeks, and in addition exhibited poorer performance on neurobehavioral assessments. PB children showed poorer autonomic reactivity, motoric reactivity and attentional skills. These results provide an association between a slower rate of cortical maturation and the neurobehavioral developmental difficulties observed in PB children.

Similar results have been obtained by another study group comparing brain volumes in PB and TB children. Peterson et al. (2000) have studied the relationship between brain morphology in PB infants, and their later cognitive function at around 8 years of age. Morphometric analyses demonstrated that the volume of the basal ganglia, corpus callosum, amygdala, and hippocampus are comparatively smaller in PB than in TB control children. The authors used the Wechsler Intelligence Scale for Children (WISC) as a measure of cognitive outcome, and found that as expected, IQ was positively related to brain volumes. Frisk and Whyte (1994) assessed the long term effects of periventricular brain damage on language and memory development. In their study, a cohort of extremely low birthweight children was assessed at the age of 6 years. Around half of the sample children had sustained periventricular brain damage in the perinatal period. The outcome of the assessments was compared to that of matched, healthy TB children. The researchers concluded that extreme prematurity itself does not result in delayed language and memory development. Instead it was the secondary consequences such as neurological damage that were responsible. The degree of damage to the periventricular region in EPB children was associated with language development into school age. The memory assessments showed difficulties primarily in the working memory domain, and were associated with mild Intraventricular Haemorrhage with or without hypoxic ischemic damage. Prematurely born children with no brain damage performed significantly better than their PB peers who had sustained damage.

In addition to PVL and IVH, there have been concerns regarding the development of the hippocampal system in PB infants. This brain area is particularly vulnerable to ischemic damage (Schmidt-Kastner & Freund, 1991; Volpe, 1997). The hippocampal system is associated with episodic memory (memory for events) and could therefore put the infant at risk for memory deficits. Isaacs et al. (2000) have investigated memory performance and related hippocampal damage in PB adolescents. The children enrolled in this study were all born at less than 30 weeks GA and weighed less than 1500g at birth. None of the children's medical records reported IVH during infancy. Compared to a group of TB control children, children in the study group had lower scores on a test of everyday or episodic memory (Rivermead Behavioural Memory Test, RBMT). In addition, volumetric analysis of the MRI scans revealed that the PB group did have abnormal scans, some with lower hippocampal volumes, other children showed reduced white matter bulk, and reduction of the corpus callosum. The authors point out that the performance on the RBMT can be considered to be independent of general cognitive level, and therefore represents a specific memory deficit.

The overview of research into neurological risk for PB children demonstrates that there is a consistent relationship between the nature and extent of brain damage and cognitive and behavioural difficulties. It seems appropriate to suggest that the cognitive deficits observed and reported in PB children have a root in brain damage which is sustained as a result of ischemic/hypoxic as well as metabolic insults of varying degree during the neonatal period. The nature of this cognitive outcome is discussed in detail in the next chapter.

2.3.2.3 An Immature CNS - The Polyvagal Theory

In addition to the risks of brain damage and chronic lung disease, PB infants have an unstable physiology, which is poorly regulated, and is therefore vulnerable to environmental stimuli. Changes in posture, abdominal pressure caused by handling, and routine medical procedures such as endotracheal suctioning may all contribute to bradycardia (heart-rate slowing) and apnoeic (cessation of breathing) events. The Polyvagal Theory (Porges, 1992) explains how external stimuli may cause such serious physiologic reactions.

The Polyvagal system functions to produce positive feedback between the brainstem and cardiopulmonary as well as digestive systems. Higher order brain systems act upon the primary nuclei involved in the vagal system. Vagal function ensures coordination of breathing, swallowing, heart rate, and vocalisation, and can thus be assessed by observation and measurement of these functions. The amplitude of respiratory sinus arrhythmia (deviation from normal rhythm) is used as an index of vagal tone (index of ability to auto-regulate in face of external stimuli), and thus autonomic nervous system functioning. This is of interest in the assessment of physiologic homeostatic control of high risk infants.

The Polyvagal Theory integrates neuroanatomical and neurophysiological information about the vagal system, and provides a theoretical basis for understanding the impact of assessments and interventions in the neonatal intensive care unit on the infants physiological state. The theory can account for life threatening responses to sensory stimulations which result from certain medical and care procedures. An example is oral-oesophageal stimulation occurring during suction or the insertion of orogastric feeding tubes. PB infants are at a higher level of risk for poor vagal tone due to the immaturity of the vagal system at the time of birth, resulting in a multitude of demands on an underdeveloped system. Porges (1996) emphasises that abdominal pressure during massage as well as posture changes which stimulate baroreceptors can stimulate CNS (dorsal motor nucleus) reflexes, and in turn bradycardia, apnoea and loss of consciousness. This highlights the importance of monitoring the infant closely during any sort of intervention especially those targeted to benefit the child, such as Kangaroo Care (see Section 2.3.4).

In addition to serving as an index to the physiological stability of an infant in the neonatal period, the Polyvagal Theory has also contributed to research into the longer term outcome of high risk infants. Vagal tone and auto-regulatory function in the neonatal period has been associated with self-regulation and inhibitory control in early childhood. Doussard-Roosevelt, McClenny and Porges (2001) examined the relationship between neonatal cardiac vagal tone and school age outcome of very low birthweight infants. Vagal tone was estimated by measuring the respiratory sinus arrhythmia at 33, 34 and 35 weeks GA. A maturation measure based on the respiratory sinus arrhythmia was calculated across this time period, and other neonatal risk factors such as low birthweight and high medical risk, in addition to preschool measures of behaviour and cognitive function were obtained. The neonatal data were analysed as predictors of school-age behaviour measures. Medical risk and preschool difficulties were significant indicators of school age risk for behaviour problems, however the single best predictor of school age social competence was neonatal vagal tone index. The authors interpret this finding within the context of maturation of vagal fibres during the neonatal period and the proficiency with which a newborn can respond to environmental changes and stressors during this time. It was argued that later behaviour builds on these basic autoregulatory skills and that therefore the respiratory sinus arrhythmia measure provides an early risk index for later social behaviour problems.

Similar conclusions were drawn by Calkins and Fox (2002), who found that a low resting Respiratory Sinus Arrhythmia (i.e. high vagal tone) is associated with appropriate emotional reactivity in longitudinal studies of self regulatory processes in early personality development. In their theory they postulate that infants display individual differences in behavioural reactivity and regulation, which hold implications for subsequent development. In particular, difficulty and failure to self regulate in the neonatal period places the child at a higher risk for developing future behaviour problems.

Porges and colleagues have developed a theory of self regulation which integrates and builds on physiological processes both early and later during development. They provide a plausible hypothesis for the way in which these basic physiological functions may affect higher order systems of self regulation. While research concerned with vagal tone regulation has addressed behavioural development in school age children, little attention has been focused on how the self regulation problems may reflect on inhibitory control and especially attention control. Furthermore, both vagal tone and brain insult are associated with the degree of prematurity, and both are related to later outcome. It may therefore be difficult to distinguish between the relative contributions of vagal tone and brain damage on later cognitive and behavioural outcome.

2.3.3 Early cortical development and brain plasticity

Certain anatomical brain structures such as dendritic arbors and synaptic connections are required in order for functional development to begin. Throughout development, there is a cyclical progression from synaptogenisis (production of neuronal connections), to synaptic pruning. This results in a period of maximal synaptic density, followed by a reduction in synaptic connections. The timing of the progression differs for different cortical regions. At 28 weeks gestational age, the synaptic density is low in several cortical areas including the prefrontal cortex (where the density is lowest) and also in the primary visual and auditory areas of the human brain. The cortex of a very prematurely born infant (<28 weeks GA) is therefore highly underdeveloped, with developmental processes in their primary stages in some cortical areas. The development of dendritic arbors and synaptic connections progresses rapidly but at different rates for different cortical areas. The prefrontal cortex reaches maximal synaptic density as late as 3 years of age, whereas primary cortical areas such as the primary visual area reach maximal density around three months of age. Similarly, myelination of subcortical white matter, which begins around 40 weeks gestational age (i.e. at term), progresses at differential rates. Myelination spreads initially posteriorly, progressing anteriorly later, reaching the prefrontal cortex around six months of age (see Huttenlocher & Dabholkar, 1997).

With cortical development at its maximum rate during the last trimester of pregnancy it is clear that premature birth which carries the risk of brain damage, particularly at less than 28 weeks GA, has the potential to seriously disrupt the normal course of cortical development. However, adaptive processes that facilitate a process of differentiation and integration during this period also hold the potential for plasticity during development, and the capacity for compensation of early insult. (Thatcher, 1997)

Brain plasticity refers to the potential of external stimuli such as sensory input to modulate synaptic connections during development, thereby affecting both the structure and functional outcome of the developing brain. Plasticity has been studied extensively in the visual system to show how early visual experiences affect patterns of connections amongst neurons, as well as their later functional organisation. The rewiring usually involves the elimination of synapses as a result of neuronal cell death.

Early brain injury has been studied extensively in an attempt to understand the capacity for an immature brain to adapt to early adverse stimuli. While Kennard (1939, cited in Kolb and Gibb, 2001) suggested that the earlier the injury, the less severe the effects would be on later functional outcome, Hebb (1947, 1949 cited in Kolb and Gibb, 2001) suggested that early injury may impede the development of certain cognitive capacities and functions. The picture is much more complicated, in that the effect of the injury depends on its timing with respect to the developmental stage of the CNS. Evidence from animal models has suggested that the period of active cell migration and cell differentiation is the time at which injury has the most detrimental outcome. While in rats this period corresponds to the first postnatal week, in humans it corresponds to the last trimester of development (between 27 and 40 weeks GA).

Not only are prematurely born infants exposed to the extrauterine environment during this critical period of brain development, they are also at the additional risk of brain damage occurring during the period with the worst potential for functional recovery. The situation is further complicated by the exact timing and nature of the injury. While animal studies have generally looked at lesion injuries postnatally, the preterm infant may sustain brain damage prenatally, perinatally and postnatally. Furthermore the nature of the damage may be hypoxic-ischemic or an intraventricular haemorrhage, either of which have different outcomes. Vulnerable brain areas have been identified using regional neuroimaging, and include periventricular structures, the hippocampus, the striatum and the frontal cortex. The behavioural correlates of hippocampal injury are poor episodic memory, while the striatum and the frontal cortex have been associated with executive functions.

The extent of functional impairment following these risks for injury is not immediately clear, unless the infant's brain has sustained severe damage which results in major neurological impairment. Cognitive functional impairment only becomes evident as development progresses. It is therefore not clear whether the effects of damage are ameliorated with time as recovery takes place, or rather, that children "grow into" the impairment, throughout the course of development (Luciana, 2003). This is particularly evident in the case of Executive Functions (EF, discussed in detail in Chapter 3, Section 3.5). While in adults, EF are mediated mainly by the frontal lobes, there is thought to be a striatal to frontal shift during childhood. Both frontal and striatal areas are vulnerable to early damage, but it is unclear how this damage may affect the developmental progression of EF. The evidence from studies of cognitive outcome in prematurely born children would suggest that these children's impairments worsen with age and that the full extent of their difficulty becomes evident from the onset of schooling (see Chapter 3).

2.3.4 Secondary risk factors for development

Research during the late 80s and early 90s has been concerned with PB infants' reactions to their environment, and how to optimise these. Whilst most of an infant's handling consists of medical procedures, (about 4h in any 24h period), positive social interaction with parents or hospital staff is minimal. Medical procedures often disturb the infants sleep pattern, and have been associated with bradycardia, apnea and behavioural distress (Gorski, Huntington, & Lewkowicz, 1990). An increase of catecholamines, an endocrine stress response, has been observed during medical procedures, particularly endotracheal suctioning and chest physiotherapy (Lagercrantz, Nilsson, Redham, & Hjemdahl, 1986). Such evidence highlights that invasive procedures, which cause aversive physiological reactions in the infant, should be kept to a minimum wherever possible.

2.3.4.1 Stress and the HPA axis

Stress as referred to in this section will be defined as stimulations which cause a state of discomfort such as hunger, thirst, pain and fear. Physiological reactions to stress are regulated through the Hypothalamic-Pituitary Adrenal (HPA) axis, which is responsible for regulating the synthesis and the secretion of glucocorticoids such as cortisol. The HPA axis is activated by stress, and the resulting physiological responses to stress are adaptive as they restore and maintain a homeostatic balance (a negative feedback cycle). Glucocorticoids are responsible for mobilising fat and amino acids from the fat and muscle cells, the long term effect of which is to harness energy substrates, which are useful in activating appropriate responses (such as escape or defence). High levels of glucocorticoids also activate receptors which are found mainly in the hippocampus, but also in the limbic system and frontal regions (Gunnar, 1998). Activation of these receptors will produce negative feedback, and an inhibition of glucocorticoids. Chronically high levels of stress and the resulting elevated levels of glucocorticoids will result in a less reactive HPA axis which is less effective in its buffering capacity (i.e. suppressing the negative feedback cycle). Elevated levels of glucocoticoids will result in an enhancement of excitatory amino acids (e.g. glutamate), and a calcium influx into neurons, resulting in cell death. Animal models have shown that high levels of glucocorticoids adversely affect the developing brain by indirectly causing cell death (see Huizink, Mulder, & Buitelaar, 2004, for review). The hippocampus contains a high level of glucocorticoid receptors, and as a result is at an increased risk of damage.

2.3.4.2 Effects of high cortisol levels

Stress levels can be estimated by measuring cortisol levels, for instance, from saliva samples. Higher levels of secreted cortisol are consistent with higher levels of stress. An infants' cortisol levels, for instance, may be measured before, during and after invasive procedures such as endotracheal suctioning to determine the level of stress these procedures result in.

As described in section 2.3.3.1, early increased levels of stress and cortisol production can have long term effects on the homeostatic control of the HPA axis. So, for instance, infants who experienced high levels of stress will have a more reactive and more sensitive stress response for some months following recovery. Maternal prenatal stress has also been associated with adverse infant outcome, for instance, a smaller head circumference corrected for birthweight, and lower scores at neonatal neurological assessment (Lou, Hansen, Nordentoft, Pryds, Jensen, Nim, & Hemmingsen, 1994).

Evidence to suggest that HPA axis hormones may have an adverse effect on infant development is described in Trautman et al. (1995, cited in Huizink et al., 2004) who reported greater levels of behaviour and temperament problems, particularly shyness, and internalising behaviours in children whose mothers were treated with early prenatal Dexamethasone (an endogenous HPA glucocorticoid hormone). Similarly, a study of low birthweight children who received prenatal corticosteroids described better cognitive outcome amongst treated relative to non-treated children of comparable birthweights (Doyle & Davis, 2000). However, others have reported an association between antenatal corticosteroids and later behaviour problems (French, Hagan, Evans, & Newnham 1999). Similarly evidence that hydrocortisone (a pharmacological preparation of the steroid cortisol) can have adverse affects on attention has been presented (e.g. Lupien, Richter, Risch, Mirow, Gillian, & Hauger, 1995). It has also been suggested that high levels of the hormone can impair the functioning of the cingulate gyrus which is implicated in the effortful control of attention (Posner, 1990). In relation to this, there is some evidence to suggest that inhalers for asthma which contain cortcosteroids can have a negative impact on the attentional skills of affected children (Naude & Pretorius, 2003).

With respect to the risk that prematurity poses in terms of a hyper-reactive HPA axis and the potential adverse effects of elevated cortisol levels, suggestions have been made to help reduce this risk. In animal models infant mother contact has been shown to ameliorate the effects of stress. The prematurely born infant may therefore benefit from a care plan which aims to minimise the negative handling of the premature infant, whilst maximising the positive parental interaction which appears to have a highly beneficial effect on the infant's developing CNS and general well-being (Tessier et al., 2003).

2.3.5 Kangaroo Care

Kangaroo Care (KC) is a care technique developed in Colombia in 1979 (Whitelaw & Sleath 1985). This technique involves holding the infant on the bare skin of the parent's chest, which helps to maintain the infants body temperature, and allows close contact between infant and parent. In many hospitals in the developing world, the technique is applied to stable, spontaneously breathing infants (and often only those who are able to breastfeed), and has proved to be of benefit to the infant's physiological stability as well as mother-infant bonding. KC has been reported to "improve infant state organisation, thermal regulation, respiratory patterns and oxygen saturation, reduce apnea and bradycardia, increase rate of infant weight gain and maternal milk production, shorter hospital stay and function as an analgesic during painful medical procedures" (cited in Feldman, Eidelman, Sirota, & Weller, 2002, page 16). Furthermore Feldman et al. report that KC can improve the mother's sense of competence in handling the infant, as well as improving the mother infant attachment process. Furman and Kennell (2000) report that infants undergoing KC are recorded to spend up to 4 times as much time in an alert quiet state, and twice as much time in a quiet sleep state which lasts for longer periods, both of which benefit normal infant development. In the longer term, KC has a positive effect on early infant development and on the quality of parenting during the first 6 months. A potential mechanism for these beneficial effects for the infant has as yet not been suggested.

The utility and benefit of KC continues to be investigated, and has recently been suggested as a protective method against developmental delay in PB infants. Tessier et al. (2003) have compared the relationship between KC and later outcome of PB and low birthweight children against infants who received standard care. Infants in the KC group achieved higher IQ equivalent scores at 12 months, when factors such as health at birth, SES and delivery characteristics were accounted for. Infants who were born at lower gestational ages, and who had required neonatal intensive care attained the most benefit from KC. The authors concluded that KC may be a form of developmentally supportive care which can enhance parenting abilities as well as promote the infants neurological development.

2.3.6 Maternal responsiveness and infant psychobehavioural outcome

The idea of maximising positive and gentle contact between parent and infant is important not only for the infant but equally so for the parents. PB infants are often very ill and unresponsive and this unresponsiveness can cause difficulties for the mother – infant dyad. Mothers of PB infants tend to develop poorer adaptation to infant signals, resulting in lower frequency of gaze, touch and vocalisation in interacting with their PB infant (Minde, Whitelaw, Brown, & Fitzhardinge, 1983). As a result, the home environment may be less stimulating and responsive than for TB infants (Barrera, Rosenbaum & Cuningham, 1987). Laucht, Esser and Schmidt (2001) emphasised the importance of early parenting on the development of PB children who are at greater than average risk of developing behavioural and emotional problems. They suggested that maternal responsivity was a moderating effect of low birthweight on internalising problems as well as hyperactivity.

A Swedish study (Cnattingius, Hultman, Dahl, & Sparen, 1999) has suggested a link between premature birth and anorexia nervosa (AN). They reported an increased risk of AN amongst VPB girls (less than 32 weeks). They propose that eating difficulties which are common amongst PB infants and toddlers may be a cause of later onset eating difficulties. Furthermore they suggested that these eating difficulties may be related to brain damage, delayed oral motor development (see Polyvagal Theory, Section 2.3.2.3) and the need for gastric tube feeding (which deprives the infant of early experiences of taste and texture of nutrition) as well as parental reactions to premature birth and prolonged hospital stay. The secondary interactional dysfunction between parent and child may then contribute to the onset of later eating disorders. Biological risk factors are likely to be primary predictors that can be mediated by environmental influences such as responsive parenting.

2.3.7 Impact on Sensorimotor Development

A further influence on infant development and outcome are the environmental stimuli which the VPB infant is subjected to, especially those related to neonatal care. While the Neonatal Intensive Care Unit (NICU) provides excellent medical care, it cannot replace the last trimester in utero, where the foetus is not subjected to much noise, any light or gravitational effects. These external stimuli will add an additional burden to the developing infant's premature CNS, and these are likely to have an impact on PB children's development.

The capacity for sensory perception, for example, is important not only from a neurological point of view, but also from a developmental perspective. Sensorimotor experiences drive the progression of the young infant's early cognitive development and learning. An infant learns to make associations between environmental stimuli through exposures to tactile, kinaesthetic, vestibular, motor, auditory and visual sensations (e.g. see Piaget & Inhelder 1969). Through these experiences learning processes such as habituation, classical and instrumental conditioning can take place, which pave the way for later more complex and advanced processes. The relative immaturity of PB infant's sensory systems, in addition to the adverse stimulation they experience, can result in a distorted process of early learning. It has been proposed that these experiences add an additional risk to cognitive development independently of that associated with neurological impairments. Saigal, Szatmari, Rosenbaum, Campbell and King (1990), for instance, studied a group of VLBW children at the age of 5 years on cognitive, visual-motor and motor functions. While the children's intellectual status was within 1 SD of the test norms, they performed poorly on tests of visual-motor integration and motor function. As the children were tested at school entry, the authors considered the possibility that enduring problems in the visual-motor integration and motor function may adversely affect their school performance, thus resulting in achievement deficits.

2.4 Conclusions

The chapter described some general information relating to premature birth and the associated risk factors for development. Brain insult through hypoxic/ischemic damage or through disruption of developmental processes has a direct impact on brain function and development. Neonatal respiratory insufficiency and respiratory support are thought to be markers for later lung pathology as well as developmental difficulties. Secondary risk factors such as elevated stress and cortisol exposure, long term hospitalisation and disruption to parent-infant bonding are thought to contribute to adverse developmental outcomes of PB children. Some psychosocial interventions are thought to have protective value, and may thereby help to reduce the effect of the biological risk that PB infants face. Both the study of protective mechanisms, and the extent to which the infant brain has the capacity to recover from injury can guide the development of neonatal medical techniques and postnatal interventions. This allows optimisation of the care of PB infants and may help to promote the best possible outcome. The cognitive difficulties that affect many PB children are discussed in the next Chapter.

CHAPTER 3

Cognitive and behavioural outcome of prematurely born children

3.1 Introduction

The cognitive outcome of PB children has been studied in the past especially after the increase in the survival of infants of lower gestational age. A meta-analysis published in 1989 (Aylward, 1989) summarised the results of studies conducted between the late 1970s and late 1980s. These empirical studies generally suggest that there are impairments among low birthweight children, and furthermore that there are significant differences between low and very low birthweight children and control groups on measures of intelligence and general development. Studies in this area consistently report more severe underachievement and poorer outcome for extremely PB children and the most fragile infants, than those at lower medical risk. Another interesting finding was that while birth weight and other perinatal and postnatal complications predict cognitive outcome, environmental factors are often found to moderate this relationship (Pfeiffer & Aylward, 1990). The meta-analysis revealed that medical and biological effects generally affect the outcome of studies conducted in younger children, while environmental factors generally affect the results of studies of older children. This suggests that early in development of PB children, it is the medical complications and risks such as prolonged requirement for ventilation and supplementary oxygen that determine the immediate, shorter term developmental progress of the young child. In older PB children however, a stimulating home environment, responsive parenting style and higher SES, for instance, moderate the effect of early medical risk and can be considered as a protective mechanism which reduces risk for poor cognitive outcome.

The literature reviewed in the above meta-analysis is based on children who were born in the early 1980s. Many of the cited studies have reported mild to severe deficits amongst these PB and low birthweight children and some studies have reported that many infants of very low birthweight have no special deficiencies, which distinguish them from full term and normal birthweight peers (Drillien et al., 1980; Eilers et al., 1986; Kitchen et al., 1980; Stewart et al., 1981; cited in Pfeiffer & Aylward, 1990). As the medical care has improved substantially since this time, more recent studies will be focusing on different outcome variables which are likely to be affected by the improved care of prematurely born children. While more recent literature still suggests a range of difficulties in the developmental outcome of prematurely born children, the focus is less on general school achievement and intellectual functioning, but on specific aspects of cognitive function that may underpin overall performance.

3.2 Preschool Years (0-4/5 years)

The study of developmental status during preschool years relies on achievement tests such as preschool IQ tests (e.g. WPPSI, Wechsler 1992) and general developmental scales, for instance, the McCarthy Scales (McCarthy, 1972). These assessment tools focus on the child's verbal understanding and expression, basic problem solving skills and fine motor skills. Assessment of specific cognitive skills such as memory and attention are difficult in this age range as children tend to have a short attention span and are limited by their understanding of task instructions and verbal ability. Table 1 provides a summary of studies that have formally assessed general cognitive function in young PB children.

Table 1: Summary of studies reporting on PB children's outcome at 4-5 years of age

Author	Age (years)	GA / BW	N	Outcome score (population mean 100)	Measure used
Doyle et al., 2001	5	23-27 weeks	221	15% had <2 SD below control	WPPSI-R
Hansen et al., 2002	4	<1500g / <2500g	241	103/110	McCarthy Scales
Herrgard et al., 1993	5	1392g / 29 weeks	60	110	WPPSI
Luoma et al., 1998	5	<32 weeks	46	115 vs 123 (control)	WPPSI-R
Mutch et al., 1993	4.5	<1000g/<1500g/ <1750g	611	92 / 92 / 93	British Ability Scales
Sajaniemi et al., 2001	4	<1000g	112	92	WPPSI-R
Wood et al., 2000	2.5	<26 weeks	283	80	Bayley Scales

The general finding in this age range is an effect of gestational age or birthweight on cognitive ability. However, studies vary in inclusion criteria, assessment methods and outcome. Effect Sizes[1] vary and are not always representative of a statistically significant difference in IQ. McCarton, Wallace, Divon and Vaughan (1996) assessed PB children between the ages of 1 and 6 years on the Bayley Infant Development Scales (BSID-II, Bayley, 1993), the Stanford Binet Scale (Thorndike, Hagan, & Settler, 2003) and the WPPSI-R (Wechsler, 1990). There was a significant difference in scores between the PB and TB children across all ages. A similar result was obtained by Doyle (2001) who assessed 5 year old PB children on the WPPSI-R. The prognosis of outcome in these children was found to vary with GA, which ranged from 23 to 27 weeks. In a group of EPB children (less than 25 weeks) Wood, Marlow, Costeloe, Gibson and Wilkinson (2000) found impairments on neuromotor function, psychomotor development, as well as sensory perception and communication skills. The assessments were carried out using Bayley Infant Development Scales and a neurological examination. Collectively these studies show a general impairment in functioning which is closely related to the child's gestational age at birth. Few studies report particular deficits, though Harvey, O'Callaghan and Mohay (1999) have attempted to specify some of the difficulties faced by PB children between birth and four years of age. Children were administered a range of tests including the Peabody Picture Vocabulary Test Revised, Tower of Hanoi, a finger sequencing task and a tapping task. In addition to the usual finding of general mild to moderate cognitive impairment, these authors report difficulty in tasks which assess planning (using the Tower of Hanoi) and inhibition (using The Tapping Task) ability. This finding of EF difficulties is more commonly reported in studies of older PB children, which is discussed in Section 3.5.4.

[1] Effect Sizes (Cohen's d, Cohen, 1992) are reported for studies in which authors provided necessary information in article.

3.3 Middle Childhood and Adolescence (5 – 15 years)

During middle childhood and adolescence, PB children are reported to be underachieving at school, to attain IQ scores lower than their TB peers, as well as to achieve lower scores on tests of different cognitive functions such as attention, memory and visuo-motor integration. Research reporting such difference in outcome is discussed in this section.

3.3.1 General cognitive ability, academic achievement and special educational needs.

Several studies have examined the incidence and nature of general cognitive impairment in prematurely born children, and the general finding is that even those children who were premature and of very low birthweight, who do not suffer from any severe impairments are more likely than TB and normal birthweight children to have impaired cognitive functioning. Table 2 summarises a large sample of studies which assessed general IQ.

Table 2: Summary of studies reporting IQ outcome of PB children at 6-12 years of age

Authors	Age	BW / GA	N	IHV	CLD	IQ
Aram et al., 1991		<1500g	249			Mean = 95
Bohm et al., 2002	5.5	<27 / <32 wks	72 / 54 (controls)			Mean = 93 / 99
Botting et al., 1997	12	<1500g / <30wks	138			Mean = 84 / 91
Bowen et al., 2002	8	893g / 27wks	82			Mean = 100
Breslau et al., 1994	6	<2500g	473			Mean = 93 (urban) / 106 (suburban)
Frisk & Whyte, 1994	6 yrs	<1000g / 24-29wks	68	yes IV n = 16		80+
Gabrielson et al., 2002	10	1060g / 27wks	51			Mean = 89
Hack et al., 1991	8	<1500g	249			Mean = 97 / 84
Hack et al., 1994	school	<750 / <1500g	68 / 65			ELBW: 21% <70; LBW: 8% >70
Hall et al., 1995	8.8	<1000 / <1500g	324			Mean = 90 / 93
Horwood et al., 1998	7-8	<1000 / <1500g	77 / 221			<85 32% / 10%
Isaacs et al., 2000	13	998g / 28wks	11			Mean = 91
Johnson & Breslau, 2000	6/11	<2500g				80-99 37% <80 15%
Largo et al., 1990	5 / 7	preterm SGA / AGA	250			Mean = 101 / 102
McCarton et al., 1996	6	<37wks	129			Mean = 91 / 85
Ment et al., 2003	6/8	962g / 28wks	368 / 296	3% Grade IV	45%	Mean = 93 (no IVH) / 96 (IVH) 90 / 94
Nickel et al., 1982	10.6	<1000g	25			Mean = 90
Peterson et al., 2000	8	<1250g	26			Mean = 93

Ross et al., 1991	7.5	1192g / 29.3wks	88			Mean = 105 / 86
Rose et al., 1996	11-12	1153g / 31.2wks	50		8Days O_2	difference of 10 points
Roth et al., 2001	14-15	1282g / 30wks	150			Mean = 97 / 62
Saigal et al., 1991	8	<1000g	143			Mean = 91
Stjernqvist & Svenningson, 1999	10	1042g / 27wks	58	11%		Mean = 94
Sykes et al., 1997	7.43	1272g / 30.4wks	221			Mean = 99
Taylor et al., 2000	7	<750g/ <1500g	60 / 55	30% / 20%	43% vs 11%	Mean = 78 / 89
Whitfield et al., 1997	8.6	730g / 26wks	115			Mean = 98.7
Wolke & Meyer, 1999	6.3	1288g / <32wks	264			84-87

Table 2 summarises 27 studies which have assessed PB children on IQ (and other measures not reported here, see Section 3.3.2 – 3.3.4). Mean IQ ranges between 80 and 110 points (Population mean 100, SD 15) which is within low average (80-90) and average (90 – 110) bounds. Studies vary on inclusion criterion (birthweight, gestational age) and the age of the children at assessment. All studies excluded children with physical disability, however only few studies specified whether children had a diagnosis of IVH. Variables that affect IQ outcome are SGA (McCarton et al., 1996), head circumference (Hack, Breslau, Weissman, Aram, Klein, & Borawskiclark, 1991), and IVH grade III or above (Ment, Vohr, Allan, Katz,Schneider, Westerveld, et al., 2003). Many studies report a gradient relationship between birthweight or gestational age and IQ (Hall, McLoed, Counsell, Thomson, & Mutch, 1995; Horwood, Mogridge, & Darlow, 1998; Hack, Taylor, Klein, Eiben, Schatschneider, & Mercuri-Minish, 1994; Taylor, Klein, & Hack, 2000; Bohm et al., 2002; Hansen, Dinesen, Hoff, & Greisen, 2002).

Based on the information from the studies summarised above, PB children tend to achieve IQ scores within the low average range (i.e. group means are around 90). This shift in mean score may either be a reflection of a shift in the normal distribution of scores amongst PB children, or it may be due to subgroups of PB children achieving much lower IQ scores, resulting in a skewed distribution. As studies do not generally report both median and mean scores, it is not possible to determine an impression of the shape of the distribution of scores. In one study (Bohm et al., 2002), frequency distributions are presented, and these do indicate a skewed distribution for the PB children. This suggests then that some PB children do attain scores in the high end of the normal IQ distribution, but that a subset of children achieve very low scores which cause the reduction in mean scores. This profile is reflected in the higher than usual rate of PB children's underachievement at school and the requirement of special educational assistance.

Recently Hack, Taylor, Klein and Mercuri-Minich (2000) have assessed functional limitations (such as the requirement for Special Educational Needs) of extremely low birthweight children at the age of 10 - 14 years. Specifically they examined the rates of disability and special needs encountered by these children. They found that their PB group of children had significantly higher rates of functional impairments than did the TB group of control children. Increased services and compensatory aid other than a greater need for glasses included special education, counselling and special arrangements in school. This finding is striking evidence that extremely low birthweight is a predictor of PB children's functional limitations during middle childhood.

The literature describing academic achievement related to premature birth is immense, and diverse in terms of participant pools, and assessment protocols. Amongst the commonly cited pieces of research is The Scottish Low Birthweight Study. In this large-scale study, a cohort of very low birthweight children in a regionally defined area was assessed. Part of the investigation was to record children's school attainment during the first few years of primary school. Hall et al. (1995) have reported the results of this assessment. Children were tested on a variety of cognitive and motor function tests, and also on tests of basic number skills and word reading. While 15% of the very low birthweight and 6% of the low birthweight children were in special schools (some due to blindness or deafness, others due to cerebral palsy), significantly more LBW children were judged by teachers as requiring special kinds of help at school. Special educational needs (SEN) were identified in 10% of the ELBW and 4% of the LBW children. As a comparison, 1% and 0% of children were identified as requiring SEN in the two control groups (two matched control children were selected for each PB child, resulting in two control groups). This aspect of the study showed that low and extremely low birthweight children are very likely to have problems at school, resulting either in the need of some special arrangements, or as a diagnosed learning difficulty.

A similar incidence of special educational needs at school was also observed in some earlier studies. Saigal et al. (1990), for instance, asked teachers to rate the school performance of VLBW children. Forty-three percent of the children were considered to perform below average, while 19% were receiving special assistance at school at age five. Similarly, Ross, Lipper and Auld (1991) assessed PB children for educational achievement and on some cognitive measures. The finding was that amongst PB children, 48% required some manner of special educational arrangement at school. Of these children, 60% were diagnosed as being neurologically abnormal or had IQ scores below the average range. There is convincing evidence that low and particularly very low birthweight children are faced with some form of adverse sequelae of their high-risk birth status. Furthermore, this seems to be apparent even into the middle school years (Taylor, Klein, Minich, & Hack, 2000).

Many studies have used teacher report, grade repetition and special needs requirements as an index of cognitive function and outcome. While these provide a useful indication of the child's school progress they offer only predictive value about the child's long-term cognitive function, and academic achievement. Pharoah, Stevenson and West (2003) compared low birthweight children to normal birthweight children by their GCSE results. Children in the LBW group all attended mainstream school and were without major disability. School and social variables were closely matched, and amongst the LBW and NBW pairs, the low birthweight children scored significantly fewer points on their GCSE examinations than their normal birthweight partners. The authors conclude that foetal or postnatal factors which may have an impact during a phase of rapid cerebral development are more likely to mediate later outcome than social factors during school age. The difference in GCSE scores does hold implications for PB student's further education and employment prospects.

3.3.2 Visual Spatial Integration and Visual Motor Skills

Several authors have included tests of visual spatial integration in their assessment of PB children (Damman, Walther, Allers, Schroder, Drescher, Lutz, et al., 1996; Foreman, Fielder, Minshell, Hurrion, & Sergienko, 1997; Whitfield, Eckstein Grunau, & Holsti, 1997). Visual-spatial integration (VSI) refers to the ability to see a shape or figure as a whole as well as identifying its component parts. An example of VSI is the ability to distinguish between the letters "P" and "R". The letters differ on a small detail in their shape. An example of a VSI task is the Block Design subtest on the WISC-III which requires the child to break down the target pattern into useful segments in order to copy it using the blocks. Tests of visual motor integration (VMI) may consist of a set of increasingly complex geometric shapes, which the participant is asked to copy by hand without the use of a ruler. Scoring is based on the accuracy of the drawing, i.e. inclusion of relevant components, and appropriate spacing and orientation with respect to the other components.

Damman et al. (1996) assessed PB (mean GA 30 weeks) children at 6 years of age on tests of VMI, and reported that PB children performed below average across these tests (Effect Size, d = 0.45). Similarly Foreman et al. (1997) assessed PB children (mean GA 29 weeks) at 5-6 years of age and found that by this age children presented with a normal developmental pattern and satisfactory visual perception, but did have significant problems with visual-spatial attention and hand eye coordination. In addition to problems with VMI, Whitfield et al. (1997) also reported difficulty with both fine and gross motor function in PB children (mean GA 26 weeks) at the age of 8 years (Visual memory d = 0.68, VMI d = 1.54). These studies demonstrate that across the range of gestational age, PB children do have difficulty with tasks that involve VMI and related skills such as eye-hand coordination and motor skills.

3.3.3 Memory and Language

As discussed previously, the hippocampus is considered an area vulnerable to hypoxic damage for which PB children are at an increased risk. Research has addressed the level of damage caused to the hippocampus in these infants, and its consequences to memory function.

Memory is broadly classified into four types, episodic memory which refers to memory of events, semantic memory or acquired knowledge, short term memory used, for instance, to remember a telephone number to write it down and finally working memory, which is related to short term memory but requires the stored information to be manipulated mentally, as in a mental arithmetic task. Memory impairments have been related to learning as well as language difficulty. Short term and working memory have, for instance, been associated with vocabulary acquisition (Gathercole & Baddeley 1993).

There is evidence to suggest that amongst PB children there is a higher incidence of memory difficulties compared to TB children. Isaacs et al. (2000) have investigated the relationship between the hippocampal volume of PB, VLB children, and the level of their everyday memory capacity as measured by the Rivermeade Behavioural Memory Test for Children (Wilson, Ivani-Chalian, & Aldrish, 1991). The PB group did have significantly smaller hippocampal volumes than the term control group, and showed specific deficits in everyday (episodic) memory. Similar results were obtained by Briscoe, Gathercole and Marlow (2001) who assessed PB children at age 5 using the same assessment tool and concluded that PB children had a higher risk of everyday memory difficulties (d = 0.58). Furthermore, memory performance was closely linked to receptive language capacity, and was not found to be associated to the general cognitive status of these children. Similarly in an earlier study (Briscoe, Gathercole, & Marlow, 1998), this group suggested that PB children are at risk of specific language impairments, and that this is in accordance with their depressed performance on tests of short term memory.

Similar results were found by a different study group and using alternative assessment tools. Rose and Feldman (1996) used the Cognitive Abilities Test (CAT; Detterman, 1990) which assesses both memory ability and processing speed. PB children were found to show deficits across all measures of memory (d range 0.59 - 0.76). Furthermore, there was a close relationship between memory performance and the severity (if any) of a child's neonatal respiratory distress syndrome. A higher level of respiratory distress syndrome (RDS) would imply a greater risk for hypoxia, which as mentioned earlier increases the risk for hippocampal damage and resulting memory impairments. These children did however, also show depressed performance on processing speed (not motor speed) compared to their TB counterparts (d = 0.05 – d = 0.38). Both processing speed and memory impairment were found to account statistically for the difference in IQ score observed between prematurely born and term born children. Processing speed is considered to be closely related to general cognitive function (Rose & Feldman, 1996), so will not be discussed further in any detail.

3.3.4 Attention and Behaviour

Prematurely born children are commonly reported to have attention and behaviour problems. The assessment of attention is generally aimed at identifying symptoms of inattention comparable to those seen in AD/HD, including, for example, difficulty concentrating, not listening when others are speaking, and not paying attention to detail. Parental and teacher report questionnaires are often used to assess attention, though some studies also use psychometric tests such as the Continuous Performance Task. Table 3 below provides a summary for studies addressing attention and behaviour problems in prematurely born children.

Table 3: Summary of studies reporting behaviour outcome of PB children at 4-15 years of age

Authors	Age	BW/GA	N	Attention & Behaviour	Outcome
Botting et al., (1997)	12	<1500g / <30weeks	136	CAPA, BAC, CMAS-R, MFQ, Rutter Scale, Connors 10 item	23% VLBW met criteria for ADHD vs 6% of controls
Breslau & Chilcoat, (2000)	11	<2500g	717	CBCL	attention probs in urban LBW vs suburban
Doussard-Roosevelt et al., (2001)	6-9	<1500g	20	CBCL	BW / medical risk did not predict behaviour, indication of social competence problems
Hemgren & Peterson, (2002)	3	<32weeks	221	Combined assessment of motor performance and behaviour	No difference between groups
Horwood et al., (1998)	7-8	<1500g	298	Rutter Scale, Conners Scale	Sig higher rates of behaviour problems in VLBW vs control (Inattention & Hyperactivity)
Hille et al., (2001)	8-10	<1000g	408	CBCL	ELBW higher total problem score, social and attention difficulties.
Ong et al., (2001)	4	1251g / 31weeks	116	CBCL, PSI	Behaviour problems predicted by stress index, maternal age and IVH. (no control)
Pharoah, (1994)	8-9	<2000g	233	Rutter Scale, Conner Scale	36% LBW vs 22% control had behaviour difficulty, sig difference
Robson & Cline, (1998)	5	<2500g	83	CPT, MFFT, CBCL	SGA attentional difficulty, both hyperactive

					behaviours
Roth et al., (2001)	14-15	<33 weeks	150	Rutter Scale	Behaviour not correlated with status at 1 yr. but see also Stewart, 1999
Stjernqvist & Svenningsen, (1999)	10	<1500g / <29weeks	61	CBCL, HSQ-r	PB vs TB: 32% vs 10% behaviour problems, 20% vs 8% ADHD.
Sykes et al., (1997)	7-8	<1500g	243	CBCL	VLBW had sig. more attention problems than controls.
Szatmari et al., (1993)	7-8	500g-1000g	129	CBCL, items from DSM-III	9.7 % ELBW vs 0.7% control had ADHD type symptoms

CAPA: Child and Adolescent Psychiatric Assessment (Angold et al., 1995)
BAC: Behaviour and Activities Checklist (Olweus, 1989)
CAMS – R: Child Manifest Anxiety Scale –Revised (Reynolds & Richmonds, 1978)
MFQ: Mood and Feelings Questionnaire (Costello & Angold 1988)
Rutter Scale (Rutter 1967)
Conners 10 item (Conners 1969)
CBCL: Child Behaviour Checklist (Achenbach 1991a)
PSI: Parenting Stress Index
CPT: Continuous Performance Test
MFFT: Matching Familiar Figures Test
HSQ-r: Home Situation Questionnaire revised (Barkley 1990)

Both externalising and internalising behaviour problems, as well as attention difficulties are often reported for PB children (Botting, Powls, Cooke, & Marlwo, 1997; Breslau & Chilcoat, 2000; Pharoah, Stevenson, Cooke, & Stevenson, 1994; Roth et al., 2001; Stewart et al., 1999; Szatzmari, Saigal, & Rosenbaum, 1993). Some studies have suggested that behaviour difficulties are severe enough to reflect AD/HD in certain PB children (e.g. Botting et al., 1997; Stjernqvist & Svenningsen, 1999; Szatzmari et al., 1993).

Hemgren and Peterson (2002) report attention difficulties in their group of low birthweight children. This is reported as an observation made during the assessment of these children's motor performance. Other studies have made similar qualitative observations, however few have addressed attention skills specifically in PB children. Breslau and Chilcoat (2000), assessed attention problems using the CBCL parent and teacher report for their cohort of 11-year old PB children. An excess of attention problems was reported for the premature group, however, this finding was stronger in those children who lived in urban (d = 0.4) rather than suburban (d = .19) areas (for maternal report). The authors conclude that while prematurity poses a biological risk for attentional deficits, this effect is moderated by the child's environment. In other words a positive SES environment may have a protective value against the risk of attentional problems.

In contrast to the relatively few studies on attention difficulty in PB children, researchers have paid more attention to the behavioural difficulties that these children may face. Reviewing the relevant literature suggests that this increased research interest is driven by theories of attachment in early infancy, during which time normal maternal bonding may be disrupted due to the nature of the medical needs of the infant. Furthermore, behavioural differences are more salient than particular deficits in attention skills, which may only be evident in certain educational and other demanding situations.

In a ten year follow-up study of children born before 29 weeks GA, Stjernqvist and Svenningsen (1999) reported that at age ten, 32% of the PB cohort had general behaviour problems. Assessment tools included the Achenbach Child Behaviour Checklist. Pharoah et al. (1994) reported that significantly more PB children scored highly on behaviour difficulties on parent and teacher ratings of behaviour using the Rutter Behavioural Scales (Rutter, 1970). Similarly, Sykes, Hoy, Bill, McClure, Halliday and Reid (1997) compared teacher rated school adjustment of PB and TB children using the Achenbach Child Behaviour Checklist (Achenbach, 1991). Measures of IQ and school performance were included in the analysis. The PB group expressed more behavioural problems (d = 0.09), were less well adjusted (d = 0.11) and were considered to have poorer self-regulatory abilities (internalising d = 0.3; externalising d = 0.08). The effect sizes for this study were small, however, due to a large sample size (N = 243) the differences were statistically significant. Poor school performance and learning were closely associated to behaviour problems, and contributed significantly to the statistical multivariate effect. These results suggest that behavioural difficulties are part of a developmental profile observed in many PB children however, the effect sizes show that this effect is subtle, suggesting that behavioural abnormalities are present but slight.

Many of the studies reporting behaviour difficulties refer to school age children. One of few studies addressing behaviour in older children is that of Stewart et al. (1999). This group assessed behaviour problems in a group of adolescents. Part of their investigation into brain structure in PB children involved relating abnormalities evident on adolescents' brain scans to behavioural difficulties. Twenty-seven percent of fourteen and fifteen year old PB adolescents whose brain scans showed abnormalities were also exhibiting behavioural problems (compared with 20% of those with equivocal scans and 11% of those with normal scans). The study group concluded that such structural abnormalities in PB adolescents are more likely to manifest themselves in behavioural problems than in neurological difficulties. Although this study provides evidence that behavioural problems may be sustained into adolescence, the children were enrolled in the study due to a medical history of brain abnormalities which were secondary to premature birth. It is not clear whether behaviour problems would also be evident in PB adolescents without a history of minor abnormality detected on brain scans.

Wolke (1998) published a report on the psychological development of PB children, which effectively draws together evidence from the domains of cognitive development, behavioural and emotional development, social functioning and school adaptation. Schooling problems are reported as ranging in prevalence from 12 to 51% across 13 different studies. There is evidence to suggest that PB children and their mothers have difficulty with dyadic interaction, which can result in either over-stimulation or excessive passiveness on the mothers' part. Later in life, these children are reported to have more problematic relationships with their peers. Those children with multiple cognitive and behavioural problems are at the greatest risk. Behavioural problems most often fell into the hyperactivity/attention deficit spectrum.

3.4 Interim Summary

The research outlined in the above discussion consistently reported that children who were born prematurely are considered a high risk group for mild to moderate developmental delay and cognitive deficit. These deficits are thought to be a result of premature birth, and the associated neonatal risk, though some authors also suggest psychosocial factors to be predictive of prematurely born children's later outcome.

Taylor, Burant, Holding, Klein and Hack (2002) investigated sources of variability in the outcome of 11 year old very low birthweight children using structural equation modelling. Taylor et al.'s model is reproduced in Figure 1. Low birthweight and SES are included as risk factors which predict cognitive sequelae (both non-verbal and verbal). The risk factors have both a direct effect and an indirect effect via cognitive sequelae on the achievement sequelae "mathematics" and "reading".

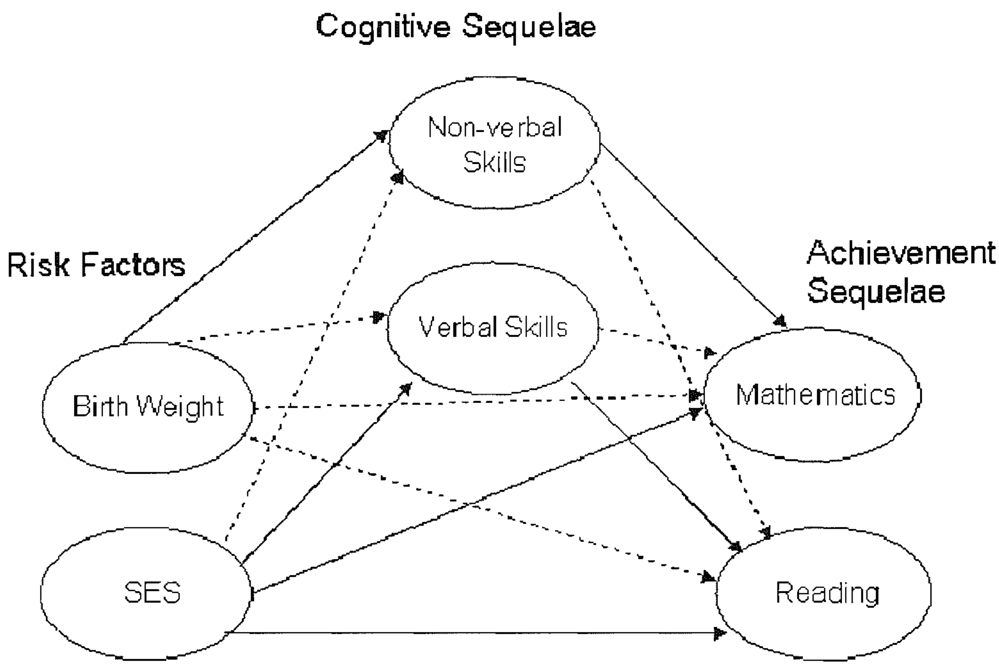


Figure 1: Model of hypothesised relationships of risk factors with cognitive and achievement sequelae of low birthweight. Taylor et al., 2002.

The model shows that as predicted, neuropsychological skills mediate the relationship between risk factors and achievement outcome. Taylor et al. suggest a differential deficit hypothesis, by which several sources of risk predict neuropsychological outcome. In the tested model, low birthweight was a stronger predictor of non-verbal skills and ultimately mathematics, while low SES had a greater impact on verbal skills and thereby later reading achievement. Similar findings are described by Wolke and Meyer (1999).

Wolke and Meyer (1999) report outcome of very prematurely born children on a range of measures and concluded that very premature birth often results in multiple cognitive deficits, which are due to pre- or neonatal treatment rather than social factors. Children's cognitive score reflected a general deficit in simultaneous information processing. It is thus suggested that the multiple cognitive problems that VPB children experience are largely a result of a deficit in the ability to perceive, process and integrate different sources and types of information at the same time. Integrating multiple sources of information is one aspect of higher order cognitive functions, referred to as Executive Functions.

Executive Functions have been the focus of a large amount of developmental research, and have not been extensively studied in PB children. The next section will discuss some research into normal development of executive functions, as well as some examples of executive dysfunction in paediatric populations.

3.5 Executive Functions

Executive functions are a set of skills which are thought of as higher order cognitive functions. The term refers to a cluster of skills, which include purposeful, goal directed activity, planning ability in a behavioural and problem-solving sense, and working memory (the ability to mentally manipulate information held in short term memory). Flexible cognitive style and attentional control (prioritising the importance of stimuli for instance) are further features of EF. The study of EF originated in adult neuropsychology, with respect to the loss of particular functions following frontal lobe injury. It is important not to use the terms Executive Functions (EF) and Frontal Functions synonymously, because although many EF are mediated by the frontal lobes, other brain areas such as the basal ganglia, hippocampus and striatum have connections with the frontal lobes and are therefore important to intact EF (Robbins, 1998).

3.5.1 Models of EF

Executive Functions have been described in two distinct frameworks. One view is that EF describes cognitive functions which are unified by an underlying concept. Barkley (1997), for instance, describes a unified model of EF which emphasises the role of inhibitory control as the main component of EF. He argues that inhibitory control is required for appropriate functioning of all skills associated with EF such as working memory and planning. Alternative to this view are fractionated models which dissociate different cognitive processes within the umbrella term EF (e.g. Shallice, 1982). Most fractionated approaches identify at least three underlying EF factors. Welsh, Pennington and Groissier (1991), for instance, describe working memory, inhibitory control and attentional flexibility as the three skills underlying EF. Denckla (1996) adopts a similar approach suggesting that the functions within the domain of EF need not be strongly associated with each other, rather that there are distinctive factors which underlie EF.

Recently, Miyake, Friedman, Emerson, Witzki, Howerter and Wagner (2000) used confirmatory factor analysis in order to investigate the factor structure underlying EF. The authors used a battery of common EF tests such as the Wisconsin Card Sorting Test (WCST), Tower of Hanoi (TOH), random number generation, operation span and dual tasking. Using confirmatory factor analysis, three factors were identified which the authors described as "shifting", "updating" and "inhibition". The factor correlations were as follows: shifting / updating $r = 0.56$; updating / inhibition, $r = 0.63$; and shifting / inhibition, $r = 0.42$. The authors stress the importance of identifying both the unity and the diversity of EF. This becomes particularly evident when studying EF in a developmental context.

3.5.2 Normal development of Executive Functions

The interest in early development of EF has emerged more recently, mainly because the capacity for EF was thought to develop relatively late in childhood, and was considered an adult cognitive function (Golden, 1981, cited in Anderson V., Anderson P., Northam, Jacobs, & Catroppa 2001). Developments in the assessment methods and materials have resulted in ways of testing EF in children using more child-friendly and easier tests, while maintaining the core aspects of EF. In addition, the developmental course of EF has been related to brain development, in particular the maturation of the frontal lobes and the associated circuitry with other brain regions. Executive Functions now play a central role in the cognitive models for several neurodevelopmental disorders including AD/HD and autistic spectrum disorder.

There is some difficulty determining the normal course of the development of EF for two main reasons. The first relates to testing each set of skills in children of different ages. The assessment measures used for IQ measurement necessarily vary in focus from Sensorimotor skills in infancy, to verbal skills in preschool age, and reasoning skills during middle childhood. This shift is required to match the capacity to express cognitive attainment changes with age. Elements of EF such as inhibition can be detected and assessed from an early age, and the core skill being assessed remains the same, but tests are adapted for different ages. Secondly, some developmental psychologists argue that EF are closely linked to general intelligence and that they are an underlying and necessary requirement for the progression of intellectual development (e.g. Duncan, 1995; Russell, 1999). For these reasons, making the distinctions between the three main EF domains inhibition, working memory and flexibility (Miyake, 2000) is more difficult.

While there is no stage like framework to describe the development of EF, by the age of around 9-10 years, children are thought to have acquired a nearly adult level of functioning. The development is considered complete by the age of 12 years. Children between the ages of 8 and 13 years can solve most tests of executive function and a factor structure parallel to that of Miyake (2000) can be established from their performance (Lehto, Juujarvi, Kooistra, & Pulkinnen, 2003; Pennington, 1997). Working memory, inhibition and shifting/cognitive flexibility have been considered as the underlying factors. Developmental trajectories of EF are thus characterised by temporal differences in the maturation of these underlying factors. The emergence of adult-levels of the different EF dimensions are discussed in Luciana, Lindeke, Georgieff, Mills and Nelson (1999), and will be considered further in Sections 5.3.2 and 5.5.

3.5.3 Executive dysfunction in childhood developmental disorders

Executive dysfunction has been studied in childhood developmental disorders such as autistic spectrum disorder and AD/HD. The behavioural profiles typical of these disorders are characterised to various degrees by difficulties with inhibition, working memory and flexibility.

Autistic spectrum disorder is a pervasive developmental disorder characterised by three primary deficits: impairment in communication, impairment in social interaction and repetitive and stereotyped patterns of behaviour. Executive dysfunction in autism is described primarily as a difficulty with cognitive flexibility (set shifting) which is described as a tendency to perseverate (Hughes & Russell 1993; Hughes, Russell, & Robbins, 1994). Furthermore, the lack of a "Theory of Mind" reported in children with autistic disorder has recently been considered in the light of EF. In normally developing preschool children, the development of Theory of Mind is closely tied to increased executive control (see Perner, Kain & Barchfeld, 2002), and the lack of Theory of Mind in autistic individuals may be associated with their difficulty with integrating multiple sources of information.

Attention Deficit Hyperactivity Disorder is a childhood developmental disorder characterised by inattention, impulsivity and hyperactivity. AD/HD is classified as three types: predominantly hyperactive, predominantly inattentive and combined type (Barkley, 1997). The disorder is characterised by inattention, a hyperactive behavioural style, and cognitive difficulties, particularly on EF dimensions and attention (Barkley, 1997; Clark, Prior, & Kinsella, 2002; Heaton et al., 2001; Shallice, 2002). Children with ADHD are reported to have difficulties mainly with inhibition and cognitive flexibility and less marked problems with tests of Working Memory, as well as an impulsive behavioural style (Sonuga-Barke, Dalen, & Remington, 2003).

3.5.4 Executive functions in prematurely born children

Only few studies of cognitive outcome of PB children have addressed the development of EF. Five studies have been identified which have assessed PB children on various domains of EF. Although the inclusion criteria varied from PB children with no neurological sequelae to extremely PB children with periventricular damage, the results consistently show that PB children perform worse compared to their peers on tests of EF.

Frisk and Whyte (1994) assessed PB children on working memory tasks. The study groups consisted of PB children with periventricular lesions, a group of premature children with no lesions, as well as a TB control group. Only the group of children with periventricular lesions were found to perform significantly worse on working memory tests, the PB children with no lesions performed at a level comparable to TB children (Effect sizes could not be calculated as standard deviations were not presented). The authors conclude that children with periventricular lesions are likely to have sustained damage to the caudate nucleus, which in turn may interfere with fronto-striatal connections. These connections are essential for effective executive functioning, of which working memory is a part.

More recently, Harvey et al. (1999) have assessed prematurely born children on a comprehensive battery of EF tests. Their study group consisted of children with extremely low birthweight (<1000g), who were aged between 4 years 6 months, and 5 years 6 months, at the time of assessment. The Tower of Hanoi, finger sequencing and tapping test were administered. Compared to TB control children, the study group showed inferior performance across all three tests (differences were statistically significant, but effect sizes could not be calculated as standard deviations were not presented). The authors suggest that poor EF may influence later learning ability, and therefore be considered a mediator between low birthweight, and later learning deficits. It is important to consider that those children who were born with extremely low birthweight, are also at higher medical risk, more often sustain brain injury, and tend to require longer periods of ventilation and oxygen therapy. It is reasonable to assume that ELBW is a marker for higher neonatal risk, and associated risk of disruption of the cerebral development, both of which are responsible for later cognitive difficulty.

Espy, Stalets, McDiarmid, Senn, Cwik and Hamby (2002) studied PB children of a younger age, and assessed their EF abilities. Twenty-nine children aged between two and three years of age and born at mean gestational age of 32 weeks were assessed using delayed response paradigms (delayed alternation and spatial reversal). Prematurely born children were found to achieve lower scores on a test of delayed alternation and made more perseverative errors, compared to a group of TB control children (again no effect sizes were calculated as standard deviations were not reported). Delayed alternation is a measure of working memory whereas spatial reversal is a task requiring shifting and cognitive flexibility. The authors report specific deficits with the working memory tasks, a finding consistent with that of Luciana et al. (1999) described below.

Luciana et al. (1999) assessed PB children (<40 weeks) at the age of 7-9 years. This inclusion criterion of less than 40 weeks gestational age is unusual, as premature birth is usually defined as less than 37 weeks GA (see Section 2.1). The children varied from being very low risk infants who were hospitalised for less than a week, to those with long-term chronic lung disease and IVH, who spent several months in neonatal care. The assessment battery consisted of EF subtests from the CANTAB (Cambridge Automated Test Battery), and included spatial working memory, spatial span, Tower of London and a cognitive flexibility (set shifting) task. The group of prematurely born children were found to under-perform compared to a control group on all tests of EF (effect sizes for these differences ranged between d = 0.2 to d = 0.6). Although no specific neonatal risk factors were identified in predicting EF performance, a composite measure of neonatal risk did predict several facets of EF performance. Luciana and her colleagues suggest that prematurely born children's poor performance on these EF tasks is proportional to the neonatal risk the child was exposed to. The authors discuss the interconnections between the frontal cortex, the caudate nucleus and the hippocampus, and how these may be at a specific risk of injury following hypoxia, IVH or periventricular leukomalcia.

Finally, Rushe et al. (2001) assessed PB children at the age of 14 and 15 years, to assess their functional status on various aspects of cognitive function, including EF. Information on the children's brain structure were available from a parallel study (Stewart et al., 1999). Although many of the prematurely born children had brain abnormalities such as ventricular enlargement and thinning of the corpus callosum, their performance on cognitive tests was not significantly different to that of controls for any tests except word production (d = -0.7). Their performance on the EF measure (Trail-Making B), was normal and comparable to their term born peers (effect sizes ranged between d = 0.2 and d = 0.3). This study suggests that there is the potential for prematurely born children to recover normal cognitive function even in the presence of structural brain abnormalities.

Although the studies presented above were heterogeneous with respect to the degree of neonatal risk experienced, the age of the children at the time of testing, and the type of assessments used to measure EF, the findings are consistently pointing to EF difficulties at least to mid-adolescence. Given the involvement of the caudate-striatal connections in EF, and the risk of damage to these areas in PB children, EF are an important area of study in this population. Addressing the level of brain insult alongside EF performance may provide insight into the potential for early plasticity of the caudate-striatal connections in addition to childhood and adolescent functional outcome of both EF and the cognitive abilities which rely on EF.

3.6 Conclusions

The review of the literature on outcome after premature birth confirms that PB children's development is affected throughout childhood and into adolescence. The degree of impairment is seen to range from mild or moderate in most cases and to severe in some cases, and seems dependent on several factors including the degree of prematurity and the severity of neonatal illness. The spectrum of deficits described includes general intellectual function, attention, memory, visuo-spatial skills and EF. Behaviour problems are reported frequently in PB children, alongside reports of general academic underachievement, and a higher rate of Special Educational Needs. EF have been addressed less consistently in PB children, however this area of cognitive function is important both in terms of its strong association with other functions via, for instance, cognitive flexibility and working memory, and via the influence of inhibitory control on behaviour.

CHAPTER 4

Methodology and Preliminary Study

This chapter provides an outline of the rationale and methodology used in the three studies described in Chapters 5-7, and reports the findings of a preliminary investigation. The studies involve four samples of children: the pilot study group, two groups of prematurely born children and adolescents, and a term born group. Children from the control group and the first PB group were assessed on two occasions approximately 18 months apart.

4.1 Rationale

In this section a justification for the study of EF and behaviour in prematurely born children will be outlined. Studying the outcome after premature birth is of importance and interest to several scientific and medical communities. As advances in neonatology continue to increase the viability of extremely prematurely born children, it becomes more important to study later developmental outcome of children born at different levels of prematurity. Not only does this help make a prognosis of likely later impairments but it can also aid ethical decision making with respect to repeated resuscitation of very ill infants. From the standpoint of paediatric neuroscience, the study of prematurely born children is valuable as it allows an insight into the effect of early insult on the developing brain. This may provide information on the capacity of the developing nervous system to recover from early injury, and can highlight maturational processes during which time disruption has differential impact. Finally, interventions and the study of protective factors such as responsive parenting may inform Neuropsychology to what extent the relationship between varying degrees of brain insult and behavioural outcome can be mediated.

Studies of outcome after premature birth tend to focus on general cognitive function. However, investigations which have addressed specific cognitive functions have concluded that impairments are often multiple and specific (e.g. visuo-spatial integration). Executive Functions have been investigated relatively less often than other domains (see Section 3.5.4). This is somewhat surprising given that EF are considered one of the central or higher cognitive processes. Many cognitive models attribute a high level of importance to EF in order for an adequate level of proficiency to be attained in other functional domains. Furthermore, when brain injury does occur, the typical nature and localisation in premature children would point towards disruption of Executive Functions. In this thesis the possible link between caudate damage as a result of intraventricular haemorrhage and periventricular white matter damage, and disrupted EF is suggested.

4.2 Aim

The aim of the project can be summarised in three sections. Firstly, to assess PB children on a battery of cognitive tests to establish a cognitive profile and to identify whether these children have particular difficulties with EF, memory and attention tasks, and elevated levels of behaviour difficulties in particular in the inattentive and hyperactive domains. Secondly, to explore which neonatal risk factors are useful in predicting later child outcome. Finally to investigate the relationships between IQ and EF and behaviour for these groups of children.

4.3 Methodology

4.3.1 Ethical approval and consent

Ethical approval for this study was obtained from the Southampton and South West Hampshire Local Research Ethics Committees and the School of Psychology Ethics Committee, University of Southampton. Informed written consent from each family was obtained.

4.3.2 Assessment measures

The studies used both child assessment measures and parent completed questionnaires. The complete child assessment battery was compiled to include tests of the following cognitive domains: general cognitive function, attention, executive function, semantic memory, episodic memory and visuo-spatial integration. The test measures were selected from the Wechsler Intelligence Scale for Children III UK (WISC, Wechsler, 1992), The Test of Everyday Attention in Children (Tea-Ch, Manly, Roberston, Anderson, & Nimmo-Smith, 1999). The Cambridge Automated Neuropsychological Test Battery (CANTAB, Cambridge Cognition Ltd), the NEPSY (Developmental Neuropsychological Assessment, Korkman, Kirk, & Kemp, 1998) a neuropsychological assessment battery for children, and The Rivermead Behavioural Memory Test for Children. (RBMT, Wilson, 1992). Standardised clinical tools were selected to avoid the recurring difficulty that arises from the modification of adult tests, as well as the use of unstandardised neuropsychological tests with a pediatric population. Many adult tests are not suitable for capturing developing skills, the task demands may be so high as to prohibit a child's ability to manage the test, and reduced versions of the tests may be so easy as to lose the measurement of the skill in question. Complex task instructions, for example, rely on a degree of verbal skills (which may be inappropriate for young children) and may require a certain level of verbal working memory. This may be inappropriate for those children with WM difficulties, and failure of a task may be due to misunderstanding the task instructions rather than the inability to complete the test. Brain-behaviour relationships in children may differ from those in adults. Test results from adult neuropsychological tests should therefore be interpreted with caution (Fletcher & Taylor, 1984; cited in Anderson, Northam, Hendy, & Wrennall, 2001).

Clinical measures may also be scrutinised for construct validity, however, standardised administration procedures, as well as the availability of normative data provide a more straightforward estimate of a child's ability compared to other children of the same age. Furthermore, data are available describing the performance of special populations, such as children with AD/HD, on these test measures. A secondary but nonetheless important issue is that clinical developmental measures are designed to be as child friendly as possible, and usually engage a child's interest well.

4.3.2.1 Wechsler Intelligence Scale for Children

While several tests of general cognitive function for children are available, the most commonly used test, WISC – III was selected for use in this study. The full version of the test requires up to an hour and a half of administration time, and several short forms have been suggested. As the present research question did not focus on IQ as a main measure, rather as a comparison standard, a short form yielding a pro-rated IQ has been selected. Short forms generally consist of four of the subtests for a reasonable level of reliability.

Spreen and Strauss (1998) provide a discussion of different short forms of the WISC-III. They conclude that in situations which require only estimates of IQ, the two and four subtest versions are most suitable, particularly in research settings. Hunter, Yule, Urbanowicz and Landsdown (1989) provided a cross-validation of short forms of the WISC-R in two British samples. Multiple regression of a four-subtest version including comprehension, block design, information and picture completion accounted for 88% of variance on comparison to results of full test administration. The regression equation: 1.60 X comprehension + 1.60 X block design + 1.58 X information + 1.37 X picture completion + 38.29. It is this latter combination of tests that is used in the present study. A study of validity of seven short forms of the WISC–III revealed that corrected validity lies between 0.70 and 0.91 for different subtest combinations. Amongst the most reliable are the four subtest versions for which validity ranges between 0.84 and 0.88 (Campbell, 1998).

4.3.2.2 Test of Everyday Attention in Children

The Tea-Ch was considered to be the most appropriate test of attention in children. The test is designed to place minimal demands on language and reasoning skills, in order to extract a pure measure of attentional skill. Three sub-domains of attention are covered: Sustained attention, attentional control, and selective attention.

The Teach consists of 9 subtests, and complete administration takes up to an hour and a half. However, a shorter screening version may be administered, using only the first four subtests. This short version includes the following:

Sky Search, a test of selective attention, requires children to find as many "target" spaceships as possible on a visual search task. The time taken for this task is recorded. A second part requires only circling the target spaceships in the absence of distracters. Subtracting the time taken for this task controls for motor speed.

Score is a test of sustained attention, and requires children to count scoring sounds on an audiotape. Due to the simplicity of the task and the long gaps between sounds, the task is not very engaging and requires the child to self-sustain attention.

Creature counting is a test of attentional control or switching, in which children switch between counting creatures upwards and downwards. The task involves counting creatures with arrows directing the direction of count. Both speed and accuracy are recorded in this subtest.

Sky Search DT is a test of sustained, divided attention. It combines the *Sky Search* task with *Score*. The child is asked to count the scoring sounds on the tape whilst simultaneously searching for target spaceships amongst distracters. Some children may show considerable decrement in performance in this dual task situation although performance on the individual tasks was satisfactory.

Two further subtests were included in the present test battery. *Walk Don't Walk,* a test of sustained attention, is a Go-No Go task, the child responds to a "Go" signal, and must inhibit the response to a "No-Go" signal. *Opposite Worlds* is a test of attentional control or switching and requires the child to read digits 1 and 2 both as normal, and opposite, in which case the child is asked to say "one" to digit 2 and "two" to digit 1. The time taken to complete trails of digits is recorded, and compared against normative data.

The authors of the TEA-Ch have described the performance of a normative sample of children aged 6-16 years on TEA-Ch subtests, and the relationship of attentional performance with IQ (Manly, Anderson, Nimmo-Smith, Turner, Watson & Robertson, 2001). Structural equation model of the results yielded a three factor model that describes the three aspects of attention (sustained, selective and attentional switching). The factor correlations were as follows: selective attention / attentional switching $r = 0.72$; attentional switching / sustained attention, $r = 0.60$; selective attention / sustained attention $r = 0.40$. This three model solution held even for the youngest children. Furthermore, in a sample of boys with an AD/HD diagnosis, deficits in selective attention were found which remained significant even when IQ was taken into account.

The TEA-Ch has been used for assessment of different patient populations, and is sensitive to the different attentional profiles of these groups. A study of paediatric traumatic brain injury (TBI), for instance, investigated whether cognitive deficits resulting from injury were global or specific to a particular cognitive domain (Anderson, Renwick, Manly, & Robertson, 1998). Results from the TEA-Ch showed that attention skills were differentially impaired in the TBI patients. This attentional impairment was specific to selective and divided attention. The opposite attentional profile was found amongst children with AD/HD, who were administered the

TEA-Ch assessment battery. These children showed impairments in sustained attention and attentional control but not in selective attention compared to a clinical group of control children (Heaton et al., 2001).

4.3.2.3 NEPSY

The NEPSY is a comprehensive neuropsychological assessment battery designed for use with children between the ages of 3 and 12 years. The NEPSY includes five functional domains: Attention and Executive Function, language, sensorimotor functions, visuospatial functions, memory and learning. Subtests can be used in any combinations according to the requirements of the clinical or research assessment.

Six subtests were chosen from the NEPSY battery: four from the Attention and Executive Function domain, one from the Visuo-Spatial Processing domain, one from the Sensorimotor Functions domain, and one from the Memory domain.

Tower is a test of inhibition (EF), conceptually identical to the Tower of London task (Shallice, 1982). Children are asked to match a target arrangement of three balls on a set of three poles, by moving the balls on their model in as few moves as possible, without violating any rules.

Design Fluency is a test in which children are asked to make up as many different designs as possible within a minute by connecting an array of dots. This test assesses flexibility and visuo-spatial processing.

Statue is a test of inhibition (EF) and requires children to stand still with closed eyes for one minute. Any sounds or movements made spontaneously or in response to four distracters cause point deductions.

Knock and Tap is another test of inhibition (EF). The child is asked to follow the action of the experimenter, first by copying the action, then by performing the opposite action (i.e. knock in response to tap). The number of errors is taken to count towards the score.

In the *Design Copying* task (visuo-spatial processing), children are asked to make as accurate a copy as possible of increasingly complex figures. Marks are deducted for missing elements, poor line orientation, and poor line straightness.

The *Finger Tapping* test (sensori-motor functions), requires children to first tap their thumb and index finger as quickly as possible, then tap their thumb with each of their fingers in turn as quickly as possible, eight complete trials are timed for both exercises and for both hands.

List Learning (semantic memory) involves 5 trials of learning a list of 15 words. The words are grouped into five semantic clusters (e.g. animals), and the child is asked to repeat as many words as possible following each exposure. After a 30 minute interval, delayed recall is measured.

The NEPSY subtests are reported as having moderate to high levels of internal consistency. Correlations with IQ measures (WISC-III) yielded moderate correlations especially between the language subtests of the two measures and between subtests that tap visuo-spatial integration. These correlations were similar when a sample of children diagnosed with AD/HD were assessed (Korkman et al., 1998). The NEPSY has been used in several studies addressing a wide range of childhood difficulties, such as outcome after premature birth (Bohm et al., 2002; Bohm & Katz-Salamon, 2003; Sajaniemi, Hakamies-Blomqvist, Katainen, & von Wendt, 2001; Westrup, Bohm, Lagercrantz, & Stjernqvist, 2004), cognitive performance in children with AD/HD (Perner et al., 2002), outcome after hemiparesis (Kolk & Talvik, 2000), as well as to document normal development of Executive Functions (Lehto et al., 2003).

4.3.2.4 CANTAB

CANTAB was originally developed for assessing cognitive aspects of dementia in elderly patients (Fray, Robbins, & Sahakian, 1996). The validity of the test for use in other adult patient populations has since been supported by numerous published reports and has more recently been tested for the use with pediatric populations (see Luciana, 2003 for review). The Cantab is a computerised assessment tool, utilising a touch screen response system. The test covers various non-verbal tests of EF (planning, set-shifting, and spatial working memory), and for the present assessment battery, three subtests were selected. In addition, the motor screening test was administered prior to the EF tests.

In the *Spatial Working Memory* test the child is presented with an arrangement of boxes on the screen, and is asked to find tokens hidden in these boxes. The task is to remember which boxes have held a token and not to search there a second time. The objective is to remember locations where tokens were previously found. The task begins with three boxes, and increases in difficulty to eight boxes.

Spatial Span requires the child to remember the location of a series of boxes presented on the screen. This tests starts with only 2 locations to be remembered, and continues with increasing number of boxes until three successive failures are recorded. The maximum span length is nine locations.

The *Intra-Extra Dimensional Shift* task is conceptually similar to the Wisconsin Card Sorting Test, in that the child is required to make sorting choices according to the shape of the stimuli. In this version of the task, there are two sorting categories (shape or line). The child is asked to point to one of two patterns presented, and if correct, continue pointing to this pattern until the rule changes, at which point the computer will indicate "incorrect" to a response which previously had been correct. Initially there are only shapes to decide between, however after six sets sorting to shape, the constraint will change to require a sort to the line pattern which is overlaid onto the shape starting from Set 4. The responses are recorded both for correct and incorrect sorts, as well as perseverative errors.

Luciana (2003) has appraised the CANTAB in particular and computerised assessment tools generally for use in paediatric neuropsychological assessment. The reliability of the CANTAB is reported to range from .73 to .95 in 4-12 year old children. Luciana suggests that children's performance on the spatial self-ordered search task (spatial working memory) provides information on the maturational course of the Prefrontal Cortex, an area closely implicated in self-ordered spatial search (Petrides & Milner, 1982). This particular aspect of Executive Function is not thought to reach adult levels until around 12 years of age. Set-shifting on the other hand improved drastically at the age of six years after which point improvement levels out. Spatial memory span follows a more gradual developmental course, with steady improvements (a sequence of 2 blocks at 6 years, 3 at eight years etc.) until 12 years of age after which children perform at adult levels.

The CANTAB battery has been used to describe the functional emergence of working memory in 4-8 year old children (Luciana & Nelson, 1998), to assess cognitive outcome of children born prematurely (Luciana et al., 1999) and to assess neurobehavioral functions in children who were hospitalised in intensive care during the neonatal period (for prematurity or other medical complications, Curtis, Lindeke, Georgieff, & Nelson, 2002).

4.3.2.5 Rivermead Behavioural Memory Test for Children

The Rivermead Behavioural Memory Test for Children consists of 9 subtests of everyday memory skills, and takes approximately half an hour to administer. The test is adapted and standardised from the adult version, for use with children between the ages of 5 and 10 years. The test consists of prospective memory tasks such as remembering the name of a person shown in a photograph, remembering an appointment and remembering a hidden belonging (within the 30 minute duration of the test). In a test of recognition memory, the child is presented with 10 line drawings of common objects (cup, pig), and later asked to recognise them from a set of 30 line drawings. Similarly, the child is presented with 5 photographs of people's faces, and after a filled delay asked to recognise these faces from 15 photographs. Prose recall involves a short story of 80 words which the child is presented once, and asked to re-tell as accurately as possible both immediately and after approximately 20 minutes delay. The route learning subtest requires the experimenter tracing a short route (5 items) around the room, and the child re-tracing the route both immediately and after about 20 minutes delay. In addition the child is asked to remember to deliver a message envelope on route at a specified location.

The standardisation sample consisted of 335 children evenly distributed between the ages of 5 and 10 years. The test manual does not provide information about validity and reliability of the measure. The RBMT has been used to assess everyday memory in clinical settings (e.g. childhood post-traumatic stress disorder, Moradi, Doost, Taghavi, Yule, & Dalgleish, 1999), and has often been used with prematurely born children (Briscoe et al., 2001; Isaacs et al., 2000; Isaacs, Edmonds, Lucas, & Gadian, 2001; Isaacs, Vargha-Khadem, Watkins, Lucas, Mishkin, & Gadian, 2003). For children and adolescents older than 10 years of age the Rivermead Behavioural Memory Test – Extended version (Wilson, Clare, Baddeley, Cockburn, Watson, & Tate, 1998) was administered. This version of the test has the same subtest structure as the children's version, but memory load and task difficulty are adjusted to be appropriate for adolescents and adults. Standardisation of test scores is available as for the children's version of the test.

4.4.3 Parent Report Questionnaires

4.4.3.1 Strengths and Difficulties Questionnaire (SDQ) parent report version (Goodman 1997)

The questionnaire consists of 18 statements of behaviour, and the parent is requested to indicate whether and to what degree this behaviour is typical of their child on a 3-point scale (1 = not true, 2 = somewhat true, 3 = certainly true; see Appendix A). The items fall into four behaviour difficulty categories (conduct problems, hyperactivity, peer problems, emotional symptoms) and one strength category (prosocial). The SDQ was considered to be a particularly appropriate test of behaviour, both because of its brevity, and because of the inclusion of a positive scale addressing strengths in a child's behaviour. The SDQ has been evaluated against the Child Behaviour Checklist (CBCL, Achenbach, 1991a) and was found to detect inattention and hyperactivity significantly better than the CBCL, and was equally as good at detecting internalizing and externalizing behaviours (Goodmann & Scott, 1999).

The questionnaire has been used in a variety of settings including Paediatric Health Psychology (Bream & Buchanan, 2003; Davies, Hayman, & Goodman, 2003; Procter & Loader, 2003), Clinical Psychology (Leavey, Hollins, King, Barnes, Papadopoulos, & Grayson, 2004; Thabet, Tischler, & Vostanis, 2004), Developmental Psychopathology (Brophy & Dunn, 2002; Glazenbrook, Hollis, Heussler, Goodman, & Coates, 2003) and Developmental Neuropsychology (e.g. Sonuga-Barke et al., 2003).

4.4.3.2 AD/HD questionnaire

DuPaul (1991) developed a rating scale which contains DSM-III-R items for Attention Deficit Hyperactivity Disorder. The scale consists of 14 items which correspond directly to the DSM-III-R criteria (see Appendix B for copy of the questionnaire). The questionnaire was initially completed by parents and teachers of a total of 264 children aged between 6 and 12 years. Validation and reliability were tested on a sub-sample of 55 children. Validity was tested using observational measures. A high level of reliability and an adequate level of criterion related validity (against the Conners Rating scale for instance) was achieved. DuPaul (1998) provides the factor structure of the parent rating scale across gender, age and ethnic group. The data are divided into the two factors an "Inattention – Hyperactivity" Subscale and an "Impulsivity Hyperactivity" subscale. The researchers found a higher frequency of AD/HD symptoms in boys, younger children and African-American participants. The scale has been used in recent research studies addressing AD/HD subtypes and source bias (self-, parent, and teacher rating) in relation to psychopathology (Burns, Walsh, & Gomez, 2003; Crystal, Ostrader, Chen, & August, 2001), and in relation to Executive Function deficits in children with Phenylketonuria (Antshel & Waisbren, 2003).

4.4.4 Calculation of Power and effect size

Based on the observed effect sizes in previous studies comparing cognitive test performance between prematurely born and term born children a Power Calculation was carried out to determine the necessary group sizes. For MANOVA analyses with power of .8 and an alpha of 0.05 at moderate effect sizes (d = 0.4 to d = 0.6, based on e.g. Luciana et al., 1999; Rose et al., 1996; Sykes et al., 1997), a group size of about 40 participants was determined (Cohen 1992).

4.5 Methodological issues

Some specifics of the methodology adopted in the thesis as a whole should be addressed. These include the initial selection of test measures, and preference for certain measures in subsequent analyses, as well as the issue of statistical and clinical significance.

4.5.1 Selection of Test Measures

Initially the research protocol included a large number of variables. The rationale for this was to be able to compare the overall cognitive profile of PB children in this study to the cognitive profiles of children reported in other studies. This served as a control to ensure that the sample of PB children recruited in this study was typical and representative of PB children with similar demographics from other samples. As a result of narrowing the research focus in the course of the three research studies, a number of variables were dropped from the analyses. The rationale for excluding certain variables (for example measures of visuo-spatial integration) was based on the research foci of Studies 2 and 3.

The benefits of standardised test measures compared to experimental paradigms include standardised administration procedures and published normative data, both of which increase the clinical significance of test results. The test selection resulted in multiple measures for each EF domain, however in many analyses only data of a selection of these measures are presented. The selection of measures for use in analyses was based on the evaluation of these measures in recent published work, as well as the similarity to experimental paradigms that have proved successful at assessing certain functions (e.g. the Walk Don't Walk test of inhibition is conceptually similar to many Go No-Go paradigms, and was therefore selected as the measure of inhibition used in Studies 2-3). The Intra-Extra Dimensional Shift task (cognitive switching) of the CANTAB, for instance, was a measure which was not selected in analyses subsequent to Study 1. The Creature Counting (cognitive switching) task of the TEA-Ch was considered favourable, as there was greater variance in scores (most children performed at ceiling on the Intra-Extra Dimensional Shift Task). A diagram illustrating the structure of the empirical work and summarising the participant groups and test measures of different studies is presented in Figure 2

I. PILOT STUDY

18 control children recruited from CHADS control sample

Full test protocol administered

→

II. STUDY 1a

40 PB children recruited from neonatal hospital records, 41 TB children recruited through local schools. Full test protocol.

→

III. STUDY 1b

Re-visit of PB and TB children from 1a, PB N = 30, TB N = 22

Measures: RBMT, Digit Span, ADHD questionnaire

→

IV. STUDY 2

PB children of Study 1 only. Neonatal data obtained from medical records. IQ, EF and behaviour from Study 1a.

→

V. STUDY 3

Analysis of IQ, EF and behaviour data of PB and TB children from Study 1a

→

VI. CHAPTER 8

Analyses using extended samples:

i. Analysis of CHADS data for PB N=31 and TB N=30 collected approx 4 years ago.

ii. Analyses of IQ and behaviour using PB and TB data from Study 1a and CHADS data (PB and TB) collected approx. 4 years ago Total PB N = 71, TB N=71

iii. Analyses Study 2, after addition of data of 7 PB children, recruited from CHADS sample (only 7 consented to take part at this point) Total N = 47 (though actual N for analyses varied due to missing data).

Figure 2: Diagram illustrating the structure of the thesis and the participant groups in each study

4.5.2 Distinction between Statistical and Clinical Significance

The work presented in this thesis addresses the cognitive sequelae of premature birth in the context of a research study. It is therefore important to make the distinction between clinical and statistical significance. PB children are often found to be underperforming compared to TB peers. While such differences may not always reach statistical significance ($p<0.05$), they may be of clinical importance. Furthermore, due to small sample sizes, it is possible that Type II errors are occurring in some analyses. However, within the scientific research context of the work presented, only statistical significance is reported. In Addition, multivariate statistical analyses (including multiple regression analysis and structural equation modelling) are used wherever necessary, in order to avoid the risk of Type I errors.

4.6 Preliminary Study

A preliminary study was carried out to test and evaluate the assessment battery described in Section 4.2.2 with a normally developing, TB group of children. The aim was to examine the suitability of the proposed test measures with respect to the tests themselves, the timing of the protocol and to determine how well this battery is received by children aged between 6 and 12 years. Test-retest reliability was planned where previous data were available.

4.6.1 Participants

The pilot study group was recruited through a database of families who had previously taken part in a developmental study (CHADS, Stevenson & Pit-ten Cate 1998-2000) in the School of Psychology. Ethical permission for this pilot study was granted by the Departmental Ethics Committee (School of Psychology, University of Southampton).

Twenty families who had provided written agreement to be contacted about future research studies were contacted by letter and followed up by telephone. Seventeen families agreed to participate in the study. The children ranged in age from 6 years 1 month to 12 years 7 months (Mean = 10 years, 3 months; SD=1.95). Ten girls and 7 boys took part in the assessment. One child did not complete the assessment, and the available data are not included in any analysis.

4.6.2 Procedure

Children were assessed in their own homes, in a quiet area. Assessments lasted just over two hours, and the children were offered regular breaks. The tests were administered in a pre-determined order, in four half-hour units (all children received tests in the same order). The WISC is an ideal initial test, as the stimuli are interesting and the test is interactive. Following the WISC subtests (30 mins), the TEA-Ch subtests were administered (30 mins). Children were offered a break of between five and ten minutes at this stage. After the break, the NEPSY items followed by the CANTAB were administered. The CANTAB was administered last, as the task is computerised and generally of greater attractiveness to the children. In most cases it served well as a motivation to work efficiently through the other tasks. Data from a previous assessment approximately two years earlier were available for children on a subset of measures. The measures which were replicated in the present pilot study were the short form IQ test and two subtests of the CANTAB battery. These data were used for a reliability analysis.

4.7 Results and interpretation

4.7.1. Qualitative observations

In general the assessment battery was well received by the children. Only one child chose not to complete the battery; her reasons were motivated by friends waiting for her arrival to play outside, rather than a particular dislike of the tasks themselves. The assessment did last slightly longer than two hours, and furthermore, some tests proved awkward to administer, therefore it was decided to remove some tests from the battery. Three tests in the NEPSY battery relied on a high level of subjectivity both for administration and scoring. *Finger tapping* varied greatly between children as it proved difficult to achieve a constant tap size, (some children consistently made very small taps even after prompting, which biased their time for completion of the task). The *Statue* task was removed from the battery as it seemed inappropriate for use with children older than 8 or 9 years. Furthermore due to time constraints it was necessary to limit the battery to 2 hours of assessment time. Finally, *Knock and Tap* was also removed from the assessment battery. On this test all children performed at near ceiling level. As the test has no time limit, children who have difficulty with this task, simply perform it at a much slower pace. However, this reduces the risk of commission errors, and the task therefore loses its potential to capture EF skills. The final test battery carried forward for Study 1 therefore consisted of 20 subtests.

4.7.2 Quantitative analysis

Correlational analysis was run to investigate whether performance across different tests is related. It is predicted that correlations will be significant within test groups, i.e. tests of IQ should be correlated with each other, but there should be lower correlation ($r<0.3$, $p>0.05$) with other tests of attention for instance. Table 4 summarises the correlational data, abbreviations for test are as follows: 1) IQ; 2) Block Design (Block); 3) Picture completion (Picture); 4) Comprehension (Comp); 5) Information

(Info); 6) Sky Search (Sky S); 7) Score; 8) Creature Counting number correct (Count); 9) Creature Counting timing score (Count t); 10) Sky Search Dual Task (Sky DT); 11) Walk Don't Walk (Walk); 12) Same world (Sworld); 13) Opposite World (Oworld); 14) Tower; 15) Design Copying (Design C); 16) Design Fluency (Design F); 17) List Learning (List); 18) Intra-Extradimensional Shift no correct (IEDS); 19) Intra- Extradimensional shift errors (IEDSerr); 20) Spatial Span (SSP); 21) Spatial Working Memory errors (SWMerr); 22) Spatial Working Memory strategy score (SWMstr).

Table 4: Correlations of 22 subtests in pilot study assessment battery, significant correlations (<.05) marked in bold script

Correlations	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1IQ	1.00																					
2BLOCK	**0.46**	1.00																				
3PICTURE	**0.78**	0.29	1.00																			
4COMP	0.46	-0.37	0.26	1.00																		
5INFO	**0.82**	0.29	0.47	0.26	1.00																	
6Sky S (Sel)	0.15	0.36	-0.19	0.15	0.04	1.00																
7Score (Sus)	-0.13	-0.06	0.03	0.07	-0.32	0.03	1.00															
8Count (Sw)	0.01	-0.32	-0.04	0.13	0.19	0.01	-0.15	1.00														
9Count t (Sw)	-0.23	-0.36	-0.11	0.21	-0.33	0.20	**0.62**	-0.14	1.00													
10Sky DT (Sel)	0.13	0.05	0.04	0.12	0.11	-0.14	**0.57**	-0.23	0.41	1.00												
11WALK (In)	-0.23	-0.10	0.01	-0.23	-0.23	0.05	**0.66**	0.01	**0.73**	0.43	1.00											
12SWORLD (In)	-0.09	-0.17	0.05	0.30	-0.35	0.19	**0.54**	-0.29	**0.72**	0.38	0.40	1.00										
13OWORLD (In)	-0.17	-0.17	-0.15	0.30	-0.39	0.36	**0.69**	-0.19	**0.82**	0.36	**0.50**	**0.82**	1.00									
14TOWER (Pl)	-0.17	0.16	-0.23	-0.43	0.05	0.39	0.03	0.09	0.19	-0.04	0.24	-0.03	0.06	1.00								
15DesignC (Vis)	0.05	-0.22	0.26	0.16	-0.05	-0.34	**0.59**	-0.36	**0.71**	0.45	**0.64**	0.49	**0.53**	-0.14	1.00							
16DesignF (Vis)	-0.40	-0.47	-0.23	-0.06	-0.27	-0.29	**0.51**	0.21	0.47	0.18	0.34	0.42	0.50	0.30	0.44	1.00						
17LIST (Sem)	0.08	-0.38	-0.04	**0.51**	0.07	0.02	0.23	0.15	0.19	0.35	0.09	0.09	0.32	-0.27	-0.07	0.01	1.00					
18IEDS (In)	0.41	0.05	0.16	0.20	**0.58**	0.16	-0.16	-0.18	-0.06	0.04	0.01	-0.12	-0.10	-0.11	0.24	-0.17	-0.03	1.00				
19IEDSerr (In)	-0.39	-0.31	-0.07	0.07	**-0.62**	-0.37	0.17	-0.07	-0.17	-0.01	-0.29	-0.05	-0.11	-0.08	-0.14	0.20	0.09	**-0.68**	1.00			
20SSP (Span)	-0.05	0.48	0.03	**-0.53**	-0.06	0.11	0.11	-0.06	-0.15	-0.17	0.18	-0.27	0.04	-0.15	-0.05	-0.24	-0.05	0.10	-0.33	1.00		
21SWMerr (WM)	0.05	-0.08	0.09	0.39	-0.24	0.04	-0.01	-0.18	0.00	-0.14	-0.16	0.10	-0.05	**-0.04**	-0.18	-0.18	0.08	-0.29	0.47	**-0.54**	1.00	
22SWMstr (WM)	0.16	0.14	0.17	0.26	-0.11	-0.09	-0.02	-0.30	0.02	0.04	-0.21	0.28	0.04	0.06	-0.05	0.01	-0.07	-0.40	0.42	**-0.59**	**0.82**	1.00

Sel – Selective attention, Sus – sustained attention, Sw – switching, In – inhibition, Pl – planning, Vis – Visual Spatial Integration, Sem – semantic memory, Span – spatial span, WM – working memory.

Inspection of the table verifies that, for the majority of cases, correlations are only significant for tests within a cognitive domain. Only few tests correlate significantly with tests from other cognitive domains. The design copy subtest in particular correlates with several of the attentional measures. This may have implications for the interpretation of low scores on the Design Copy subtest. Failure to achieve a score within the normal range may be a result of both poor visuo-spatial skills and poor attentional skills.

4.7.2.1 Test – retest stability analysis

Children's test scores on the IQ and CANTAB tests were compared to their scores obtained in the previous assessment approximately two years earlier (CHADS Study). Table 5 provides a summary of test scores for the two assessments.

Table 5: Means and Standard Deviations of test scores at Time 1 and Time 2

Test	Time 1 (CHADS study) Mean (SD) N = 16	Time 2 (Pilot study) Mean (SD) N = 16
IQ	103.82 (10.26)	110.17 (10.98)
Block Design	9.05 (2.53)	11.68 (2.57)
Picture Completion	10.88 (2.78)	12.00 (2.82)
Information	12.35 (2.83)	10.76 (2.72)
Comprehension	10.76 (2.80)	12.88 (3.12)
CANTAB		
S W M (errors)	49.12 (15.52)	42.94 (16.02)
S W M (strategy)	37.53 (4.17)	35.29 (4.42)
IEDS (no. correct)	7.82 (1.01)	7.81 (0.98)

Scores presented for IQ subtests are standardised for the age of the child, and as such are expected to be stable over time. The CANTAB scores are unstandardised therefore some improvement over time is expected (Luciana, 2003) However, for the spatial working memory task, there is a sudden increase in performance when children reach about 11/12 years of age. Improvements before this age are gradual (Luciana, 2003). Similarly on the set-shifting task there is a shift in performance, which takes place between 5 and 6 years of age, after which performance levels close to adult level are reached and little improvement is expected.

Paired sample t-tests were non significant in all tests except the Block Design test ($t_{(15)} = 3.18$, $p<0.01$). Inspection of the distribution of test scores revealed that for two cases the standard score on the Block Design subtest increased by 10 points between assessment 1 and 2, suggesting an unusual increase in performance on this particular subtest. The test-retest correlations for scores at the two time points are presented in Table 6 below.

Table 6: Paired Samples Correlations for IQ and Cantab scores at Time 1 and 2

	Correlation N=16 (N=14)*	Significance
IQ	.46 (.65)	.07 (.01)
Block Design	.15 (.24)	.58 (.41)
Picture Completion	.50 (.59)	.05 (.03)
Comprehension	.23 (.31)	.40 (.43)
Information	.79 (.83)	.00 (.00)
IEDC	.31 (.38)	.25 (.19)
SWM err	.57 (.52)	.02 (.05)
SWM str	.45 (.51)	.07 (.06)

*Correlational analysis after elimination of two cases with unusual increase in scores.

The stability coefficients for the WISC-III are between .72 and .89 for the four subtests presented above, in children aged between 6 and 12 years (Wechsler 1992). Test- retest stability are in a similar range (Block Design r = .74; Picture Completion r = .80; Comprehension r = .68; Information r = .80), based on a sample of 111 children ages 6-7. The median re-test interval was 23 days (Wechsler, 1992). The correlations obtained in the present study are considerably lower. The most likely reason is the dramatic change in test scores for two subjects, which in a very small sample size has significant impact on the results (results of the analysis after exclusion of these two cases is shown in the brackets in Table 6). Inter-rater reliability of the scale is high ($r = .75 - r = .87$; Wechsler, 1992) but nevertheless may have contributed to the difference in scores between the two testing times, which may explain the low correlations even after outliers were removed. As mentioned above, performance on the CANTAB does not follow a linear relationship over time. It is therefore expected that children would perform at similar levels between the two assessments.

4.8 Conclusion

The purpose of the pilot study was to administer the test battery on a range of TB normally developing children to check administration time, appropriateness of tests for children of various ages, and to confirm that the individual tests chosen do tap different, non-overlapping cognitive skills.

Following administration of the battery to the pilot study group, three subtests ("finger tapping", "statue" and "knock and tap") were omitted due to relative unimportance of these tasks, and time constraints. The remainder of the tests were considered appropriate for inclusion in the final test battery, and the correlational analysis confirmed that the tests were suitably specific and did not excessively overlap between cognitive domains.

Overall the test-retest analysis of the IQ and CANTAB tests produces satisfactory levels of reliability, with the exception of the Block Design subtest of the WISC, on which two subjects made unusually large improvements across the testing interval.

As discussed by Robbins (in Roberts, Robbins & Weiskrantz; 1998), if a three dimension structure of EF is accepted, it is not necessary to expect high intercorrelations between EF measures from the three different domains. It is therefore less surprising that the WM tasks did not correlate well with the tasks of inhibition and cognitive switching in this study. Examining neural correlates of the three dimensions of EF has shown that inhibition and cognitive flexibility are largely functions attributed to the dorsolateral and orbito-frontal prefrontal cortex, as well as parietal and temporal areas, whereas working memory has been attributed to the dorsolateral prefrontal cortex (see Roberts et al., 1998). While it is important to note that EF are not localised to any particular areas of the prefrontal or more temporal cortices, differential magnitudes of activation in certain areas are associated with different EF dimensions. As the dimensional approach to EF is taken in this thesis, WM will be considered separate from inhibition and cognitive flexibility for the purposes of further cognitive assessments.

On the basis of the results of the pilot study, tasks were grouped according to dimensions of EF, attention, memory and visual-spatial integration. This is illustrated in Table 7 below.

Table 7: Summary of tests according to cognitive domain.

Domain	Assessment
Inhibition	Walk Don't Walk
Cognitive Switching	Creature Counting
Working Memory	Spatial Working Memory, Spatial Span
Planning	Tower
Attention	Sky Search, Score, Opposite Worlds
Semantic Memory	List Learning
Visuo-Spatial Integration	Design Fluency, Design Copying

Executive Function tests were grouped as tests of Working Memory (Spatial Working Memory and Spatial Span), Inhibition, Cognitive Switching and Planning. Support for classification of TEA-Ch subtests is presented in the TEA-Ch manual (Manly et al., 1999), *Walk*, the Go-No-Go task was selected as it had one of the highest factor loadings for inhibition. Similarly, *Creature-Counting* was selected as the task best representing cognitive switching. The remaining tests were classified as different Attention measures (Sustained Attention, *Score* and Selective Attention, *Sky Search*). The Tower of London task is consistently described as a task of planning and does not classify neatly as either a test of inhibition or cognitive flexibility (Robbins, 1998). This grouping of EF tests is followed in Study 1, which investigates PB children's performance on these tasks compared to the performance of TB children.

CHAPTER 5

Study 1a & b Cognitive outcome, Executive Functions and Behaviour of school age prematurely born children

5.1 Introduction

The literature addressing the outcome of prematurely born children suggests developmental difficulties in general intellectual function, visuo-spatial integration, fine motor control, everyday memory, attention and concentration, and executive function (see Chapter 3). Some of these areas of cognitive function have been more thoroughly investigated than others. Specifically, attention and Executive Functions outcomes in prematurely born children have been investigated relatively less. The present study investigated cognitive outcome, particularly EF, and was carried out in two parts, with assessments being approximately 12 months apart.

5.1.1 Study 1a

The first objective of the study was to assess a group of prematurely born children on a range of cognitive functions, comparing their performance to a group of term born control children. In particular, differences in EF and Attention were investigated. Three hypotheses were addressed: Hypothesis 1: Prematurely born children have an IQ within the low average range, but which is lower than that of term born peers; Hypothesis 2: Prematurely born children have difficulties with EF and Attention tasks, and perform worse on these tasks than their term born peers; Hypothesis 3: Prematurely born children have more behavioural problems, particularly with hyperactivity and inattention, than their term born peers.

The second objective of this study was to collect information about other cognitive skills such as visuo-spatial integration and semantic memory. Hypothesis 4 predicted that prematurely born children would have difficulty with visuo-spatial integration tasks, but would perform equally well as their peers on semantic memory tasks.

5.1.2 Study 1b

The second part of the study involved re-visiting the participants for a second assessment. The purpose of this second part of the study was to assess episodic memory. Based on previous literature, Hypothesis 5 predicted that mild difficulties on episodic memory can be expected in prematurely born children (Isaacs et al., 2000). A digit span test was used as an auditory test of WM, performance on which was compared to the spatial working memory tasks in Study 1a. As an additional measure of hyperactive behavioural style, the DuPaul ADHD symptoms questionnaire was completed by parents.

5.2 Method

5.2.1 Participants

The group of prematurely born children was recruited via hospital records at the Princess Anne Hospital, Southampton. A total of 295 patients were identified, who fulfilled the inclusion criteria. Children were born at less than 32 weeks of gestational age and multiple births as well as children with a severe disability were excluded. Of these, 138 patients whose medical records were available and who had not moved out of the area were contacted. Forty-nine replies were received and appointments arranged (35% response rate). As nine families failed to attend their appointment, the final number of participants was 40.

The group of control children was recruited through local schools. Information letters were sent through the class teachers, and parents returned their contact details if they were interested in taking part. A total of 710 letters were distributed and 44 replies were received (6% response rate). Three families failed to attend their appointment, leaving the final group size at 41 children.

The response rate for the PB group was around 30% which is not unusual for this type of sample (e.g. Pit-ten Cate, Kennedy, & Stevenson, 2002 reported 44% response rate to a questionnaire study). The response rate within the control group was around 6%. Analysis of the responders and non-responders in the prematurely born group in terms of gestational age, birthweight and birth year show that there were no significant differences although the non-responders did have a slightly higher mean birthweight. (GA $t_{(319)} = 0.51$, $p = .61$; Birthweight $t_{(326)} = -1.94$, $p = .053$). The demographics of the PB and TB groups are presented in Table 8.

Table 8: Demographic variables of the two study groups.

	Premature N = 40	Control N = 41
Age: Years; Months	8;5 (SD 2)	8;5 (SD 1.5)
Gestational Age (weeks)	28.4 (2.15)	-
Birthweight (grams)	1200 (368.31)	-
Gender	24 female (60%)	21 female (52.5%)
	16 male (40%)	19 male (47.5%)
Wears Glasses	4 (10.5%)	4 (10.0%)
Right Handed	29 (72.5%)	36 (90.0%)

The ages ranged between 6;0 and 11;6 in the TB group, and between 6;4 and 13;0 in the PB group. There was no significant effect of age between the groups, as tested by an independent subjects t-test ($t_{(79,1)} = -0.09$, $p = 0.92$, ns.). Gender proportions were slightly biased towards girls in the PB group only. However this difference was not found to be significant (Gender χ^2 (1) = 0.632, $p = .43$). The PB groups gestational ages ranged between 23 and 32 weeks, and the groups birthweight ranged between 460 and 2210 grams (LBW N=6, VLBW N = 22, ELBW N = 12). This is a typically heterogeneous group of PB children. The number of children requiring visual aid was low in both groups (Glasses χ^2 (1) = 0.01, $p = .97$). In the PB group, there was a significantly larger proportion of left handed children, (Handedness χ^2 (1) = 4.23, $p<0.05$).

4.3.6 Socioeconomic background of participating families

Participating families were grouped into social grades as a broad estimate of socioeconomic background on the basis of the home postcode. Postcodes were classified using a website based on information from national statistics census (www.checkmyfile.com). Letter combinations representing seven social groups are used, the top social group being represented by "AB" and the lowest by "DE". The middle group "C" is divided into C1 and C2. The social grade was based on the type of housing in the area, the type of occupations of the residents, the quality and abundance of primary and secondary schools and colleges. The group ABC1 is classified as an upper middle class standard, with C2DE representing lower middle class standard. Table 9 provides the crosstabulation of social class and prematurity status.

Table 9: Crosstabulation of social class by prematurity status

Social class	Term	Prem	Total
AB	0	3	3
ABC1	13	11	24
C1	0	1	1
C1C2	8	6	14
C2	4	5	9
C2DE	14	10	24
Total	39	36	75*

*Post code information was not available for six families, therefore total was not 81

Chi-square analyses of these data were non significant χ^2 (5) = 5.11, p = .40. In both groups of children there are comparable numbers of families amongst the upper middle class and lower middle class bands. No families represented the extreme social band DE. Equal numbers of both groups are represented from the middle class social bands. Families of lower social background are generally more likely to have prematurely born children due to poorer lifestyle quality and elevated rates of teenage pregnancy. As the present sample is representative of middle class families for both the prematurely born and the term born groups, it can be assumed that any cognitive differences between the two groups are not likely to be caused by significantly different social backgrounds.

Participants from study 1a were followed up approximately 12 months after the first assessment. Of the original 40 premature children and 41 term born children 30 and 22 respectively agreed to take part in the second part of the study. Twenty three PB (Age: Mean=8.27 years, SD=2.07) and 12 TB children (Age: Mean=8.49, SD=1.25) were available for the assessment, the remainder only consented to post the completed questionnaires. The mean birthweight of the PB children was 1157.39g (SD = 382.65), and mean gestational age was 28.26 weeks (SD = 2.49).

5.2.2 Materials

5.2.2.1 Study 1a

The assessment battery described in Section 4.2.2, which was tested in the pilot study, was administered to all participants. The battery consisted of the final 22 measures selected on the basis of the pilot study (see Table 7), and in addition, parents were asked to complete a questionnaire about their child's behaviour. The questionnaire selected was the Strengths and Difficulties Questionnaire (SDQ, Goodman, 1997) a copy of which is in Appendix A).

5.2.2.2 Study 1b

The assessment consisted of the Rivermead Behavioural Memory test for children, and the digit span subtest from the WISC-III. Parents completed the DuPaul ADHD symptoms questionnaire.

5.2.3 Statistical Analysis

One-way multivariate analysis of variance (MANOVA), and t-tests were conducted to test for differences between the study and control groups in both parts of the study. Multivariate analysis of covariance was used to control for IQ on between group analyses of EF measures.

5.2.4 Results Study 1a

Differences between the two groups on measures of IQ, EF and behaviour were tested using multivariate analysis of variance.

5.2.4.1 Hypothesis 1: prematurely born children have lower IQ than peers

The measure of IQ includes the scores of four subtests of the WISC-III. Mean standard scores are presented in Figure 3, Table 10 summarises the means and SD for PB and TB children.

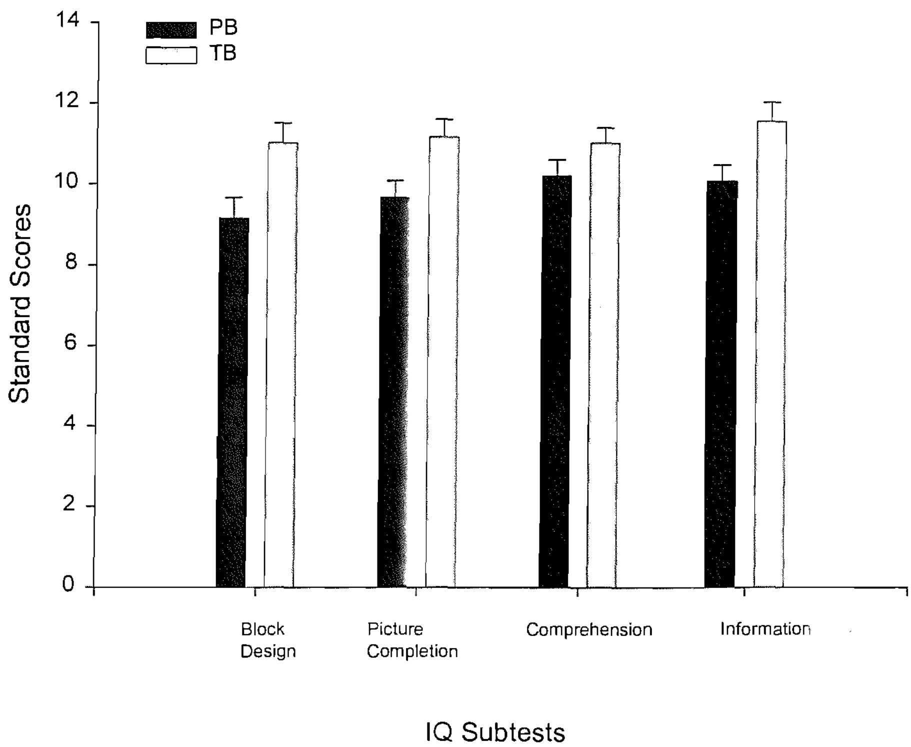


Figure 3: Means and SE of IQ subtest scores for PB and TB children

Table 10: Mean and SD scores of IQ subtests for PB and TB groups.

	PB	TB
	Mean (SD)	Mean (SD)
Block Design	9.15 (3.22)	11.02 (3.13)
Picture Completion	9.67 (2.61)	11.17 (2.85)
Comprehension	10.20 (2.57)	11.02 (2.41)
Information	10.08 (2.52)	11.56 (3.07)

Term born children achieved higher scores on all four subtests of the WISC-III. Mean differences in overall IQ were significant $t_{(79)} = 3.34$, $p<0.01$. (TB mean = 107.14 (12.32), range 77.93-131.44; PB mean = 98.42 (11.15), range 70.58 – 116.89). Univariate effects were significant for all tests except comprehension, the Statistics are summarised in Table 11.

Table 11: F ratios and effect sizes for univariate main effects of birth status on IQ measures

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus (λ = .854)		4	3.24	.02	
Univariate						
Birthstatus	Block	71.13	1	7.06	.02	0.56
	Pict	45.30	1	6.08	.01	0.47
	Info	44.71	1	5.65	.01	0.51
	Comp	13.76	1	2.21	.14	0.32
Error	Block	10.07	79			
	Pict	7.45	79			
	Info	7.91	79			
	Comp	6.22	79			

It is of interest to note that the median IQ score for the PB group was higher than the mean score (Median = 99.91, mean = 98.42) indicating a skewed distribution. In the TB group, median and mean scores were equal (Median = 107.00, mean = 107.14) as expected in a normal distribution of IQ scores. This indicates that a group of PB children did score at the high end of the IQ score distribution, but that a subgroup of children achieved very low IQ scores, which negatively affected the mean (N = 8 had IQ<90; N = 28 had IQ 90 – 114; N = 4 had IQ > 115).

5.2.4.2. Hypothesis 2: Prematurely born children have difficulties with attention and EF tasks.

The EF tasks were grouped according to the EF dimensions measured, and three separate analyses were carried out. The results of the pilot study indicated that the CANTAB measures of EF were only weakly associated with other EF measures. The spatial working memory task and the spatial span task were therefore not included in the MANOVA of EF scores, but analysed separately. Figure 4 below summarises the mean scores of the PB and TB groups on these tests. It is evident that there was no difference between the groups and that the variability in scores was also comparable. No analyses were therefore carried out to test for between group differences.

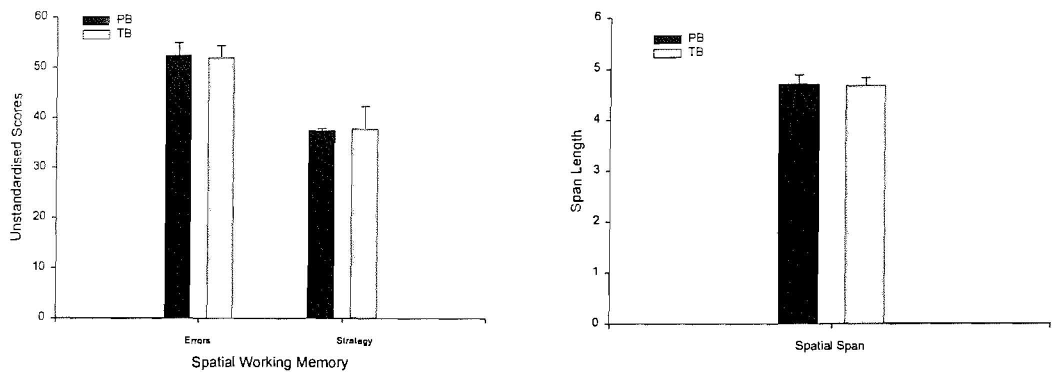


Figure 4: Means and SE of scores of PB and TB groups on the SWM and SSP tasks.

The Mean scores and SE of the Tower test, the tests of Inhibition and Cognitive Switching, and the Attention tests (Sustained Attention and Selective Attention) are summarised in Figure 5 below (Note that Accuracy Score was used for Creature Counting).

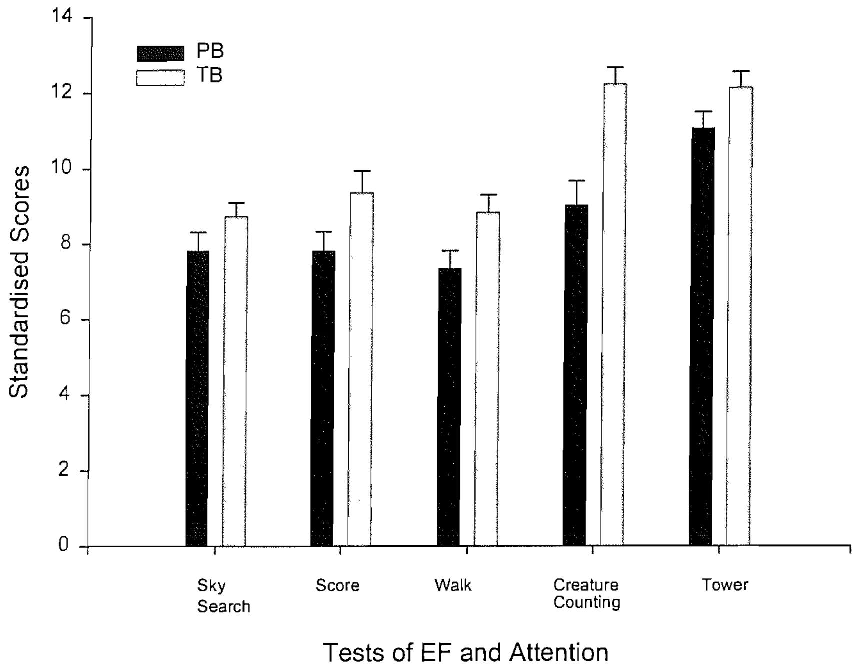


Figure 5: Means and SE of scores of PB and TB groups on EF tasks.

The Tower task scores were analysed separately from the remaining EF tasks, as a test of planning ability. An independent t-test indicated that the difference in means was not significant $t_{(78)} = 1.79$, $p = 0.08$.

As discussed in the Preliminary Study (Section 4.6), inhibition and cognitive flexibility were considered as dimensions of EF following the three dimension model (Lehto et al., 2003), and were analysed using MANOVA (Table 12). Attention measures were analysed in a separate MANOVA (Table 13).

Table 12: F ratios and effect sizes for univariate main effects of birth status on tests of EF

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus ($\lambda = .757$)		2	10.74	<.01	
Univariate						
Birthstatus	Cog Switch	213.20	1	20.89	<.01	0.83
	Inhibition	37.30	1	4.46	<.05	0.51
Error	Cog Switch	10.21	69			
	Inhibition	8.38	69			

Note: Cognitive Switching Test is Creature Coutning (accuracy score), Walk Don't Walk is Inhibition Score.

The univariate effects of birthstatus on both Inhibition and Cognitive switching were significant. The MANOVA results for the analysis of the attention measures is summarised in Table 13 below.

Table 13: F ratios and effect sizes for univariate main effects of birth status on tests of Attention

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus (λ = .896)		5	1.58	.18	
Univariate						
Birthstatus	Sky Search	14.72	1	1.98	.16	0.32
	Score	53.65	1	4.61	<.05	0.44
	Dual Task	23.83	1	1.40	.24	0.31
	S World	.12	1	.01	.93	0.01
	O World	8.45	1	.29	.59	0.13
Error	Sky Search	7.44	72			
	Score	11.65	72			
	Dual Task	16.99	72			
	S World	16.45	72			
	O world	28.76	72			

Multivariate analysis of the attention tests was not significant, and only the univariate effect of Birthstatus on sustained attention (Score) was significant.

The results of the multivariate analysis of variance show that the children born prematurely do have difficulty with tests of EF as indicated by their performance compared to children born at term. This difficulty was reflected across two dimensions of EF, cognitive flexibility and inhibition as well as on tests of sustained attention.

Effects of IQ on EF

In order to draw conclusions about EF in children born prematurely, the effects of general IQ must be taken into consideration. As the PB group was found to have both significantly lower IQ scores than the control group as well as achieving lower EF scores, it cannot be ruled out that the poor EF performance is a result of low IQ. By covarying the effects of IQ on the group difference on EF, it is possible to determine whether EF difficulty is independent of IQ. Multivariate analysis of covariance was therefore carried out in order to determine group differences in EF which are independent of IQ differences. The results are presented in Table 14 below.

Table 14: F ratios and effect sizes for univariate main effects of birth status on tests of EF

Source		Mean Square	df	F	p
Multivariate					
	Birthstatus (λ = .826)		2	6.96	<.01
Covariate					
IQ	Cog Switch	16.31	1	1.61	.21
	Inhibition	9.71	1	1.16	.29
Univariate					
Birthstatus	Cog Switch	139.04	1	13.75	<.01
	Inhibition	19.05	1	2.28	.14
Error	Cog Switch	10.12	67		
	Inhibition	8.36	67		

After covarying for IQ scores, the multivariate effect remains significant for cognitive switching. However, when the between group difference in IQ is accounted for the univariate effect for inhibition is no longer significant. This indicates that, independent of lower IQ, children born prematurely have difficulty with tasks that involve cognitive flexibility. However, their difficulties with inhibition seem to be more closely linked with low IQ. This finding is consistent with models of IQ and EF described in Section 7.1.

5.2.4.3 Hypothesis 3: prematurely born children have more behavioural difficulties than their term born peers

The SDQ parent version was used in order to assess behavioural function in both groups of children. SDQ scores are grouped into four problem and one strength domains, a higher score indicates higher prevalence of behaviour. Therefore, a high score on difficulties domains indicates more behaviour problems. The mean scores and standard errors for the two groups are presented in Figure 6.

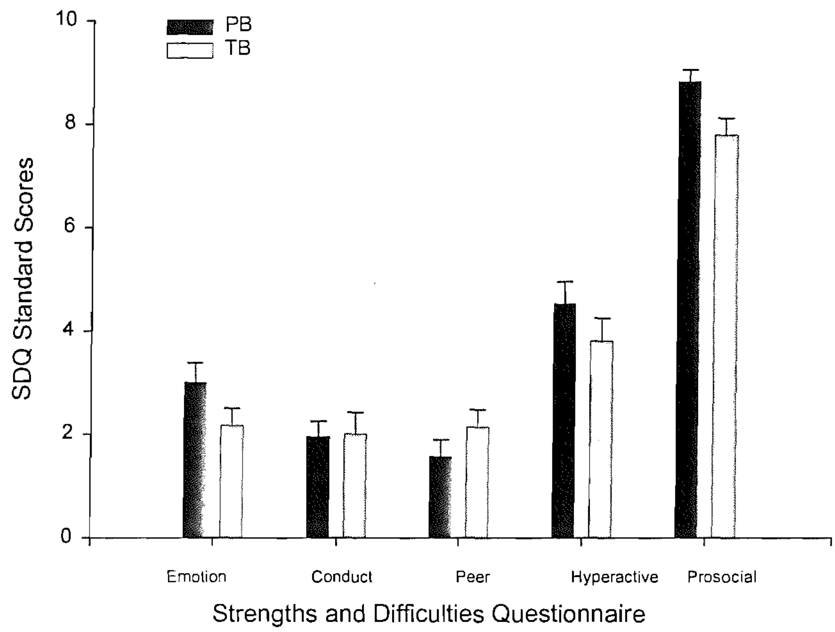


Figure 6: Mean and SE of scores on SDQ problems scales

Representation of the mean scores on the SDQ shows higher scores on the problem domains emotion and hyperactivity for the study group, as well as higher mean scores on the prosocial behaviour subscale. Multivariate analysis revealed that there were no between groups differences on any problem scales (Table 15).

Table 15: F ratios and effect sizes for univariate main effects of birth status on problems scales of the SDQ

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus (λ = .899)		4	1.96	ns	
Univariate						
Birthstatus	Emotion	12.84	1	2.64	ns	0.37
	Conduct	0.04	1	0.01	ns	0.02
	Peer	6.02	1	1.56	ns	0.30
	Hyper	9.81	1	1.38	ns	0.27
Error	Emotion	4.86	73			
	Conduct	4.82	73			
	Peer	3.86	73			
	Hyper	7.06	73			

The strength domain prosocial behaviour was analysed separately using an independent t-test. Mean scores were significantly higher in the study group, $t_{(73)} = -2.63$, $p<.01$ (d = 0.58), however, scores for both groups fell within the normal range (Population mean score = 8.9 (SD = 1.4) for females and 8.4 (SD = 1.7) for males).

5.2.4.4 Hypothesis four: Prematurely born children have difficulties with Visuo-Spatial Integration, but not with Semantic Memory

Children born prematurely are reported to have difficulty with visuo-spatial integration (Damman et al., 1996, Foreman et al., 1997; Whitfield et al., 1997). It was therefore predicted in Hypothesis 4 that between group differences would be found on the visuo-spatial integration tests. Mean scores for the Design Copying test were lower for the PB group (M=10.90, SD = 3.99) than for the TB group (M = 12.94, SD = 2.28). Independent t-test showed that this difference was significant ($t_{(70)}=2.57$, $p<0.05$). The design fluency test, though tapping aspects of EF, relies heavily on motor control as well as visuo-spatial integration. Mean scores on this test were similar for

PB (M = 9.71, SD = 3.54) and TB (M = 9.74, SD = 3.24) groups. Independent t-test showed no significant group differences for the Design Fluency test $t_{(71)} = 0.41$, $p = 0.97$.

As predicted, children born prematurely did not perform any worse on the test of semantic memory, than did term born control children $t_{(57)}=0.33$, $p=0.75$.

5.3 Discussion

Study 1a had two objectives, the first was to address IQ, EF, attention and behaviour in PB compared to TB children. The second addressed other cognitive skills, visuo-spatial integration and semantic memory. Four hypotheses were proposed, consistent with these objectives.

5.3.1 Hypothesis 1

Hypothesis 1 stated that prematurely born children would have an IQ within the normal range but lower than that of term born peers. The results supported this hypothesis. Prematurely born children achieved IQ scores which fell within the low average range, however there was a significant difference between the two groups across three of the four subtests administered. Since TB children's IQ scores also fell within the normal range, and were not above average, the hypothesis was confirmed. This finding is consistent with most studies reporting IQ of premature children within this age range, and inspection of mean and median scores suggests that a subgroup of PB children achieve very low IQ scores, affecting the average score, while some PB children do achieve high IQ scores. (see Section 3.3.1)

5.3.2 Hypothesis 2

Hypothesis 2 stated that PB children would have difficulties on tests of EF and Attention compared to their TB peers. This hypothesis was partially supported by the results. Prematurely born children did score significantly worse on tests of sustained attention and two dimensions of EF (inhibition and cognitive flexibility) but not on WM tests. These findings are somewhat consistent with published reports on EF in PB children. Previous studies addressing EF in prematurely born children of similar age to those in the present study have found WM difficulties (Frisk & Whyte, 1994; Luciana et al., 1999). Luciana et al. (1999) reported 7 – 9 year old prematurely born children's difficulties with WM tasks taken from the CANTAB test battery. In her study children achieved lower scores than controls on spatial working memory, spatial span and set shifting tasks. This finding was not replicated in the present study. A possible reason for this is that Luciana et al.'s sample consisted of a heterogeneous group of prematurely born children with respect to level of prematurity and severity of lasting effects. It is possible that the difficulties observed in the prematurely born group were experienced mainly by the very premature children and those with the most severe damage. Indeed Frisk & Whyte (1994) report a WM deficit only in those premature children who had sustained periventricular lesions in the neonatal period. As no information regarding potential brain damage is available for the children in the present study, it is not possible to determine why the WM deficit was not apparent in this group. One possibility is that the children in this group were high functioning, the other is that the spatial WM tasks on the CANTAB are not sensitive enough to detect very subtle difficulties. In study 1b the issue of WM is explored further, by assessing children on an auditory WM task.

5.3.2.1 EF and IQ

Executive Function and general cognitive function (IQ) are thought to be closely linked during development. It is therefore necessary to put any observed EF difficulties into context with the reduction in general IQ. As there was a significant difference between groups on IQ, it may be this reduction in general cognitive function that is contributing to the prematurely born children's difficulties with the EF tasks. The analysis of covariance showed that in part, differences in attention and EF were associated to IQ test performance. However, the EF dimension of cognitive flexibility was found to be impaired independently of the IQ reduction. The group differences on this task remained significant after effects of IQ were controlled for statistically. This suggests that there is a dissociation between some aspects of EF and IQ. The relationship between EF and IQ is investigated in further detail in Chapter 7.

5.3.3 Hypothesis 3

The third hypothesis stated that PB children would have more behavioural difficulties especially with respect to hyperactive and inattentive behaviours compared to TB children. The results do not support this hypothesis, and furthermore suggest a difference in the prosocial behavioural domain that was not considered in the hypothesis. Both groups of children scored within normal limits on all five scales. Based on the difficulties that PB children in this study showed with executive control, it would be expected that these executive difficulties are reflected in behaviour, particularly in the hyperactivity scale (Brophy, Taylor, & Hughes, 2002; Clark et al., 2002). Difficulties with inhibition and executive control may be reflected in behavioural markers which are identified by questions on the SDQ describing difficulty waiting one's turn, ease of distractibility, not thinking things through before acting, and not seeing tasks through to the end.

The PB children did not show a higher level of behavioural problems on conduct, hyperactivity or emotional difficulties scales. This finding is inconsistent with the cognitive profile (inhibition problems and low IQ) and is not consistent with previous literature (summarised in Table 3). In these studies, PB children had higher rates of hyperactive behaviour than control children. The children assessed in previous studies were similar with respect to degree of prematurity and severity of neonatal illness to children in the present study. The most likely explanation for the discrepancy is down to sample sizes and effect sizes. Effect sizes are moderate in the present study, and small to moderate in studies summarised in Section 3.3.4. While the findings of the present study are based on less than 50 children per group, sample sizes of more than 100 children per group report between group differences in behaviour problems. It is highly likely that with an increased sample size, between group differences would reach significance at $p<0.05$ for the present study. In order to further investigate the behaviour of the present group of children, particularly with respect to inattentive behaviour, the DuPaul AD/HD behavioural rating scale was administered in Study 1b.

A curious finding which was not considered in the hypothesis was that PB children scored within the normal band but significantly higher in the prosocial behaviour scale than did the control children, suggesting that they have better social skills and are generally more helpful and partial to requests from parents or teachers. The prosocial scale was introduced to the original Rutter Scale (an older behavioural measure from which the SDQ was developed) in response to parental feedback concerning the original scale's focus on primarily negative behaviours. Prosocial items were found to have satisfactory internal consistency, and inter-rater reliability. Goodman (1994) pointed out that the prosocial behaviours scale should be considered important in its own right rather than as a "cosmetic padding" (p. 1493). With this in mind it seems justified to explore the present findings further.

A positive character strength of PB children has not been reported in previous studies. Instead, it has previously been suggested that PB children have poor social skills and are less likely to be competent at prosocial behaviour (e.g. Tessier, Nadeau, & Boivin, 1997). A possible reason for the discrepancy between past findings and the present results is a parental reporting bias. Parents of PB children may place emphasis on positive aspects of their child's behaviour, and hold a biased view as a result of the poor prognosis many PB children are given early on in life. Parents of PB children may therefore be inclined and have the desire to report positive aspects of their child's character. This assumption is consistent with that made by Goodman (1994) with respect to parental report on children with hemiplegia. The significantly elevated ratings on the prosocial behaviour scale may therefore result from parents of TB children having less desire and need to identify positive aspects of their children's behaviour than parents of PB children. Other studies may not have reported this finding as most behaviour scales do not include items on prosocial behaviour. In future studies of behavioural outcome of PB children it would be beneficial to investigate whether parents of extremely PB children and those who had higher neonatal risk more consistently report higher prosocial behaviour in their children compared to parents of lower risk PB children. A further tests of this theory is to compare parent and teacher ratings of prosocial behaviour. The desire to attribute positive characteristics to a PB child would be expected to be less pronounced if not absent in teachers of PB children.

5.3.4 Hypothesis 4

The secondary aim of this study was to gain a rounded impression of prematurely born children's cognitive abilities. To this end assessments of visuo-spatial skills and semantic memory were carried out. Consistent with the literature summarised in Chapter 3, PB children were expected to have difficulties with visuo-spatial skills, however semantic memory difficulties were not expected.

5.3.4.1 Visuo-spatial integration

Two tasks were administered which assessed children's visuo-spatial skills. The design copy test involved copying line drawings of increasing difficulty. The drawings were scored on accuracy of the drawing i.e. line straightness and orientation, and completeness of the drawing. Prematurely born children in the study group achieved significantly lower scores on this test than TB children in the control group. The former group tended to produce more messy drawings, which represented the target drawing, but were inferior in quality. These results are difficult to interpret, in that the poor quality drawings may represent poor motor/pencil control, in other words a weakness in fine motor skill, rather than a visuo-spatial impairment. If the drawings were generally misrepresentative of the target drawing, it could be more likely to interpret this as a visuo-spatial deficit. However, scoring on this test takes into account only the accuracy of the drawing. The difference between visual spatial integration problems and difficulties with fine motor control may be better assessed by administering tests of visuo-spatial integration such as the Beery VMI (Beery & Buktemica, 2002). However, the main focus of the thesis was to evaluate Executive Function and Attention, and therefore visuo-spatial integration was not investigated further in subsequent studies.

The design fluency test is described in the NEPSY manual as an Executive Function test. However, in this study the test was not selected to represent EF, as it was considered to represent a strong element of visuo-spatial ability in addition to fluency, or cognitive flexibility. Difficulty with consistent administration further deemed the test unsuitable. Children were asked to design as many different pictures as possible in the given 60 seconds, and even with repeated prompts, many children did not attempt to complete the task as quickly as possible, paying too much attention to neatness, and what their pictures might represent (an "M" or a "BOX"). Whilst this is evidence for poor executive control, and the tendency to be distracted from the main purpose of a task, the measure of fluency itself was lost, and observations were too subjective to produce reliable scores. Given that there were no significant group differences on this test, no conclusions could be made concerning the study group's potential difficulty with visuo-spatial integration on this task.

The first part of Hypothesis four was not clearly supported. The tests used to address whether prematurely born children in this study have visuo-spatial integration difficulties did not produce clear results. Poor performance could have been influenced by poor motor control as well as visuo-spatial integration difficulties.

5.3.4.2 Semantic Memory

On the list-learning task, both groups of children achieved scores within the average range, and as expected, PB children did not show semantic memory difficulties. This result supports the second part of Hypothesis 4. In contrast, episodic memory difficulties are expected amongst children born prematurely (Isaacs et al., 1999, 2000), and will be addressed in Study 1b.

5.3.5 Results Study 1b

Despite measures to maintain participants in the second part of the study 12 months later (using follow-up letters and phone calls), there was a drop out rate of 25% in the PB group and 50% in the TB group between the two assessments. The non-responders at Time 2 did not differ from the responders across age, IQ, EF scores or behaviour. It can therefore be assumed that the responders at Time 2 do not differ systematically from the original sample. This drop out between the two assessments did however, reduce the power for statistical analyses in Study 1b.

5.3.5.1 Rivermead Behavioural Memory Test

The maximum score possible on the RBMT is 22, and expected normal scores are banded according to age of the child. Children between 7 years and 7 years 11 months are expected to score between 18-20, while children in the older age groups should score between 20 and 22. Scores below this for respective groups indicates borderline everyday memory problems. Table 16 below provides a summary of classification of scores (normal, borderline and impaired) on the RBMT for both groups. Children whose score falls into the "impaired" category are likely to experience significant difficulties in everyday living on account of poor episodic memory (e.g. having trouble finding their way home, forgetting homework instructions etc.).

Table 16: Distribution of scores on the RBMT for premature and control groups.

RBMT scores	Premature N=23	Term N=12
Normal	19 (82.6%)	11 (91.7%)
Borderline	3 (13.0%)	1 (8.3%)
Impaired	1 (4.3%)	

In the PB group, 17% of children achieved scores that fell below the normal level for their age. In comparison, only 8.3% of children in the TB group achieved a score below normal for their age. Although within the premature group there is a higher frequency of borderline or impaired scores than in the term born group, these differences are not significant: $\chi^2_{(1)} = 0.53$, $p = 0.47$.

Individual subtests were scored using standardized profile scores for age. Scores on these subtests were scored at 0, 1 or 2, where a score of 2 indicates highest performance. Analysis of the frequency of scores below 2 in the PB and TB groups shows that although on certain subtests PB children more frequently scored less than 2 than TB children, no significant group differences were found. The Chi-square results are summarised in Table 17.

Table 17: Results of Chi square analysis for RBMT subtests.

	Chi Square
Name	$\chi^2_{(1)} = 2.23$, $p = 0.35$
Belonging	$\chi^2_{(1)} = 0.17$, $p = 0.68$
Appointment	$\chi^2_{(1)} = 0.68$, $p = 0.41$
Pictures	$\chi^2_{(1)} = 0.17$, $p = 0.69$
Faces	not computed – all scored 2
Message	not computed – all scored 2
Story Immediate	$\chi^2_{(1)} = 2.36$, $p = 0.13$
Story Delay	$\chi^2_{(1)} = 0.54$, $p = 0.46$
Route Immediate	$\chi^2_{(1)} = 1.97$, $p = 0.16$
Route Delayed	$\chi^2_{(1)} = 0.23$, $p = 0.63$
Orientation	$\chi^2_{(1)} = 0.54$, $p = 0.46$

5.3.5.2 Digit span

Performance on the Digit Span subtest of the WISC (forward and backward presentation) was compared between groups. For the PB group the mean score was $M = 9.34$, $SD = 2.52$ ($N = 23$) and for the TB group $M = 9.33$, $SD = 2.42$ ($N = 12$). No significant difference between groups was found on an independent t-test: $t_{(33)} = -0.02$, $p = 0.99$.

5.3.5.3 DuPaul ADHD screener

The scores for each item of the DuPaul questionnaire are added to give a total symptoms score (a higher score indicates more behaviour problems). Furthermore symptoms scores for hyperactive and inattentive behaviour types can be calculated. The mean scores for prematurely born and term born children are summarised in Table 18.

Table 18: Means (SD) for premature and term born groups on DuPaul total score and subscale scores.

	Premature group N=30	Term Group N=22
Total Score	11.73 (8.33)	14.41 (12.46)
Hyperactive Scale	6.43 (4.72)	7.32 (6.34)
Inattentive Scale	5.60 (4.38)	7.64 (6.93)

Between group differences were not significant: Total Score $t_{(50)} = 0.93$, $p = 0.36$; Hyperactivity Scale $t_{(50)} = 0.58$, $p = 0.57$; Inattentive Scale $t(_{50}) = 1.30$, $p = 0.30$.

Scores were standardised for age and gender of the child. A score which fell above the 80th percentile for the child's age and gender (DuPaul 1998) was coded as "1", a score which fell below the 80th percentile was coded "0". No group differences were found on the scaled scores; AD/HD total score: $\chi^2_{(1)} = 0.01$, $p = 0.96$; Hyperactivity scaled score: $\chi^2_{(1)} = 0.01$, $p = 0.93$; Inattention scaled score: $\chi^2_{(1)} = 0.31$, $p = 0.58$.

5.4 Discussion

Study 1b was a follow up from Study 1a, addressing children's episodic memory, auditory working memory (digit span) and testing for the presence of a hyperactive type behavioural style.

There were no between group differences on the RBMT. In both groups children attained normal scores on this test, and the rate of borderline or abnormal scores did not differ between groups. This finding is inconsistent with previous work (Issacs et al., 2000) who found a mild impairment of episodic memory in PB children. In particular Isaacs et al. found that PB children have difficulties with tests of prospective memory (such as the appointment task on the RBMT). This finding was not replicated in the present study, the analysis of the individual subtests of the RBMT revealed no between group differences. The group of PB children in the Isaacs study had lower median birthweights (998 g vs. 1200g), longer median time on ventilation (9 days vs. 2 days) and oxygen therapy (35 days vs. 10 days) than the children in the present study. Both groups of children did however have the same median gestational age (28 weeks), suggesting that the children enrolled in Isaacs et al., were at greater biological risk of, for instance, hypoxic damage than those in the present study. Especially the longer periods of respiratory support received by the children in Isaacs et al. point to the increased likelihood of hypoxic damage, and associated hippocampal compromise. Additionally these children were born between 1982 and 1985 during which time the administration of surfactant was not yet routine. In contrast the majority of children in the present study received surfactant if the need was indicated. As described in Section 2.3.2.1 surfactant reduces the duration of time for which infants require assisted ventilation and oxygen therapy. The issue of neonatal respiratory support and its effect on later outcome is discussed in Chapter 6.

5.4.1 Auditory Working Memory

The test of auditory working memory (digit span) did not differentiate between the two groups. Both PB and TB children achieved scores in the average range on this task. The hypothesis that PB children have difficulties with auditory working memory was therefore not supported. These results are consistent with those of Study 1a, in which no difficulties with spatial working memory were noted in this group of children.

5.4.2 Behaviour

The results from Study 1a suggested that PB children do not present with a hyperactive behavioural style more than TB children do. Study 1b confirmed this finding. Children were assessed on hyperactive behavioural style using the DuPaul AD/HD screening questionnaire. Neither group of children had elevated rates of hyperactive or inattentive behaviour as indicated by the normative data provided in DuPaul (1998).

5.5 General Discussion

The objective of Study 1 Part a & b was to obtain information about PB children's cognitive profile, and in particular, to investigate whether these children have specific difficulties with EF and Attention. Overall, the study successfully investigated the hypotheses.

5.5.1 Sample limitations

A limitation of the study which may have affected the results are the properties of the two samples. The sample size for the PB group was limited by the availability of eligible participants. The birth and discharge records for the Princess Anne Hospital Neonatal Unit were checked for PB children that fulfilled the selection criteria. All children who were eligible to take part, and whose address was retrieved from the records were contacted. As described earlier, the response rate was around 30% which is not unusual for this type of sample (e.g. Pit-ten Cate et al., 2002 reported 44% response rate to a questionnaire study). Analysis of the responders and non responders in the prematurely born group in terms of gestational age, birthweight and birth year showed that there were no significant differences. This suggests that there was no systematic exclusion of children within, for instance, certain gestational age or birthweight bands. It is, however, likely that there was a degree of self-selection bias in both groups.

An impression of the motives for participation may be gained on the basis of some parental comments. In the PB group, many parents commented and stressed the point that they were pleased with their child's development and thought there would not be any major difference between their PB children and controls. It is possible that the parents of PB children who agreed to participate did so to neutralise the belief that these children will face severe developmental problems. Similarly those who chose not to participate may have decided against subjecting their children to additional testing and assessment, especially if their PB children had relatively more difficulties. Thus the study sample may be biased towards high functioning PB children.

In the control group, there was an extremely low response rate of only 6%. Participating parents often stated that their interest in the study was because they were waiting for educational assessment of their child, or were worried about aspects of their child's academic achievements. Many parents hoped that the assessment would give them a better idea whether their child was in need of extra help at school. The control group may therefore be made up of TB children who are slightly more likely than expected to have mild cognitive difficulties.

The consequences of the possible selection bias in both groups is that the study group may be higher functioning than expected, while the control group may be lower functioning than expected. This would reduce the potential differences between the two groups, and therefore reduce the chances of finding significant results. However, this type of bias is more conservative and acts against a false positive finding. In future studies it would be helpful to obtain a parental rating on the impressions of their child's development, and how they perceive the comparison between their child and a normally developing child of similar age. Unfortunately it was not possible to collect these data retrospectively as too few families agreed to take part in future studies after the completion of Study 1b.

Accounting for this limitation in the sample tested, the implications of the main findings relating to the specific EF deficit observed in prematurely born children will be discussed.

5.5.2 Executive Functions of prematurely born children

The primary purpose and aim of the first study was to investigate EF performance in PB children in comparison to TB peers. The findings have suggested an EF deficit which is specific to two dimensions of EF, cognitive flexibility and inhibition. The third component of EF, working memory (both spatial and auditory), was not found to be impaired in the PB group in this study. These findings imply a dissociation of functions across the three EF domains. This interpretation is consistent with recent literature describing EF as three dimensions rather than a single unitary function not only in adults but also within a developmental context (Lehto et al., 2003). The results suggest that in the present sample, inhibition and cognitive switching deficits occur independently of any working memory difficulties.

In addition to supporting a dissociation of EF domains, these findings suggest that different domains are differentially vulnerable to developmental delay or deficit. This differentiation of deficits may be explained in three ways, described below.

The first suggested mechanism for the differentiation of EF deficits in this study is that different subdivisions of the prefrontal cortex are differentially vulnerable to early insult, and therefore affect EF in different ways. In adults, anatomical correlates for a spatial working memory task, the Self Ordered Pointing Task (Petrides, 1998) are the dorsolateral and ventrolateral prefrontal cortex. Set-shifting abilities as assessed using the WCST have been associated with dorsolateral and orbitofrontal regions, as well as temporal and parietal lobe structures (see Robbins, 1998 for review). Furthermore, EF do not rely solely on the prefrontal cortex but involve interactions with subcortical regions. Afferent connections from the striatum, as well as connections with limbic structures (amygdala and hippocampus) are important for EF (Robbins, 1998). Damage to either prefrontal areas, or their connections may therefore be responsible for an EF deficit. Given the relative homogeneity of brain insult in PB insults, a common cognitive dysfunction would be expected. However, without further study it is not possible to offer details of a mechanism whereby WM is spared amongst the EF deficits.

A second mechanism suggests a link between differential rates of maturation of the three EF domains, and the timing of the emergence of a particular deficit. For instance, Lehto et al. (2003) report results that suggest that the three EF domains mature at different developmental rates. In Lehto et al., performance differences between age groups (range 8-12 years) were only significant for tests loading on the inhibition and cognitive flexibility factors, but not on tests loading on the WM factor. It is therefore possible that prematurely born children do have WM deficits, but that these are most apparent either very early or very late in development, but were not picked up by studying children between the ages of 8 -12. Alternatively, WM deficits are evident only in extremely PB children, or those who were exposed to the greatest neonatal risk. Luciana et al., (1999) did suggest that the level of impairment that PB children showed on EF tasks was proportional to the level of neonatal risk they were exposed to. Neonatal risk and associated cognitive deficits in the present sample of PB children is addressed in Study 2 (Chapter 6).

5.6 Conclusions

The study assessed the cognitive profile and behaviour of PB children. Low IQ and difficulties with two aspects of EF (inhibition and cognitive switching) were reported. When IQ was controlled for statistically cognitive switching was found to be impaired independently of low IQ. The mechanisms by which EF are dissociated in this group of children is discussed with reference to early neonatal risk. This is further investigated in Study 2 (Chapter 6). Furthermore, contrary to expectations both from previous literature, and from the children's inhibition difficulties, behaviour problems were not reported. The relationship between IQ, EF and Behaviour is investigated further in Study 3 (Chapter 7).

CHAPTER 6

Study 2: Oxygen therapy and cognitive outcome in prematurely born children

6.1 Introduction

As reviewed in Chapter 2, the literature describing the cognitive outcome and educational attainment of prematurely born children is extensive. Birthweight and gestational age are most often reported as predictors of cognitive outcome, with the children at the lower end of the scales achieving the poorest cognitive outcome. Other neonatal variables also play an important role in the possible consequences for outcome in these children. Lung disease associated with the requirement for respiratory support has been considered as a predictor for cognitive and developmental outcome (e.g. Short et al., 2004). Research is heterogeneous in terms of the criteria used to define the level of neonatal respiratory weakness that indicates a long-term risk. Many studies have used the formal diagnoses of Bronchopulmonary Dysplasia (BPD) and Chronic Lung Disease of Prematurity (CLD) as an index of risk. However, the diagnostic criteria can be variable according to the time of publication and the local practices of different hospital centres. Some diagnoses have been made on the basis of abnormal radiographic findings on chest x-ray, and oxygen dependency for more than 28 days (e.g. Bohm & Katz-Salamon, 2003). Others (Kennedy et al., 2000) have suggested that a more conservative cut-off of 20 days of oxygen therapy or longer, is predictive of later lung function in PB children. More recently BPD has been defined as radiographic evidence of pulmonary abnormality and oxygen dependence after 36 weeks of gestational age (Gregoire, Lefebvre, & Glorieux, 1998; Short et al., 2004), and this criterion alongside the 28 day cut-off continue to be commonly used in recent literature.

Neonatal lung disease and the requirement for oxygen therapy are considered to have predictive value for middle childhood lung function. A consistent finding is that children diagnosed with BPD have abnormal pulmonary function during middle childhood (Bhandari & Bhandari 2003; Gross, Iannuzzi, Kveselis, & Anbar, 1998), although not necessarily in the clinical range (Doyle, Chavasse, Ford, Olinsky, Davis, & Callanan, 1999). Ng, Lau and Lee (2000) however, reported that at 5.5 years of age, 44% of prematurely born children had symptoms of asthma (a chronic inflammation and narrowing of the bronchial airways) and 63% had abnormal chest x-rays, however all children had normal oximetry levels, suggesting that although early BPD has had a long term effect on lung pathology, this does not result in abnormal oximetry levels which would indicate a risk for intermittent hypoxia. Amongst very-low birthweight children treated with surfactant, Korhonen, Laitinen, Hyodynma and Tammela (2004) describe a higher incidence of bronchial hyper-reactivity, and a lower diffusion capacity. Predictors of this poor respiratory outcome were prolonged oxygen therapy, low socio-economic status and low birthweight.

In line with these findings, asthma has been reported as a common long term sequelae of BPD. Grishkan et al. (2003) report that after controlling for maternal asthma and demographic factors, chronic lung disease of prematurity, neonatal mechanical ventilation and neonatal corticosteroid administration were associated with childhood asthma. It is important to consider the incidence of asthma in prematurely born children, as childhood asthma and corticosteroid treatment (in the absence of histories of prematurity) have been associated with poor school achievement, impaired short term memory, concentration deficits, inattentiveness and a functional impairment of psychosocial functioning (Naude & Pretorius, 2003). It is possible therefore, that childhood asthma especially when it requires corticosteroid treatment, poses an additional risk factor for outcome of PB children.

In terms of the relationship with later cognitive outcome, there are two ways in which BPD may have an effect. Ischemic damage sustained during the neonatal period as a result of hypoxia and events of acidosis may have long term impact on brain development and function (Luciana, 2003). Furthermore BPD may have a distal effect, either via asthma and associated medication, or via a mechanism by which poor lung function may compromise oxygenation levels causing sub-clinical levels of hypoxia, which in turn affect the cognitive function of older children. This latter mechanism is less likely however, given results such as those reported by Ng et al. (2000) which suggest that despite a high incidence of lung pathology, oximetry levels are not affected in these children.

Several researchers have addressed the role of Bronchopulmonary Dysplasia in the neurodevelopmental outcome of prematurely born children. Hakulinen, Jarvenpaa, Turpeinen and Sovijarvi (1996) suggest that structural changes in the lungs and airways are persistent throughout childhood even in the absence of BPD. It is possible that these long term consequences on lung function will continue to have an effect on children's cognitive performance, though the mechanism by which this could occur is not clear.

There is a large body of evidence which supports the notion that BPD is a risk factor for later cognitive outcome. Short et al. (2004), for instance, addressed the effects of very low birthweight and BPD on the cognitive achievement of PB children at the age of eight years. The authors compared the intellectual competence, academic achievement, gross motor function and attention of three groups of children: 98 premature children with BPD, 75 premature children without BPD and 99 term born control children. The BPD group achieved lower scores than the premature group without BPD on measures of IQ, reading, maths, gross motor function and special educational needs. The BPD group was also significantly worse than the term born group in tests of attention (there was no difference between the two premature groups on attention tests). In addition, when birthweight and neurological problems were controlled for statistically, BPD and duration of oxygen therapy were predictive of low IQ, and poor attentional and gross motor skills. The authors concluded that the duration of oxygen therapy and BPD have long term negative effects on cognitive and academic development of prematurely born children, and that these effects are beyond those of very low birthweight.

Bohm and Katz-Salamon (2003) reported similar findings in their study of prematurely born children at the age of 5.5 years. The authors studied 70 children born with birthweight of <1500g who had a diagnosis of CLD (defined as acute pulmonary injury during the first week of postnatal life, abnormal radiographic findings and oxygen dependency for more than 28 days) but no IVH/PVL greater than Grade II. CLD severity was classified according to clinical and radiographic guidelines described in Toce et al. (1994, cited in Bohm & Katz-Salamon, 2003). CLD grades I and II were classified as "mild" while grade III was classified as "severe". Cognitive function was assessed using the WPPSI (Wechsler Preschool and Primary Scale of Intelligence) for IQ, and the complete NEPSY and tests of eye-hand coordination. Children in the CLD group achieved mean IQ scores within the normal range (Full scale IQ 94.4, Verbal IQ 99.6 and Performance IQ of 90.6), but below the control group (FSIQ 99.1, VIQ 101.5, PIQ 96.7). A significant difference in IQ was found only when comparing children with severe CLD with those with mild CLD (FSIQ 87.6 vs. 104.6 respectively). No differences were found between groups on scores on the NEPSY or of eye-hand coordination.

Further studies reporting evidence of an association between BPD/CLD and cognitive outcome have described results in agreement of Bohm and Katz-Salamon (2003) and Short et al. (2004). O'Shea, Goldstein, deRegnier, Schaeffer, Roberts and Dillard (1996) compared the outcome of 31 very low birthweight children with BPD diagnoses with a group of very low birthweight children with no BPD. At the age of 5 years, the BPD group had significantly lower Full Scale IQ and Performance IQ scores (assessed using the WPPSI). These findings suggested that in children of similar risk on the basis of birthweight category, the presence of BPD in the neonatal period further increases their risk of poor cognitive outcome. Sullivan and McGrath (2003) report BPD and CLD as perinatal precursors for educational underachievement (particularly in mathematics and the use of special school services) in prematurely born children at 8 years of age (with IVH Grade 2 or below). In younger, preschool age prematurely born children, poorer developmental outcomes are reported for those children who are diagnosed with CLD/BPD in the absence of neurological risks or symptoms defined as IVH Grade II or below (Katz-Salamon, Gerner, Jonsson, & Lagercrantz, 2000; Singer, Yamashita, Lilien, Collin, & Baley 1997). Farel, Hooper, Teplin, Henry and Kraybill (1998) summarise evidence to show that prematurely born children with prolonged requirements for respiratory support (which may be an indicator for later BPD) are more likely than prematurely born children without this respiratory insufficiency to experience increased morbidity associated with infections, more frequent need for hospitalisations, delayed fine motor and cognitive development, growth problems and increased post-neonatal mortality rates. The evidence therefore suggests that the requirement for prolonged oxygen therapy or assisted, mechanical ventilation (even in the absence of a formal diagnosis of BPD) will worsen the prognoses for prematurely born children.

The aim of the present study was to investigate whether neonatal indices of respiratory insufficiency are better predictors of cognitive and behavioural outcome than other neonatal factors. It was predicted that those children who required longer durations of ventilator support, and those who received more than 28 days of oxygen therapy would have significantly lower scores on tests of IQ, and attention and EF, and more behavioural problems than those children who had lower dependence on ventilator support and / or oxygen therapy. In addition the rates of asthma symptoms and sleep related breathing problems (such as apnea) were investigated, with the expectation that increased rates would be observed amongst the children with the most respiratory difficulties neonatally.

6.2 Method

6.2.1 Participants and procedure:

Neonatal data were obtained for the group of forty prematurely born children described in Section 5.2.1. Information about neonatal oxygen requirements was available for 31 children. Duration of oxygen dependence ranged from 0 to 365 days. Radiographic information about lung abnormality and was not available, nor were formal diagnoses of BPD/CLD, therefore the group was split by oxygen duration into those requiring more than 28 days (long O_2) and those requiring 27 or less days of oxygen therapy (short O_2) in line with the diagnostic criteria for BPD (e.g. Bohm & Katz-Salamon, 2003). The demographic variables of the two groups are summarised in Table 19.

Table 19: Demographics of prematurely born children with long and short oxygen dependence

	Short O_2 N = 18		**Long O_2 N = 13**	
	Mean	**SD**	**Mean**	**SD**
Gestational Age	29.56	1.54	27.30	1.93
Birthweight (grams)	1335.56	300.26	1016.15	320.14
Age (years; months)	8;9	1.15	8;1	1.88
Maternal Age (years)	28.21	5.84	28.92	5.59
Time Ventilation (days)	0.94	1.46	10.54	13.12
Time Oxygen (days)	2.72	5.74	107.61	87.07
Gross Motor*	1.81	0.75	1.77	0.67
Fine Motor*	2.27	1.27	2.44	1.23
Speech*	2.00	0.00	2.00	0.00
Problem solving*	2.09	1.13	2.11	1.30

*As assessed at follow up clinic, scores reflected the degree of developmental delay in months from corrected age. A score of 2 reflects developmental level within 1 month of corrected age.

The short O_2 group consisted of nine girls and nine boys. The long O_2 group was less equally distributed, with nine girls and only four boys. This difference was not found to be significant ($\chi^2_{(1)}$ = 1.94, p = 0.16.) Comparisons between the two groups showed that the slight difference in age was not significant ($t_{(29)}$ = 1.18, p=.29). Comparisons on the neonatal data using independent t-tests (equal variances not assumed) revealed that children in the Long O_2 group had a significantly lower gestational age $t_{(22.27)}$ = 3.47, p<0.01) and birthweight ($t_{(24.98)}$ = 2.81, p<0.01) than children in the Short O_2 group. As expected the long O_2 group received ventilatory support ($t_{(11.19)}$ = -2.52, p<0.05) and oxygen therapy ($t_{(12.08)}$ = -4.34, p<0.01) for significantly longer than the short O_2 group. There were no differences between groups on any other neonatal variables.

6.2.2 Asthma and Sleep Disordered Breathing

In addition to the neonatal variables, information was obtained about children's asthma related symptoms and breathing and behaviour during night time sleep from parent report questionnaires.

6.2.2.1 Sleep Disordered Breathing Questionnaire

A questionnaire was chosen which addresses breathing abnormalities during night-time sleep, in order to relate these to children's cognitive performance (Gozal, 1998). The questionnaire consists of 37 items asking about the child's sleeping environment and habits (see Appendix C). Parents rate the frequency of sleep related behaviours during the past six months on a scale of 1 (Never) to 5 (Almost always). The questionnaire has been used for assessment of sleep related to behaviour problems (Chervin et al., 2002; O'Brien et al., 2003), as well as academic performance (Gozal & Pope, 2001). Of particular interest in the present study were items relating to disrupted sleep and snoring.

6.2.2.2 Asthma and Rhinitis symptoms Questionnaire

In order to obtain an insight into the frequency of children's asthma related symptoms, a short and straightforward questionnaire was chosen. Asher et al. (1995) have designed a short 8 item questionnaire which examines the frequency and severity of asthma related symptoms (such as wheezing) in the past 12 months (see Appendix D). The questionnaire was designed for the International Study of Asthma and Allergies in Childhood (ISAAC), and has been used in several other studies addressing the prevalence and severity of asthma and rhinitis symptoms in childhood (e.g. Kaur et al., 1998; Robertson, Roberts, & Kappers, 2004; Braun-Fahrlander et al., 2004; Arif Borders, Patterson, Rohrer, Xu, 2004).

6.3 Results

6.3.1. Neonatal factors

In order to test which neonatal variables predict IQ, inhibition, cognitive switching and behaviour outcome, a correlational analysis was run. The results are presented in Table 20.

Table 20: Correlation analysis between neonatal variables and outcome measures

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1.GA	1.00												
2.BW	.70**	1.00											
3. Maternal Age	.18	.31	1.00										
4. APGAR	.14	.13	-.06	1.00									
5. Time Hospital	-.69**	-.60**	-.24	-.43*	1.00								
6. Time Oxygen	-.51**	-.50**	-.17	-.22	-76**	1.00							
7. Time Ventilation	-.60**	-.48**	-.07	-.18	.72**	.65**	1.00						
8. IVH grade 1 or 2	-.46**	-.22	.01	.01	.31	.19	.31	1.00					
9. IQ	.21	.23	.31	-.06	-.23	-.28	-.29	-.04	1.00				
10. Switching	.26	.28*	-.03	.02	-.33	-.26	-.24	-.05	.34*	1.00			
11. Inhibition	.18	.22	-.03	.32	-.34	-.23	-.40*	.28	.29	.39*	1.00		
12. Hyperactive	.01	.06	-.05	-.02	.02	.22	.10	-.16	-.38*	-.29	-.21	1.00	
13. Behaviour total	-.02	.05	.00	.10	-.12	.05	-.01	.01	-.21	-.10	-.12	.80**	

*p<.05, **p<.01

The correlational analysis shows that there is a high degree of correlation between certain measures of neonatal risk, such as time on oxygen, time on ventilation and time in hospital. The only significant correlations between neonatal risk factors and cognitive and behavioural outcome scores are for birthweight and cognitive switching ($r = .28$, $p<.05$), and for time on ventilation and inhibition ($r = -.40$, $p<.05$). Correlations between time on oxygen and cognitive outcome scores were low, but in the expected direction. Other neonatal risk factors such as maternal age, APGAR score and IVH did not significantly correlate with the outcome measures, and in most cases effect sizes were small.

Gestational age did not significantly predict any of the outcome measures, and birthweight was significantly associated only with switching. As the aim is to identify neonatal risk factors associated with prematurity (which includes low birthweight and low gestational age by definition) further analyses will be carried out on the variables "time on ventilation" and "time on oxygen therapy".

Only the variables time on ventilation and birthweight are significantly correlated with outcome measures, and these two variables will be considered in more detail in addition to the long and short term oxygen groups.

In line with previous research (e.g. Bohm et al., 2002; Taylor et al., 2000) children were divided into birthweight category. The median birthweight was 1200g, children born between 2000g and 1500g are generally considered as low birthweight, children born at less than 1500g are considered as very low birthweight. The sample was therefore split according to low and very low birthweight categories in order to investigate differences between birthweight groups. Twenty-two children fell into the very low birthweight category, and the remaining 18 into the low birthweight category. There were no mean differences for IQ (VLBW Mean = 98.12, SD = 13.28, LBW Mean = 98.77, SD = 8.19; $t_{(35.57)} = -0.17$, $p = 0.83$), or behaviour problems ($t_{(30.27)} = -0.34$, $p = .74$). For the MANOVA of the EF subtests there was no significant main effect ($F_{(2,33)} = 0.32$, $p = .73$), and neither of the univariate effects was significant.

A median split was used to form a long-term ventilation and a short-term ventilation group. The short term ventilation group received 10 or less days of ventilation (N = 20), and the long term ventilation group received 11 or more days (N=20). The data were analysed using independent samples t-tests and MANOVA. Means and Standard Deviations are presented in Table 21 below.

Table 21: Means and Standard Deviations of scores for the long- and short-term ventilation groups.

	Short term ventilation Mean (SD)	Long-term ventilation Mean (SD)
Gestational Age	29.25 (1.52)	27.60 (2.39)
Birthweight	1295.00 (315.80)	1106.50 (400.01)
IQ	100.81 (9.93)	96.04 (12.02)
Switching	9.90 (3.20)	7.71 (4.00)
Inhibition	8.32 (2.50)	6.23 (2.81)
Hyperactive behaviour	3.60 (2.28)	5.45 (2.87)
Behaviour total score	9.00 (5.88)	13.10 (6.45)

Differences were significant for gestational age $t_{(38)} = -2.60$, $p<.05$ (d = 0.69) total behaviour score $t_{(38)} = -2.10$, $p<0.05$ (d = 0.63) and hyperactive behaviour score $t_{(38)} = -2.26$, $p<0.05$ (d = 0.68). There was no significant difference between groups for IQ $t_{(38)} = 1.37$, $p = .18$, (d = 0.41); or birthweight $t_{(38)} = -1.64$, $p = 0.11$, (d = 0.47). The results of the MANOVA of EF scores are presented in Table 22.

Table 22: F ratios and effect sizes for univariate main effects of duration of ventilation on tests of EF

Source		Mean Square	df	F	p	d
Multivariate						
	Ventilation (λ = .832)		2	3.32	<.05	
Univariate						
Ventilation	Cog Switch	42.99	1	3.33	.08	0.53
	Inhibition	38.84	1	5.52	<.05	0.74
Error	Cog Switch	12.92	34			
	Inhibition	7.03	34			

In the multivariate analyses for the EF measures there was a significant multivariate effect $F_{(2,33)} = 3.22$, $p<.05$, and the univariate effect for inhibition was significant $F_{(1,36)} = 5.52$, $p<.05$. The univariate effect of switching was not significant. When GA was covaried, the main effect of ventilation was no longer significant $F_{(1,36)} = 2.82$, $p = 0.07$. However, the univariate effect on inhibition remained significant $F_{(1,36)} = 4.14$, $p<0.05$.

The data were analysed for short and long oxygen therapy groups (see Table 19 for demographics). The categories were defined according to one of the diagnostic criteria for BPD (27 days of oxygen or less; 28 days or more, Bohm & Katz-Salamon, 2003), as no radiographic information on lung pathology was available, this served as an index of respiratory insufficiency rather than a marker of disease status. Table 23 provides a summary of the means and standard deviations of outcome for the two groups.

Table 23: Means and standard deviations of outcome measures for children on long and short oxygen therapy.

	Short O_2 N = 18		Long O_2 N = 13	
	Mean	SD	Mean	SD
IQ	99.31	9.24	100.76	9.40
Switching	9.83	3.05	7.15	4.61
Inhibition	8.44	2.53	6.15	2.15
Hyperactive	3.70	2.62	4.73	6.13
Behaviour total	9.40	2.28	10.67	5.45

Differences were not significant for the total behaviour score ($t_{(33)} = .63$, $p = .53$, $d = 0.19$), hyperactive behaviour score ($t_{(33)} = 1.22$, $p = .23$, $d = 0.81$) nor for IQ ($t_{(33)} = -0.27$, $p = .79$, $d = 0.08$). Results of the MANOVA of the EF scores is summarised in Table 24 below.

Table 24: F ratios and effect sizes for univariate main effects of duration of oxygen therapy on tests of EF

Source		Mean Square	Df	F	p	d
Multivariate						
	Oxygen ($\lambda = .788$)		2	3.77	<.05	
Univariate						
Oxygen	Cog Switch	54.20	1	3.79	.06	0.86
	Inhibition	39.61	1	7.00	<.05	0.81
Error	Cog Switch	14.28	29			
	Inhibition	5.66	29			

The multivariate effect of oxygen therapy duration on EF measures was significant, $F_{(2,28)} = 3.77$, $p<.05$. The univariate effect on inhibition was significant $F_{(1,31)} = 7.00$, $p<.05$, however for switching it was not significant $F_{(1,31)} = 3.79$, $p = 0.06$. When gestational age and birthweight were added as covariates, the multivariate effect of oxygen therapy remained significant

$F_{(2,26)} = 3.58$, $p<0.05$; as are univariate effects on inhibition $F_{(1,30)} = 6.17$, $p<0.05$; and cognitive switching $F_{(1,30)} = 4.16$, $p<0.05$.

6.3.2 Asthma

The asthma symptoms questionnaire (a copy of which is in Appendix D) was completed by parents. A score of "1" was assigned to those cases for whom some symptoms of asthma were noted either at present or in the past. Those cases who were reported never to have had asthma or related symptoms were assigned a score of "0". Chi square analysis was carried out to determine whether there was a larger number of cases with asthma symptoms among the long term oxygen group. The result was not significant $\chi^2_{(1)} = .74$, $p = 0.39$. Within the long oxygen group 50% of children were reported to have had asthma symptoms at some time, compared to 33% in the short oxygen group. Although this difference was not significant, it is in the expected direction. Correlation analysis revealed that the asthma score did not significantly correlate with any of the cognitive or behavioural outcome measures; these results are summarised in Table 25 below.

Table 25: Correlations of Sleep Disordered Breathing Questionnaire and Asthma Symptoms Questionnaire against outcome measures.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. IQ	1.00														
2. Cog. Switching	.34*	1.00													
3. Inhibition	.29	.39*	1.00												
4. Ventilation (days)	-.29	-.24	-.40*	1.00											
5. Oxygen (days)	-.28	-.26	-.23	.68**	1.00										
6. Total SDQ	-.21	-.10	-.12	-.01	.05	1.00									
7. Hyperactivity	-.38*	-.29	-.21	.10	.22	.80**	1.00								
8. Emotion	-.12	.08	.09	-.05	-.17	.74**	.39*	1.00							
9. Conduct	-.20	-.22	-.14	.04	.06	.68**	.54**	.26	1.00						
10. Peer	.17	.19	-.10	-.14	-.01	.60**	.21	.40*	.17	1.00					
11. Prosocial	.31	.02	-.07	.17	.27	-.33*	-.24	-.13	-.51**	-.10	1.00				
12. SDB-A	-.29	-.04	.27	.06	.32	.47*	.37*	.41*	.39*	.25	-.12	1.00			
13. SDB-B	-.22	-.27	.04	.04	.21	.24	.21	.33	-.02	.14	-.03	.63**	1.00		
14. SDB-T	-.16	-.09	.08	.13	.22	.41*	.32	.42*	.22*	.24	.07	.85**	.75**	1.00	
15. Asthma	.20	-.16	-.01	.09	.15	.26	.15	.35	.05	.22	-.08	.21	.43*	.25	1.00

*p<.05, **p<.01

6.3.3 Sleep Disordered Breathing Questionnaire

The sleep disordered breathing questionnaire consisted of two parts. Part A contained questions relating to the quality of the child's sleep and unusual sleep behaviour such as sleep walking. Part B consisted of questions relating to breathing during sleep, such as snoring, struggling to breathe while asleep and moming headaches. The between group difference (short vs long oxygen therapy) on total breathing problems was significant (Total Score: $t_{(24)}$ = 2.51, p = .02, d = 0.71), as was the between group differences for Part B of the Sleep questionnaire (Part B: $t_{(25)}$ = 2.59, p = .02, d = 0.85). However, there was no differences between groups scores on Part A of the questionnaire (Part A: $t_{(25)}$ = 1.96, p= .67, d = 0.56). These results indicate that children with longer oxygen therapy did present with more sleep related problems with breathing during sleep than children in the short-term oxygen group. When scores on the sleep disordered breathing questionnaire were correlated with scores on cognitive and behavioural outcome measures, an association was found only with behaviour scores (see Table 24). Part A of the Sleep Disordered Breathing Questionnaire correlated significantly with the total behaviour score and with the hyperactive behaviour subscale. As neither the total score for Sleep A nor any individual items were significantly associated with any other outcome measures, no further analyses were carried out. Part B of the questionnaire was not significantly associated with any outcome measures.

6.4 Discussion

As expected, there was a strong association between the duration of ventilation and the duration of oxygen therapy requirements of the PB children. It was therefore expected that both variables would be comparable in predicting cognitive outcome. Both long ventilation and long oxygen therapy were associated with poor scores on EF especially inhibition. In addition, children who received longer ventilation had significantly more behaviour problems. These indices of respiratory support were better predictors of outcome than any of the other neonatal risk factors (including gestational age and birthweight) within the PB group. There was a higher (though non-significant) rate of asthma symptoms among those PB children who received longer respiratory support, and these children also had significantly higher scores on the sleep related breathing questionnaire than children with lower respiratory insufficiency neonatally.

These results confirmed the hypothesis that longer durations of respiratory support neonatally (rather than birthweight) are associated with cognitive outcome in middle childhood. Piecuch et al. (1997) reported similar findings. In their study no association was found between outcome and birthweight, and this finding has also been reported by other groups (e.g. Taylor et al., 2002).

Differences in general IQ were not found in this sample of children, which is inconsistent with the findings of Short et al. (2004) who did find a difference in IQ scores between PB children with BPD and those without the diagnosis. The effect size reported in their study was moderate, $d = 0.3$, however in the present sample the effect size for IQ was only small at $d = 0.16$. The lack of significant difference is therefore not due to small sample sizes. Scores on the attention tests did not differ between PB groups in the Short et al. study ($d = 0.27$), nor in the present study ($d = 0.02$). Although there are no significant differences in either study, the effect size in Short et al. is considerably larger than that in the present study. Short et al. did not specify whether the PB children in their sample had IVH and if so to what degree. It is however possible that the larger effect sizes observed in that study are due to the sample including children with a more severe degree of IVH than the children in the present sample.

Bohm and Katz-Salamon (2003) tested children (5.5 years of age) who had IVH status of less than Grade II, and are comparable in terms of severity of brain insult to children in the present study. In Bohm and Katz-Salamon differences in IQ were significant between the PB group with severe CLD compared to that with mild CLD. In their study CLD significantly distinguished children's IQ scores, whereas in the present study this was not the case. Some studies do support the present findings however. Similar results were reported in Robertson et al. (1992). In their study only children who received oxygen after 36 weeks of normal gestational age (i.e. more than 8 weeks of oxygen for an infant born at 28 weeks, or more than 6 weeks of oxygen for an infant born at 30 weeks etc), showed an impairment in general cognitive function at 8 years of age. Giaccoia, Ventkataraman, West-Wilson and Faulkner (1997) also reported a difference in IQ scores only between prematurely born children with BPD and term controls (but no difference between premature groups with and without BPD). It is suggested that the sample assessed in the present study may not be representative in terms of the severity of neonatal respiratory insufficiency. As no formal diagnosis is available, it is not possible to speculate about the severity and lasting damage that the long term oxygen therapy or mechanical ventilation actually had on these children.

Other studies have not reported on behavioural outcome or Executive Functions in relation to neonatal respiratory support. Differences on these measures were found in the present study, and it is possible that similar findings would be found on assessing the samples of Bohm and Katz-Salamon

(2003) and Short et al. (2004). The rational for this assumption will follow the line of argument presented in Study 1. The cognitive deficit of the PB children overall was more pronounced for the EF tasks than for IQ scores (See section 5.3.2). It was argued that more subtle consequences of preterm birth would be evident as EF deficit rather than a global intellectual deficit. The nature of the neurological damage that occurs as a consequence of preterm birth affects predominantly white matter in the region of the cerebral ventricles. While this is associated with global cognitive deficits, it also has a direct impact on the association fibres between the frontal cortex and the striatum, as well as connections to the caudate head of the basal ganglia. These structures are strongly implicated in EF tasks, therefore a disruption of these fibres may manifest itself as EF difficulties (see Robbins, 1998). It is agreed that IQ and EF are closely related cognitive functions. While the nature of the relationship remains an area for discussion (See Section 7.2) it is likely that a deficit in EF will also affect IQ. In the present sample therefore, long term respiratory support could be seen as a marker for neonatal illness and risk for hypoxic brain injury. This in turn would affect subcortical white matter, damage to which manifests itself specifically in EF difficulties, but also causes a small decrease in general IQ. This would explain why PB children in this sample have low average IQ scores alongside a more serious EF difficulty.

Luciana (2003) provides a comprehensive review of neonatal brain injury associated with premature birth, and presents evidence in favour of two theories of developmental brain plasticity. Early damage to the developing brain with later functional impairment questions the capacity for plasticity, as the damage has had a lasting effect on function. However, early damage followed by later recovery of function, or an appropriate developmental emergence of a skill suggests that plasticity has resulted in at least partial recovery or a compensation of function. In the present group of children with a relatively mild deficit, the second explanation in favour of plasticity is most likely. It is plausible that early brain damage has led to partial recovery and/or compensation of function. In other words, as these children have some difficulty with attentional and EF tasks, with the impairment being relatively mild, it is possible that through compensation children are engaging other resources and brain structures, with the result of being less accurate and efficient at the given tasks. Evidence in favour of this suggestion is described in a case study of a 22 year old man born at 26 weeks gestation (Maguire, Vargha-Khadem, & Mishkin, 2001). This patient suffered from episodic memory difficulties, yet achieved a full scale IQ in the normal range. Structural scans revealed bilateral hippocampal atrophy, however, in functional imaging analysis, the hippocampus was appropriately activated during retrieval tasks, but in conjunction with other brain areas, notably the frontal cortex. These areas were not activated in control subjects performing the tasks, which led to the conclusion that the tasks were more effortful for the patient, resulting in several brain areas being activated, and a suboptimal task performance.

Although the arguments presented above are the most likely in explaining the mechanism linking neonatal respiratory insufficiency with later outcome, the findings of elevated asthma symptoms and sleep disordered breathing amongst these children should be considered. Children in the long oxygen therapy group did have a slightly higher rate of asthma than the PB children with less respiratory requirements. These children's cognitive function may additionally be affected by their asthma status, however, there was no evidence to support this. There was no association in this sample between asthma and cognitive outcome, and furthermore, the evidence for a connection between asthma and cognitive outcome is mixed. Asthma was therefore not considered as a factor which could have severe impact on children's cognitive outcome. In contrast, the link between sleep disordered breathing and cognitive performance is more widely accepted. Gozal and Pope (2001), for instance, reported that early childhood snoring was related to lower academic achievement at 13-14 years of age. It was therefore a possibility that an elevated score on sleep disordered breathing problems questionnaire for the

PB group with higher neonatal respiratory insufficiency is contributing to these children's cognitive difficulties. The results did not support this possibility. Part A of the sleep questionnaire (Sleep Behaviour) was however significantly associated with children's total behaviour score, as well as the hyperactivity, conduct and emotion subscales.

Evidence linking sleep disturbances and behaviour is mixed; Blunden, Lushington, Kennedy, Martin and Dawson (2000), for instance, report no association between childhood obstructive sleep apnea and snoring and behaviour. On the other hand Chervin, Dillon, Bassetti, Ganoczy and Pituch (1997) have reported such an association. Others (Corkum, Tannock, Moldofsky, Hogg-Johnson, & Humphries 2001) have suggested that the reason for an association between sleep problems and behaviour in children with AD/HD is related to disrupted bedtime routines in children with problematic behaviour. The latter suggestion is most appropriate in explaining the results of the present study. Since behaviour was related to Part A of the Sleep questionnaire which addresses sleep behaviour, it is likely that daytime behaviour problems are affecting sleep behaviour rather than the opposite effect by which a lack of sleep would be responsible for daytime behaviour problems.

6.4.1 Implications

The findings of the present study highlight the importance of considering neonatal variables in addition to gestational age and birthweight when studying the outcome of prematurely born children. Classifying children by birthweight or gestational age only does not allow adequate study of the mechanism behind cognitive impairment. Understanding these mechanisms is of importance in order to establish prevention and intervention. Birthweight and gestational age are generally correlated with other neonatal factors (lower gestational age tends to be associated with poorer lung maturation and therefore greater respiratory insufficiency). However, the treatment of respiratory insufficiency varies, and different levels of risk may be evident within birthweight categories. Lung maturation can vary greatly depending on whether maternal Dexamethasone was administered, whether the child received surfactant, the type of mechanical ventilation used and neonatal management decisions regarding weaning the infant from respiratory support. These factors should be considered when addressing the outcome after premature birth, and when making prognosis on morbidity.

6.4.2 Limitations

Although the study did successfully address the aims and hypotheses, some limitations were identified. The sample size of 31 prematurely born children for whom complete neonatal information was available was adequate, however, a larger sample of children would be preferable. Further investigation of this work would benefit from more specific respiratory risk categories, including, for instance, severe, moderate and mild respiratory insufficiency. Additionally more detailed neonatal information would be beneficial in determining the mechanisms behind the respiratory insufficiency and cognitive outcome link. Outcome can, for instance, vary according to the type of ventilation administered. Two available techniques are high frequency oscillation ventilation, and standard ventilation, each of which has benefits and drawbacks in terms of long term lung function (Courtney et al., 2002). Similarly, it may be more informative to record the maximal oxygen saturation used during oxygen therapy, in addition to the duration of the therapy. Setting oxygen saturations at too high a level has the risk of Retinopathy of Prematurity, and may also have other adverse effects. Although Dexamethasone is administered in order to aid maturation of the lungs, the drug has been associated with some negative side effects. As discussed in Section 2.3.2.1, corticosteroids have been associated with poor growth, and suppression of the development of protein matrix which may have involvement in the rupture of blood vessels of the germinal matrix causing intraventricular haemorrhage.

6.5 Conclusions

Neonatal respiratory support was found to be more important in the prediction of outcome than any of the other neonatal factors including birthweight and gestational age. A mechanism was suggested which explains the link between neonatal respiratory support, brain insult, and associated cognitive outcome. It is thought that prolonged respiratory support requirement was a marker for neonatal illness and the associated risks of hypoxic / ischemic brain insults. As the brain areas affected by this type of damage are also strongly implicated in EF, these functions were considered as most vulnerable. It was argued that EF are closely linked to and perhaps to some extent underpin general cognitive function. By this rational it is likely that an EF deficit caused by hypoxic damage will also have a certain degree of impact on general cognitive function. Previous studies have addressed general cognitive outcome in relation to neonatal respiratory requirements, but not EF specifically. If the argument presented is accurate, children in these studies would also show EF impairments if tested on these measures. Behaviour problems were only somewhat related to respiratory requirements, but were more strongly related to sleep behaviour problems. However, neither sleep related breathing difficulties nor asthma was related to respiratory insufficiency or cognitive outcome. The relationship between IQ and EF and Behaviour is addressed in Study 3.

CHAPTER 7

Study 3: Testing the relationship between IQ, EF and behaviour

In Study 1 Prematurely born children were assessed on both cognitive outcome and behaviour, and were found to have difficulties with the inhibition and cognitive switching dimensions of EF, but were not reported to have behaviour difficulties. This chapter discusses evidence for the relationship between IQ and EF in adults and children, and explores the associations between both IQ and EF with behaviour in child populations. In this study the relationship between both IQ and EF with behaviour was investigated using data from the sample of PB and TB children described in Study 1.

7.1 Adult neuropsychology

General intelligence often conceptualised as the "g-factor" (gF) is generally defined as individual differences in ability on multiple cognitive measures. So, for instance, the WAIS (Wechsler Adult Intelligence Scale) is a measure of intelligence based on the performance across a set of tests, which individually tap into both verbal and non-verbal skills. Investigation of gF remains an important issue of interest to cognitive researchers. One aspect of investigation is to identify to what extent Executive Functions contribute to gF, and whether they should be considered to be a separate entity. Sternberg (Sternberg & Gardener, 1982; Sternberg, 1985, cited in Berg & Sternberg 1985) argued that EF are common to all tasks, and therefore responsible for a large proportion of gF. However, some researchers (e.g. Crinella & Yu, 1999) have refuted this argument, claiming instead that EF should be considered as a completely separate entity. They support this notion using evidence from rodent EF systems, adult neuropsychology and developmental disorders (AD/HD). While they successfully present evidence to show a dissociation between gF and EF, i.e. a dysfunction in the executive system with a sparing of IQ, the issue concerning to what *degree* EF contribute to gF in healthy and normally functioning cognitive systems is not addressed. In particular this issue becomes increasingly important when considering the relationship between EF and IQ in a developmental context (discussed in the next section).

A strong association between gF and attentional control has been reported (Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Engle, Tuholski, Laughlin, & Conway, 1999; Kane & Engle, 2003). Recently Gray et al. (2003) used magnetic resonance imaging to investigate the neural substrate of this association. In their study, brain activation patterns in participants undergoing two versions of a challenging working memory task were measured. In one version there was low interference, the second version involved high interference. Participant's gF was measured using Raven's Advanced Progressive Matrices. The researches report an association between gF and performance on the high interference WM task, which is mediated by cortical activity levels in the lateral prefrontal cortex (PFC). The results suggested that participants with high gF and associated strong performance (i.e. high accuracy despite interference) also showed high levels of activation in the lateral PFC. On the other hand, participants with low gF also made more errors on the high interference trials and showed less activation in the lateral PFC.

Brain imaging thus suggests that individuals with high gF also have strong EF, which in terms of brain activation is evident through the recruitment of the PFC in tasks involving high EF load.

7.2 Developmental Neuropsychology

In a developmental context, investigating the relationship between IQ or gF and EF becomes more complex for a variety of reasons. To begin with, suitable assessment measures are needed in order to estimate children's IQ and EF at various ages. The definition of IQ changes with development, and so does the focus of the testing instruments. While the Bayley's Infant Development Scales (BIDS) is focussed on sensorimotor functions, the WPPSI (Wechsler Preschool and Primary Scale of Intelligence) assesses language oriented skills. The WISC (Wechsler Intelligence Scale for Children) is made up of tests of both performance and language related skills. This transition in assessment focus reflects the developmental transition of the infant from expressing abilities through sensorimotor actions, through early language to more complex language and reasoning. The difficulty however, is that the skills which describe general intelligence at one age, are not necessarily comparable to those of an older age. In EF testing however, the assessments have more continuity in terms of both content and task demands. The skills measured are the same throughout, and the tests are adapted for younger children.

On the basis of the difficulties arising from the assessment techniques used, trying to distinguish between IQ and EF within a developmental context is problematic. However, the view adopted by many of the influential developmental psychologists is that EF are closely tied to gF during development. Russell (1999), for instance, describes the role of EF as action monitoring, which is considered essential for development and the acquisition of skills and knowledge which together contribute to gF. Action monitoring is described as a combination of inhibition and working memory, which matures alongside the anatomical maturation of the prefrontal cortices. Berg and Stenberg (1985) make a strong argument for the idea that a novelty response is a continuous qualitative feature of intelligence that can be observed from infancy to adulthood, and should therefore be considered as a core feature of intelligence.

Duncan (1995) adopts a similar position. He suggests that general intelligence, as assessed in formal IQ tests, is in fact partially a function of Executive Control. According to Duncan's theory, failing to carry an action through successfully can be considered as a goal neglect, which is directly related to low IQ (or low gF).

In conflict with the theories of Duncan (1995) and Russell (1999), Diamond (1996; Diamond et al., 1997, cited in Diamond, 1998) has presented evidence for a dissociation of EF and IQ during development. Diamond refers to the example of children who received early treatment for Phenylketonuria (PKU). In this disorder, there is a depletion of dopamine in the ascending neural circuits which are responsible for Executive Control. In line with this, on neuropsychological assessments, these children have a specific deficit on EF tasks. However, despite these executive difficulties, children with early treated PKU are likely to achieve an IQ within the normal range.

While Duncan and Russell argue that the development of EF involves attaining EF competence, Diamond argues that children who fail EF tasks exhibit a performance deficit. In other words, children's underlying competence is in place, but cannot be expressed due to a performance error, for instance, in inhibiting a prepotent but irrelevant response.

The focus of the present study is not to tease apart the conceptual and practical issues concerned with assessment of the development of EF and gF. In summary there are two ways of conceptualising the relationship between EF and IQ. The first identifies IQ as a fluid intelligence, which is the fundamental underlying cognitive function subserved by, amongst others, EF. Alternatively, EF could be seen as an underlying and driving force, which is required in order to facilitate intellectual development, for instance, through response to novelty (Berg & Sternberg, 1985). In this way, the executive attention system must be functional in order to direct the child's attention to relevant stimuli and inhibit interference from non-relevant sources. Taking this viewpoint, EF and IQ are closely related, and certain aspects of EF play an indispensable role in coordinating the individual's response to novelty and action monitoring, both of which are essential to the acquisition of fluid intelligence.

7.3 The relationship between IQ, EF and Behaviour in a developmental context

Hyperactive behavioural style in children has been associated with several causes including genetic origins, environmental factors, and cognitive factors. Psychopathological disorders of childhood such as AD/HD and conduct disorders are strongly associated with hyperactive behavioural style (e.g. Hughes, White, Sharpen, & Dunn, 2000). Learning disabilities such as dyslexia (Heiervang, Stevenson, Lund, & Hugdahl, 2001) have also been associated with hyperactive behavioural style.. There is evidence to suggest that both IQ and EF play an important role in hyperactive behavioural style, and findings in support of both will be discussed. The focus of this introduction is to identify studies that report on factors that contribute to hyperactive behavioural style, and less emphasis will be placed on whether IQ and EF are dissociable or how they were assessed.

Executive Dysfunction can be characterised by any combination of poor working memory, lack of cognitive flexibility, and lack of inhibition. In terms of behaviour, Executive Dysfunction is most often associated with inhibition difficulties and lack of cognitive flexibility. Questionnaires addressing behavioural style are thus composed of items such as those on the SDQ ("Restless, overactive, cannot stay still for long"). It is therefore likely, though not necessary that children with poor EF will show some degree of Hyperactive Behavioural Style. In favour of this hypothesis, Clark et al. (2002) found that EF scores correlated with all adaptive behaviour outcomes. EF predicted adaptive behaviour, communication and socialisation domains. Similarly, Brophy et al. (2002) described a group of hard to manage preschoolers at age 7, who had inhibitory control problems, which were related to their behavioural difficulties. Cognitive flexibility was, however, not related to behaviour problems. Kuntsi, Oosterlaan and Stevenson (2001) studied pervasively hyperactive children and compared their cognitive and behavioural style to that of control children. Between group effects were significant for WM scores, however, these effects were mediated by IQ. In other words, hyperactive children's lower WM scores were not independent of their lower IQ scores. Responding on delay aversion tasks was found to be characteristic of a hyperactive behavioural profile. Kuntsi et al.'s findings therefore suggest that hyperactive behaviour is related both to IQ and to impulsive behavioural style.

An alternative to EF and especially inhibition deficits being at the root of behaviour problems, is the suggestion that early neuropsychological deficits may impact behaviour via brain-environment interactions. From this perspective, impulsive behavioural style is a consequence of early cognitive deficits, which in turn contributes to poor interpersonal adaptation and social maturity (Stuss & Alexander, 2000). In this case, PB children with more serious neuropsychological difficulties are at the greatest risk for subsequent behaviour problems, regardless of whether the neuropsychological difficulties are specific to EF and inhibitory control. From a similar perspective Gadeyne, Ghesquiere and Onghena (2004) suggest that poor academic achievement contributes to children's psychosocial problems. Hinshaw (1992) summarises evidence from several studies addressing the association between academic underachievement and externalising behaviour. The findings suggest that in younger children inattention is specifically associated with IQ, while in adolescents, aggressive behaviour is most closely associated with IQ. Hinshaw explores factors contributing to the association between externalising behaviour and academic underachievement, such as low IQ, family adversity and neurodevelopmental delay, pointing out the complexity of the causal mechanisms linking these factors.

In a large scale epidemiological twin-study, Goodman, Simonoff and Stevenson (1995) studied behavioural deviance in children with IQ scores that varied within the normal boundaries (i.e. excluding below average IQ). The results showed that children with lower IQ scores were rated as having more behaviour problems, a finding that was consistent for both parent and teacher reports of behaviour. The authors explore possible casual explanations for this association and conclude that the models in which IQ is a *marker,* or IQ is a *cause* of behaviour problems, are best supported by the results. Lower IQ as a *consequence* of behaviour problems was not supported by the results. The findings therefore suggest that IQ as a marker for aspects of brain organisation is a possible causal link. Alternatively lower IQ may be considered as a cause of poor behaviour in which case low IQ may lead to higher levels of psychopathology through, for instance, low self-esteem.

The direction of a causal relationship between neuropsychological functioning and behaviour remains unclear, and given the nature of environmental influence, and the range of brain-environment interactions, defining a direction of effect may not be helpful (see Hinshaw, 1992). The evidence presented favours a hypothesis by which neuropsychological difficulties contribute to behaviour problems possibly but not necessarily via common biological insult or risk, and through psychosocial factors.

7.4 Aim

The aim of this analysis was to test the relationship between the variables IQ, EF, prematurity and hyperactivity. Based on the conclusions drawn from the literature in Section 7.3, no attempt is made to establish a causal relationship between IQ and EF. Instead, both are examined as potential influences on hyperactive behavioural style (HBS). It was predicted that both IQ and EF would account for hyperactive behavioural style, however, this relationship may differ when accounting for the effect of prematurity.

7.5 Method

The relationship between EF, IQ and hyperactive behavioural style was analysed using hierarchical linear regression analysis in the first instance. The dependent variable (hyperactive behaviour score, SDQ) was predicted from prematurity, IQ and their product term in one analysis, and from prematurity, EF and their product term in a second analysis. The EF term was computed for each participant using the mean of the inhibition and cognitive flexibility scores. Working memory was not included in the EF term, since the results of the Study 1 suggested a dissociation between working memory and the other two EF dimensions. The interaction term was computed using the product of the z-transformed data (i.e. prem x zIQ; and prem x zEF). Missing data were excluded using listwise deletion leaving the sample size at 28 TB children, and 36 PB children.

The second analysis used Structural Equation Modelling, a statistical technique used to examine the relationships between one or more independent variables, and one or more dependent variables. SEM is the only technique available that makes it possible to test several relationships simultaneously (Tabachnik & Fidell, 2001). In the present study therefore, the effects of IQ and EF on hyperactive behavioural style can be estimated simultaneously, rather than in two separate analyses as is the case for the hierarchical regression analyses. The benefit of this analysis is that the relationship between IQ and EF is taken into account, which is essential as the two variables are not independent of each other. A further advantage of SEM is that the relationships between factors are free from measurement error, as this is estimated and removed, resulting in only common variance. SEM is a confirmatory technique, and therefore appropriate for testing a theory, and is not used as an exploratory method. In the present study, the relationship between IQ, EF and hyperactive behaviour in the two groups of children is predicted, and tested using SEM analysis. The present example is a two group model; the model is tested for the TB group and the PB group. In multigroup analyses, the null hypothesis that both groups are from the same population is initially assumed. The second stage of the analysis involves testing the differences between the two groups. If the overall fit of the model changes significantly, a difference in the relationship between IQ, EF and HBS in the two groups is suggested.

7.6 Results

A correlational analysis was carried out to determine the relationship between IQ, EF and hyperactive behavioural style. These analyses are based on data of PB and TB children described in Study 1a for whom complete data on IQ, SDQ, inhibition, cognitive switching and SDQ were available (missing data were dealt with by list-wise deletion, 28 TB and 36 PB children). The results are presented in Tables 26 and 27.

Table 26: Correlational analysis of EF, IQ and hyperactive behavioural style PB group

	IQ	EF	Hyperactive
IQ	1.00		
EF	.26	1.00	
Hyperactive	-.38*	-.35*	1.00

*p<.05

Table 27: Correlational analysis of EF, IQ and hyperactive behavioural style TB group

	IQ	EF	Hyperactive
IQ	1.00		
EF	.10	1.00	
Hyperactive	.09	-.16	1.00

The correlational analysis showed moderate correlations between EF and IQ, and EF and hyperactive behavioural style only in the PB group.

7.6.1 Effect of prematurity

Stepwise regression was carried out, using hyperactive behavioural style as the dependent variable. In the first block, two independent variables were entered, prematurity status as a binary variable, and IQ as a continuous variable. In the second block a third variable, the interaction term of prematurity (binary variable) and IQ, was added. The results of this regression are shown in Table 28 below.

Table 28: Regression analysis of EF, Prematurity and interaction on hyperactive behavioural style

Block	Adjusted R2	Variable	beta	t-value	p-value
1	0.06				
		EF	-.31	-2.23	.03
		Prematurity	-.02	-.11	.91
2	0.05				
		EF	-.08	-.16	.87
		Prematurity	-.00	-.02	.99
		Interaction	-.23	-.46	.65

In the regression analysis, the predictor EF is significant in the first block of the analysis. The predictor prematurity is not significant, as expected from the results of Study 1a (Section 5.3.3). When the interaction term is added, none of the independent variables significantly predict hyperactive behavioural style. These results are displayed in Figure 7.

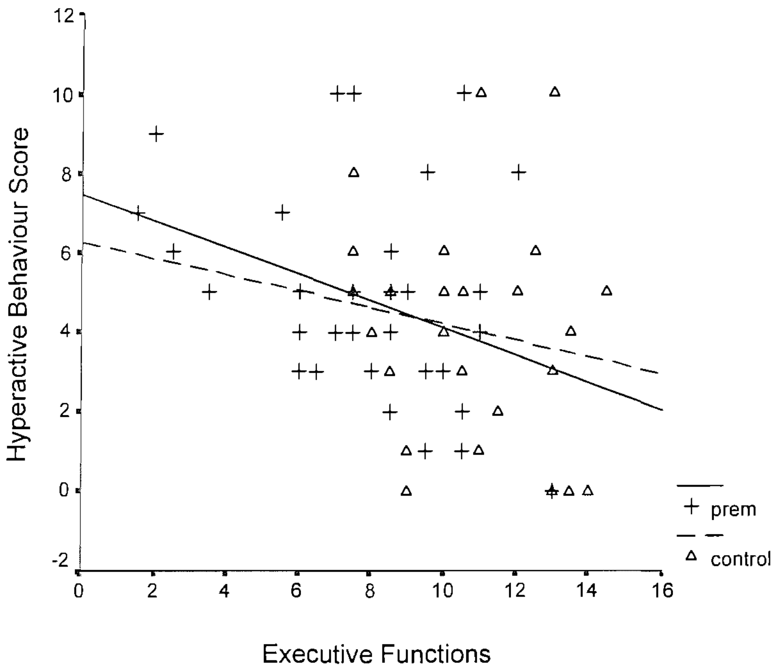


Figure 7: Scatterplot and regression line of EF against hyperactive behavioural style, for premature and control cases.

For both PB and TB children, there is a trend for increasing hyperactive behavioural style with a decrease in EF. As expected the mean EF scores for the prematurely born children lie below those of the control group.

The analysis was repeated using IQ as an independent variable in place of EF. The results of the regression analysis are presented in Table 29.

Table 29: Regression analysis of IQ, prematurity and interaction on hyperactive behavioural style.

Block	Adjusted R2	Variable	beta	t-value	p-value
1	0.01				
		IQ	-.16	-1.30	.99
		Prematurity	-.08	.66	.51
2	0.07				
		IQ	.62	1.67	.10
		Prematurity	.07	.62	.54
		Interaction	-.82	-2.21	.03

In the first block of the regression, the predictors IQ and prematurity are non – significant. However, the interaction term IQ x Prematurity added in the second block of the regression significantly predicts hyperactive behavioural style. This interaction in presented in Figure 8.

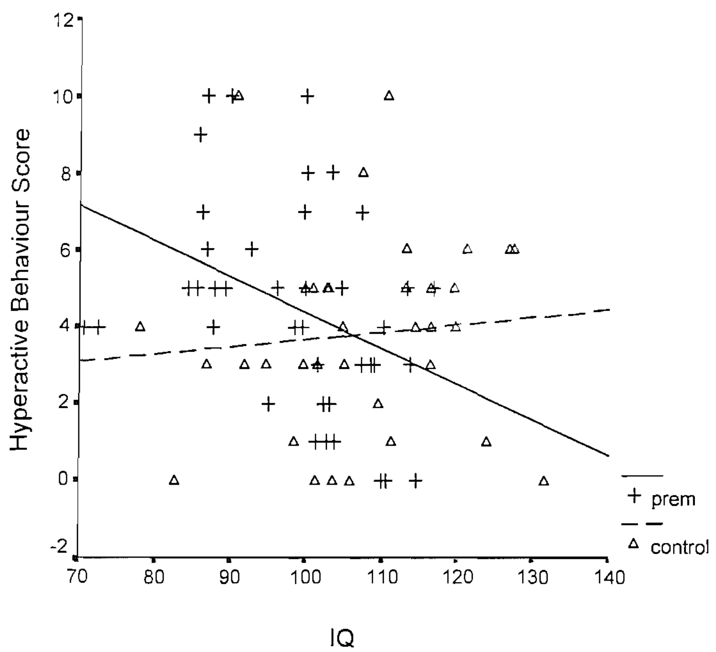


Figure 8: Scatterplot and regression line of IQ against hyperactive behavioural style, for premature and control cases.

The scatterplot clearly shows the interaction effect of IQ x prematurity. As IQ decreases, the hyperactive behaviour score increases for the prematurely born group only. For the control group on the other hand, IQ is relatively stable across the range of hyperactive behaviour scores.

7.6.2 Structural Equation Model

Figures 9 and 10 illustrate the relationship between the variables in the structural equation model (SEM). In the model, boxes represent measured variables (IQ and hyperactivity score for instance, labelled "V_n") and circles indicate latent variables (EF). A latent variable (or Factor, thus labelled "F_n") is not directly measured (as for example IQ) but is predicted by a combination of other measured variables (in this case inhibition and cognitive switching). In the model, double sided arrows represent covariation between variables, whereas straight arrows represent a directional link. In the model, IQ and EF have a correlational relationship. Both IQ and EF predict hyperactive behavioural score in this model. EF, the latent variable, is estimated using two variables, cognitive switching and inhibition.

Initially a constrained model was tested (Figure 9) in which all paths were constrained to be the same between the two groups.

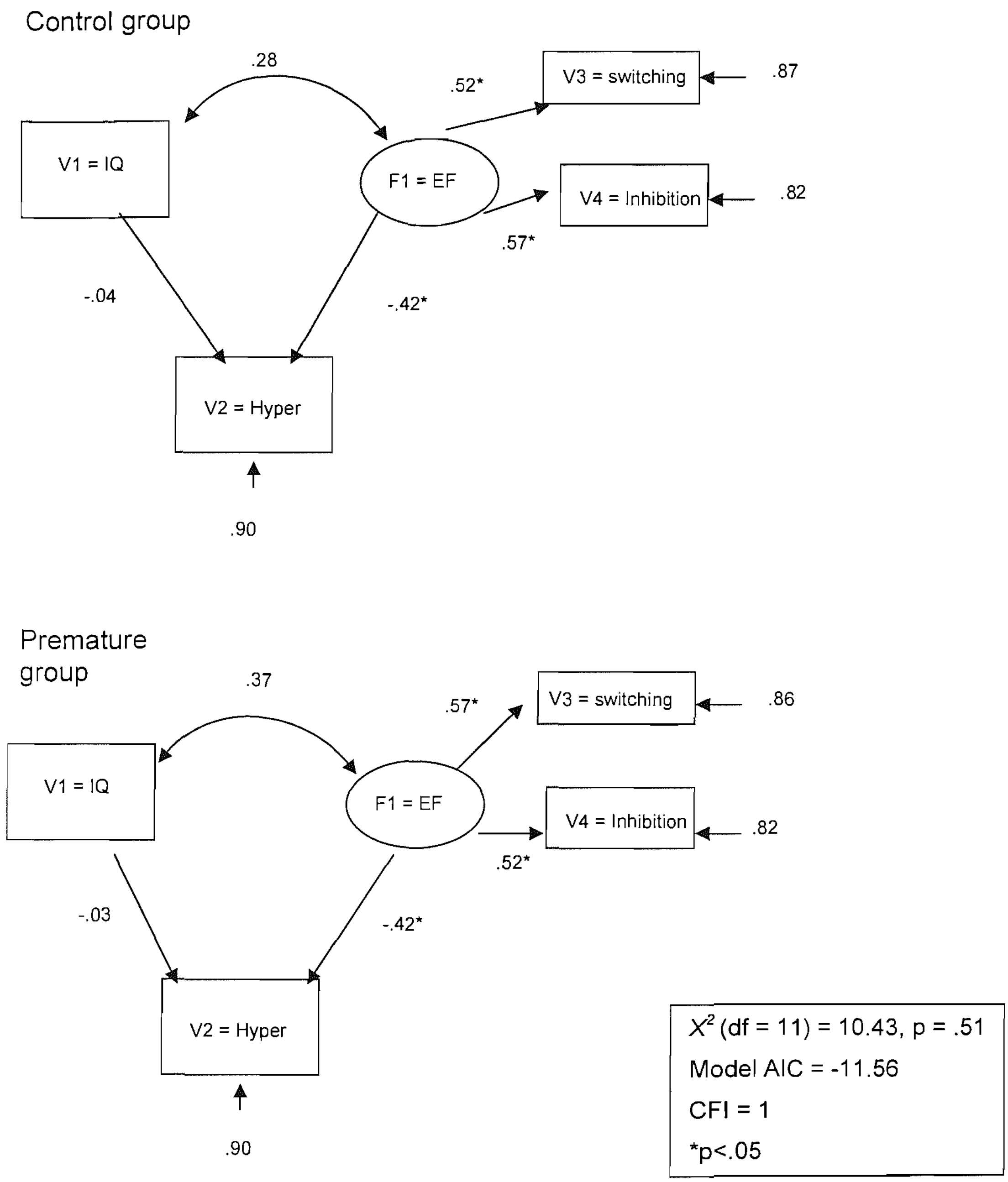
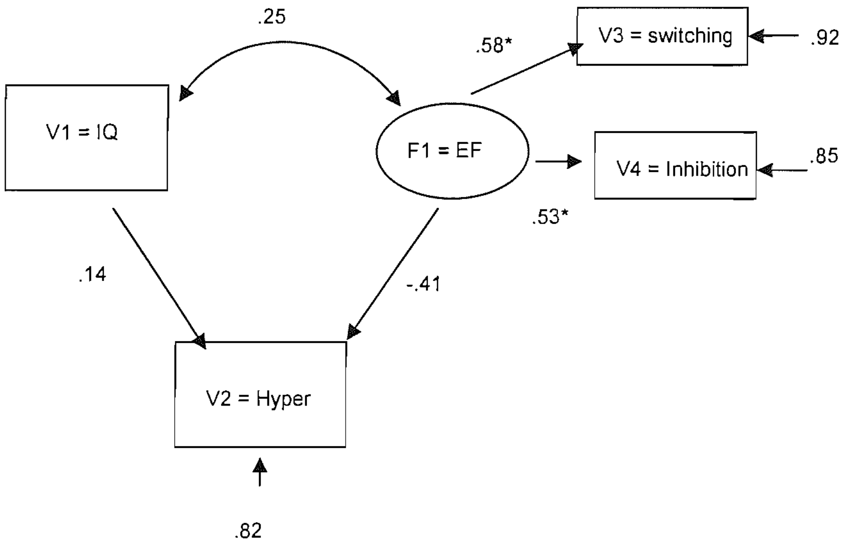


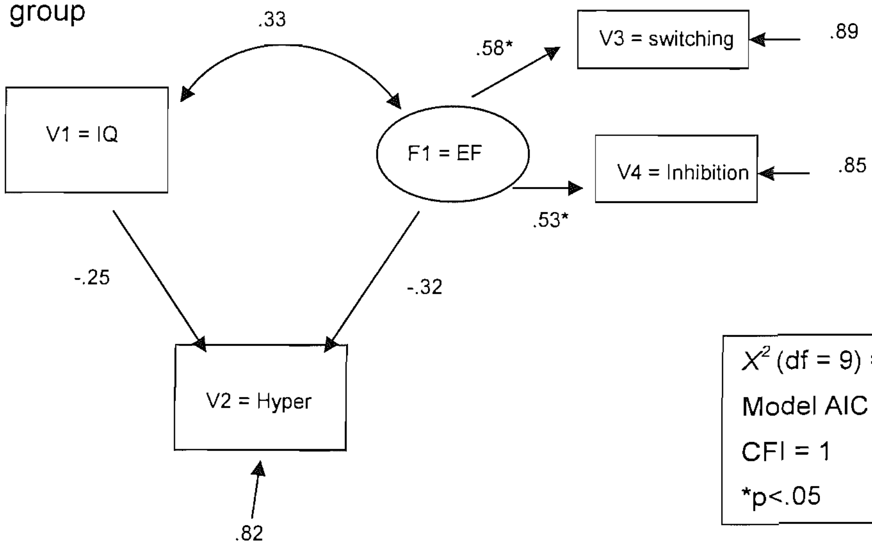
Figure 9: Structural model relating IQ, EF and hyperactive behaviour score (constrained model)

The fully constrained model has a good fit (Chi-Square (df = 11) = 10.43, $p = .51$; Model AIC = -11.56; CFI = 1). The path between IQ and the hyperactivity score was close to zero and non significant. The correlation between EF and IQ is positive as expected, but also non significant. EF did significantly predict hyperactive behaviour score, as expected from the results of the regression analyses. In order to test whether the relationship between IQ, EF and hyperactive behavioural style differs between the two groups, an unconstrained model was tested. In this model (Figure 9) the paths between IQ and hyperactive behaviour score, and EF and hyperactive behaviour score were unconstrained. The remaining paths were constrained, as the relationships indicated by these paths was not expected to differ between the two groups.

Control group



Premature group



X^2 (df = 9) = 8.00, p = .53
Model AIC = -10.00
CFI = 1
*p<.05

Figure 10: Structural model relating IQ, EF and hyperactive behaviour score (unconstrained model)

This model again has a good fit (Chi Square (df = 9) = 8.00, $p = .53$; model AIC = -10.00; CFI = 1). For both groups only the path between EF and hyperactive behaviour score was significant. The relationship between IQ and hyperactive behaviour score was not significant, nor was the correlation between IQ and EF in either the PB or the TB control groups. Overall, comparison of the two models did not result in significant change in Chi Square (Δ Chi Square = 2.43, Δ df = 2, $p > 0.05$). These results suggest that prematurity does not moderate the relationship between EF or IQ and hyperactive behaviour respectively. However, the patterns observed in the path model replicate the findings of the regression analyses. In the unconstrained model, both groups show a strong negative association between EF and hyperactive behaviour score. A decrease in EF score is associated with an increase in hyperactive behaviour score (more hyperactive behaviour). While the relationship between IQ and hyperactive behaviour score is close to zero in the control group, in the premature group this relationship is in a negative direction and of greater magnitude. This relationship in the premature group indicates that lower IQ scores are associated with a higher hyperactive behaviour score, and higher IQ scores are associated with lower hyperactive behaviour scores.

7.7 Discussion

The purpose of this study was to investigate the relationship between two measures of cognitive outcome (IQ and EF) and hyperactive behavioural style. Although study 1 did not show higher levels of behavioural problems in prematurely born children, the relationship between cognitive outcome and behaviour was tested for both groups of children. A higher behavioural score was expected for lower cognitive scores.

7.7.1 IQ and behaviour

IQ was found to be related to hyperactive behaviour in the PB group. In this group IQ varied within the low to average range (70.58-116.89, although only 2 children had scores below 85). This finding is in line with the results of Goodman et al. (1995), who described behaviour variances with normal ranges in IQ. Given that there was an association between IQ and behaviour only within the PB group, it is likely that Goodman et al's. (1995) "IQ as a marker" and "IQ as a cause" are likely explanations for the results. Many PB children are faced with developmental delays and difficulties, which may contribute to poor academic self-concept (Gadeyne et al., 2004). Low average IQ can therefore be considered as a marker for behaviour problems in PB children. The behaviour problems may be considered as a result of both low academic concept, and as a result of a neurobiological deficit (subcortical white matter damage).

7.7.2 EF and Behaviour

As expected hyperactive behavioural style was related to EF in both groups of children. Children within the TB group scored at or above average on the EF tasks. The findings therefore suggest that variation in behaviour scores are common even within the normal range of EF scores. This finding is comparable to that for IQ and behaviour reported in Goodman et al. (1995). A likely interpretation is that low EF scores are often associated with behaviour problems, however, children with hyperactive behavioural style may not necessarily have poor EF. Teasing apart the contribution of either IQ or EF on behavioural style is made difficult because of the close association between EF and IQ.

7.7.3 SEM analysis

The SEM analysis tested the same sets of relationships but with the advantage of modelling the effects of EF and IQ on hyperactive behaviour score simultaneously, taking into account the covariance between the two cognitive outcome scores. In the initial constrained model, the relationship between IQ and EF with hyperactive behaviour score was constrained to be equal for the two groups, which resulted in satisfactory model fit. In the unconstrained model, the relationship of IQ and EF with hyperactive behaviour respectively was unconstrained. This model tested for a difference in the strength of association between these variables across the two groups. Although this model still resulted in a good fit, the change in Chi-Square between the two models was not significant. This indicates that prematurity does not significantly moderate the relationship of IQ and EF with hyperactive behavioural style. However, in multi-group SEM analyses with small sample sizes, a significant Chi-Square change is unusual (Tabachnik & Fidell, 2001). It is therefore worthwhile to examine the patterns of differences between the two models in the unconstrained solution.

The association between EF and hyperactive behaviour score remains similar between the two groups, indicating that decreases in EF scores are associated with increased hyperactive behaviour in both groups of children. Interestingly, the relationship between IQ and hyperactive behaviour score changes in both direction and magnitude between the two groups. In the TB control group the association between IQ and hyperactive behaviour is positive but of small magnitude. In the PB group on the other hand, the relationship is larger in magnitude and negative in direction. This suggests that while the relationship between IQ and hyperactive behaviour is negligible in the TB group, a decrease in IQ in the PB group is associated with an increase of hyperactive behaviour. This pattern of results replicated the results of the regression analysis.

7.7.4 Conclusions

There was some evidence to suggest that IQ was a more important contributor to behaviour problems in PB children than in TB children. The relationship EF and behaviour was equivalent for both PB and TB children. These results indicate that neuropsychological impairments contribute to hyperactive behaviour in children between the ages of 6 and 12 years. Furthermore, PB children who have more IQ and EF difficulties, accordingly have slightly elevated levels of hyperactive behaviour, with those children who have lowest cognitive scores exhibiting most behavioural problems. The fact that prematurity does not moderate the relationship between cognitive scores and hyperactivity provides support for the hypothesis that low academic self concept contributes to behaviour problems in PB children. More severe hyperactive behaviour problems would be expected in this group of children if neurobiological risk had a direct impact on behaviour. This conclusion provides an explanation for the low levels of behavioural problems observed in the children enrolled in the present study. Within a very prematurely born group (28 – 32 weeks GA), who may be considered relatively high functioning, less behavioural problems are expected, on the basis that learning difficulties are mild compared to extremely prematurely born children (<28 weeks GA) studied in some previous studies (see section 3.3.4). Given PB children's inhibition problems, more hyperactive behaviour problems would be expected if this lack of inhibition were directly responsible for behaviour problems. If the hypothesis that poor academic self concept is contributing to the behaviour problems in these children gains more support following future work, this would hold implications for intervention. Those children at risk for poor academic self concept would require not only special educational support but also psychological support to avoid behavioural problems.

CHAPTER 8

Study 4: Re-analysis of Studies 1 to 3 with an enlarged sample

8.1 Introduction

The aim of the final study was to reanalyse the main findings of Studies 1 to 3 using an enlarged sample. The rational for this was the loss of children to follow up, and the low group size for Study 2 (Neonatal Factors) which was the result of missing medical records.

8.2 Method

Data available from a previous research study carried out in the Developmental Brain Behaviour Unit (CHADS, Stevenson & Pit-ten Cate, 1998-2000) were revisited for further analysis. This sample is referred to as the CHADS sample, the sample described in Studies 1-3 is referred to as the PhD sample. Data from these two groups were combined for some analyses in order to achieve a larger sample size.

8.2.1 Participants

The CHADS study sample consisted of 31 prematurely born children, and 30 term born children. Prematurely born children were recruited through the neonatal hospital records at the Princess Anne Neonatal Unit between 1999 and 2000. Inclusion criteria were less than 32 weeks gestation, singleton birth, and absence of Hydrocephalus or Spina-Bifida. Mean gestational age of these children was 29.13 weeks (SD = 2.15), and their mean birthweight was 1307g (SD = 334.91). This group of PB children was recruited as a control group, whose development was compared against that of children with Hydrocephalus and Spina Bifida (e.g. Pit-ten Cate, Kennedy & Stevenson, 2002). The healthy, TB control group was recruited through local primary schools. Mean age at the initial time of testing was 9.30 years (SD = 1.78) for the PB children (16 girls and 15 boys) and 9.08 years (SD = 1.93) for the TB control children (18 girls and 12 boys).

The CHADS control group was contacted and invited to take part in the pilot study as described in Section 4.4.1. The CHADS PB group was contacted at a later time in order to increase the sample size and age range of PB children for the studies described in Chapters 5-7. Of the PB children, only 22 families indicated a willingness to participate in future research. Of these, seven families agreed to participate on this occasion and two returned the questionnaires only. The primary reason for choosing not to participate was exam pressure; most adolescents in this group were preparing for and taking GCSE exams. The mean age of participants was 12.84 years (SD = 2.19), 4 females and 5 males took part.

8.2.2 Procedure

The protocol for the CHADS follow up study consisted of the TEA-Ch subtests, and the RBMT – Extended version which were completed by the PB adolescents. The DuPaul AD/HD questionnaire, Sleep Disordered Breathing questionnaire and Asthma questionnaire were completed by parents. All measures are described in detail in Section 4.3. Table 30 below summarises the data available from the CHADS study and the data from the re-assessment for the present study. The time span between assessment at Time 1 and Time 2 is approximately 3.5 years.

Table 30: summary of assessments available for CHADS Sample at times 1 and 2.

Assessment	Time 1 (N = 16)	Time 2 (N=16)
IQ (four subtests)	Yes	No
EF		
Inhibition	No	Yes (Go No-Go)
Switching	Yes (IED)	Yes (Creature Counting)
Planning	Yes (SOC)	No
Working Memory	Yes (SWM)	Yes (Digit Span)
SDQ	Yes (Parent)	No
DuPaul ADHD	No	Yes (Parent)
Sleep Questionnnaire		Yes (Parent)
Asthma Questionnaire		Yes (Parent)
Rivermead	No	Yes

IED = Intra- Extra Dimensional Shift Task (CANTAB)

SOC = Stockings of Cambridge (Tower of Hanoi equivalent, CANTAB)

SWM = Spatial Working Memory (CANTAB)

Go No-Go = inhibition subtest (TEACh)

Creature Counting = switching subtest (TEACh)

8.2.3 Analyses

Initially the relevant data of the total CHADS study were reanalysed. CHADS PB children were compared to CHADS TB controls on their IQ, behaviour and on the available EF scores, data which were made available from the initial assessments. These results were then compared to results of the PhD sample presented in Study 1.

The second set of analyses made use of a combined sample, consisting of the data of the total CHADS group (data of both PB and TB children) and the data presented in Study 1 (data of PhD PB and TB samples). This combined database consisted of 68 PB children and 71 TB controls. For the combined sample the mean age of PB children (31 boys and 37 girls) was 8.70 years (SD = 1.86), and for the TB controls (32 boys and 39 girls) the mean age was 8.67 years (SD = 1.74). The mean gestational age of the PB group was 28.78 weeks (SD = 2.07) and mean birthweight was 1237.50 grams (SD = 363.41). Measures of IQ (four subtest version) and behaviour (parental SDQ) were available for both groups. Scores on the EF subtests of the CANTAB were available for the CHADS sample, however as CANTAB data were not further analysed for the PhD sample, it was also excluded from this re-analysis using the combined sample.

In the third analysis, the 9 CHADS cases which were available for assessment at Time 2 were added to the sample of 40 PB children described in Studies 1-3. The purpose was to compensate for the cases lost to follow up, and to investigate EF, and Everyday Memory in a larger group

8.3 Results

8.3.1 Re-analysis of data from initial CHADS assessment

Data made available from the initial CHADS assessment were available for 31 PB children and 30 TB children. A between groups analysis of IQ, EF and behaviour tests was run, and the results compared to the between groups analysis of these variables in Study 1. The association between IQ, prematurity and hyperactive behaviour was tested, and the results compared against those of Study 3.

8.3.1.1 Between groups analysis of IQ, EF and behaviour

Data from the initial CHADS assessment are presented in Table 31 and includes measures of IQ, EF and behaviour.

Table 31: Descriptive statistics of the relevant assessments of the CHADS sample from Time 1.

	Prem N = 31 Mean (SD)	Term N = 30 Mean (SD)
FSIQ	97.53 (14.51)	104.05 (9.70)
Block Design	8.74 (3.78)	9.67 (2.43)
Picture Completion	9.71 (2.37)	11.07 (2.39)
Information	10.29 (3.54)	11.50 (2.87)
Comprehension	9.81 (3.00)	10.60 (2.69)
EF		
IED	7.70 (0.92)	7.80 (1.00)
Tower	6.73 (1.57)	7.30 (1.70)
SWM	54.00 (17.66)	50.80 (15.80)
SDQ total	9.45 (7.44)	7.70 (5.42)
Conduct	1.42 (1.84)	1.70 (1.64)
Emotion	2.45 (2.31)	1.73 (1.78)
Hyperactivity	4.03 (2.98)	3.00 (2.74)
Peer	1.55 (2.08)	1.27 (1.36)
Prosocial	8.45 (1.59)	8.23 (1.76)

In the original CHADS sample, there was a significant difference between groups on overall IQ score ($t_{(59)} = -2.06$, $p<.05$). Results of the multivariate analysis are presented in Table 32 below.

Table 32: F ratios and effect sizes for univariate main effects of birth status on IQ measures for CHADS sample

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus (λ = .907)		4	1.44	.23	0.5
Univariate						
Birthstatus	Block	13.03	1	1.29	.26	0.29
	Pict	28.07	1	4.96	.03	0.56
	Info	22.31	1	2.14	.15	0.37
	Comp	9.60	1	1.06	.31	0.26
Error	Block	10.15	59			
	Pict	5.67	59			
	Info	10.44	59			
	Comp	9.09	59			

Multivariate analysis of the WISC subtests was not significant ($F_{(4,59)} = 1.44$, p = 0.23). Only scores on the picture completion test were significantly different between groups ($F_{(60)} = 5.00$, $p<.05$).

For SDQ total score, there was no significant difference ($t_{(59)} = 1.05$, p = 0.30). Multivariate analysis showed that none of the univariate effects were significant for the SDQ subscales (Table 33).

Table 33: F ratios and effect sizes for univariate main effects of birth status on problems scales of the SDQ

Source		Mean Square	Df	F	p	d
Multivariate						
	Birthstatus (λ = .874)		4	2.02	0.11	
Univariate						
Birthstatus	Emotion	7.87	1	1.85	0.18	0.35
	Conduct	1.20	1	0.39	0.53	0.17
	Peer	1.21	1	0.39	0.36	0.16
	Hyper	16.24	1	1.98	0.17	0.36
Error	Emotion	4.86	73			
	Conduct	4.82	73			
	Peer	3.86	73			
	Hyper	7.06	73			

For the EF tests of the CANTAB (Stockings of Cambridge, Intra-Extra Dimensional Shift, Spatial Working Memory), there was no significant multivariate effect, nor were any of the univariate effects for the EF tests significant. (Table 34)

Table 34: F ratios and effect sizes for univariate main effects of birth status on CANTAB scores

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus (λ = .952)		3	0.95	0.42	
Univariate						
Birthstatus	SWM	129.08	1	0.47	0.50	0.18
	Stockings	7.89	1	2.62	0.11	0.41
	IEDS	2.76	1	0.02	0.39	0.06
Error	SWM	277.44	59			
	Stockings	3.01	59			
	IEDS	130.17	59			

8.3.1.2 Analysis of the association between IQ, prematurity and behaviour

An analysis was run to replicate findings of Study 3, which investigated the relationship between IQ prematurity and behaviour using multiple regression analysis. In Study 3 it was found that the association between IQ and behaviour was stronger for the PB group than for the TB group. This analysis was run for the CHADS sample, in order to replicate this finding. The results of the regression analysis are summarised in Table 35.

Table 35: Regression analysis of IQ, Prematurity and interaction on hyperactive behavioural style in the CHADS sample

Block	Adjusted R2	Variable	beta	t-value	p-value
1	0.03				
		IQ	-.18	-1.38	.17
		Prematurity	.13	1.01	.31
2	0.04				
		IQ	.47	.93	.36
		Prematurity	.15	1.17	.25
		Interaction	-.66	-1.34	.19

None of the predictors entered into the regression analysis significantly predicted hyperactive behaviour scores. However, the effect size for the interaction between IQ and prematurity is moderate. The scatterplot in Figure 11 illustrates this trend in the data.

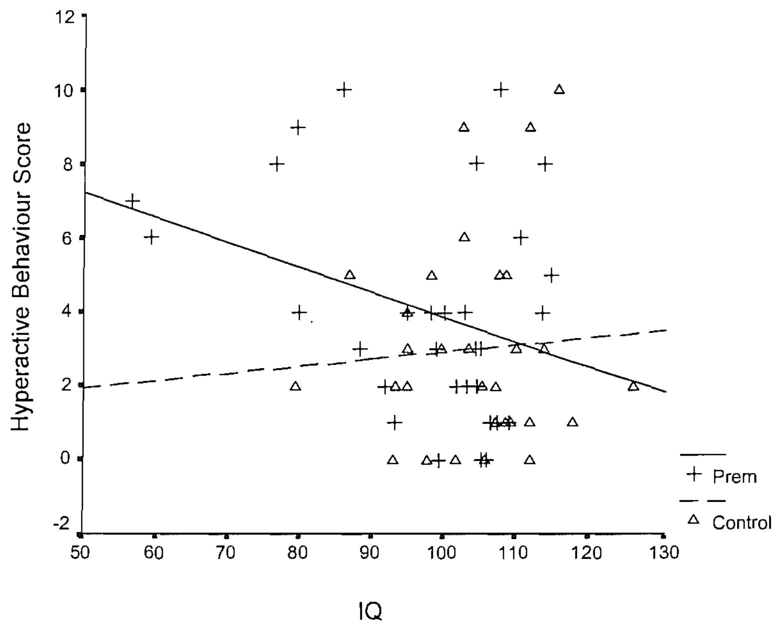


Figure 11: Scatterplot and regression line of IQ against hyperactive behavioural style, for premature and control cases.

Hyperactive behaviour scores varied only slightly and within the average range for the TB control children. Within the PB group however, low IQ scores were associated with high hyperactive behaviour scores. This is the same pattern of results as was found in Study 3.

8.3.1.3 Analysis of the association between EF, prematurity and behaviour

The regression analysis was repeated using EF (mean of inhibition and cognitive switching scores) as one of the predictors. The EF variable was calculated using scores from two EF tests, Stockings of Cambridge and Intra-Extradimensional shift, which are measures of planning and shifting respectively. These two tests most closely matched the EF tests used for the analysis in Study 3. EF, prematurity and their interaction were entered into stepwise regression analysis. The results are presented in Table 36 below.

Table 36: Regression analysis of EF, prematurity and interaction on hyperactive behavioural style in the CHADS sample

Block	Adjusted R2	Variable	beta	t-value	p-value
1	0.07				
		EF	-.16	-1.23	.21
		Prematurity	.21	1.62	.11
2	0.07				
		EF	-25	-.57	.57
		Prematurity	.21	1.60	.12
		Interaction	-.09	.20	.84

In this regression analysis neither EF nor prematurity or their interaction significantly predicted hyperactive behaviour scores, and effect sizes were small. This is reflected in the small gradient of the regression lines which are presented in Figure 12.

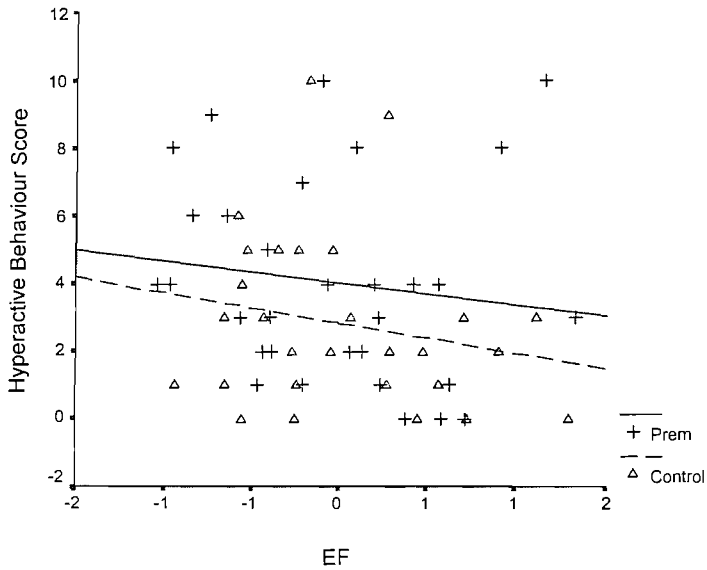


Figure 12: Scatterplot and regression line of EF against hyperactive behavioural style, for premature and control cases.

The scatterplot (Figure 12) shows a modest association between EF and behaviour scores. The effect is smaller than that observed in Study 3, in which different measures of EF were used (inhibition and cognitive switching).

8.3.2 Analysis using the combined CHADS and PhD sample

The analyses of the CHADS data have produced findings which are similar to those of Studies 1 and 3. A difference in overall IQ score was found in both studies, and between group differences on CANTAB scores were non-significant for both the PhD and CHADS sample. In neither sample was there a significant difference between PB and TB children on behavioural problems as indicated by parental SDQ. These findings indicate that the two samples are comparable. This allowed for the two samples to be combined, which nearly doubled the sample size for both TB and PB groups. Data for children's IQ and Behaviour, which were consistently available for children from both samples, was analysed.

8.3.2.1 Between groups analysis for IQ and behaviour

Between group analyses of IQ produced significant results, with multivariate $F_{(4,134)} = 3.96$, $p<0.01$. Significant differences were found for all four IQ subtests (Table 37)

Table 37: F ratios and effect sizes for univariate main effects of birth status on IQ measures for combined PhD and CHADS sample

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus (λ = .894)		4	3.96	.01	
Univariate						
Birthstatus	Block	65.87	1	6.54	.01	0.43
	Pict	68.68	1	10.51	.01	0.53
	Info	35.06	1	4.34	.04	0.34
	Comp	56.25	1	6.71	.01	0.35
Error	Block	10.07	137			
	Pict	6.53	137			
	Info	8.08	137			
	Comp	8.38	137			

Analysis of the SDQ data (Table 38) revealed a significant between group difference for emotional problems $F_{(1,132)} = 4.67$, $p<.05$.

Table 38: F ratios and effect sizes for univariate main effects of birth status on problems scales of the SDQ

Source		Mean Square	df	F	p	d
Multivariate						
	Birthstatus (λ = .907)		4	3.27	0.01	
Univariate						
Birthstatus	Emotion	21.81	1	4.67	0.03	0.74
	Conduct	0.42	1	0.01	0.75	0.05
	Peer	1.45	1	0.41	0.52	0.11
	Hyper	25.62	1	3.31	0.07	0.31
Error	Emotion	4.67	131			
	Conduct	4.08	131			
	Peer	3.56	131			
	Hyper	7.74	131			

Independent t-test analysis of the prosocial scale was significant $t_{(131)} = -2.16$, $p<.05$, $d = 0.37$. Prematurely born children had a higher score on both emotional problems and prosocial behaviour subscales, indicating more emotional problems, and a higher level of prosocial behaviour. The difference for hyperactive behaviour was not significant, although the trend was in the expected direction, with PB children exhibiting more hyperactive behaviour problems. Table 39 summarises the distribution of emotion problems scores across normal, borderline and abnormal scores for TB and PB groups.

Table 39: Percentages of children with normal abnormal and borderline SDQ emotion scores

	Term Born	Premature	Total
Normal 0-3	51 (78%)	44 (64%)	95
Borderline 4	7 (10.8%)	8 (11.7%)	15
Abnormal 5-10	7 (10.8%)	16 (23.5%)	23
Total	65	68	133

Distribution of scores reflects that approximately 1 in 5 PB children has an emotion score in the abnormal range, compared to only 1 in 10 control children. This pattern of scores is reflecting abnormally high emotional problems scores, rather than increased number of children with borderline scores. The differences were, however, not significant $\chi^2_{(2)} = 4.032$, $p = 0.13$.

Univariate analysis was carried out to determine whether the children from the CHADS study had significantly more emotional problems than children in the PhD study, and whether the interaction of study sample by prematurity status was significant. The results are summarised in Table 40 below.

Table 40: ANOVA of emotion problems, by study, and prematurity.

	Mean Square	F	p
Corrected Model	10.35	2.22	.09
Study	8.93	1.91	.17
Prematurity	21.15	4.53	.04
Study*Prematurity	0.22	0.05	.83

The main effect of study was not significant indicating that children in the CHADS study did not have more emotion problems than children in the PhD sample. As expected the main effect of prematurity was significant, indicating that PB children from both samples had higher emotional problems scores than

TB children. Finally the interaction between study and prematurity was not significant, indicating that PB children from one sample did not have significantly higher emotional problems scores than PB children from the other sample.

8.3.2.2 Analysis of the association between IQ, prematurity and behaviour

A regression of IQ and prematurity onto hyperactive behaviour score was repeated for the combined sample. The results are summarised in Table 41 below.

Table 41: Regression analysis of IQ, Prematurity and interaction on hyperactive behavioural style in the combined sample

Block	Adjusted R2	Variable	beta	t-value	p-value
1	0.05				
		IQ	-.15	-1.77	.08
		Prematurity	.11	1.25	.22
2	0.09				
		IQ	.56	1.93	.06
		Prematurity	.12	1.36	.18
		Interaction	-.75	-2.56	.01

In this combined sample the interaction between IQ and prematurity significantly predicted hyperactive behaviour score (β = -.75, $p<.01$). The result is clearly illustrated in the scatterplot in Figure 13.

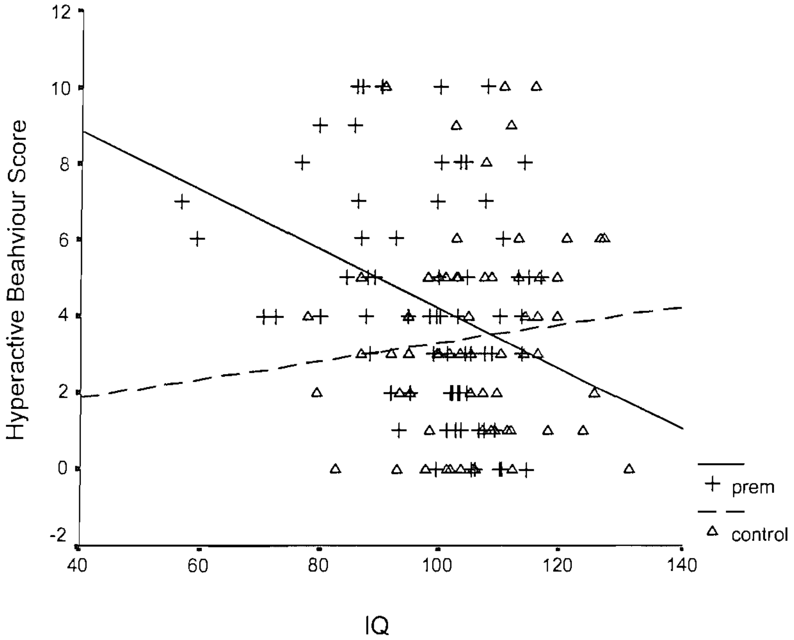


Figure 13: Scatterplot and regression line of IQ against hyperactive behavioural style, for premature and control cases for the total sample

Across the range of IQ scores, the hyperactive behaviour score remains within the normal range (0-5) for children in the TB control group. For PB children there is a strong association between IQ and hyperactive behaviour score. In addition, the regression analysis was repeated with emotional problem score as the dependent variable (Table 42). The MANOVA analysis of behaviour problems revealed a significant difference between groups on the emotional problems scale, indicating more emotional problems among the PB children. This finding is interesting in light of the interpretation of findings in Study 3, where it was concluded that IQ contributed to behaviour problems in PB children. Low IQ may therefore not only affect externalising but also internalising behaviour problems.

Table 42: Regression analysis of IQ, Prematurity and interaction on emotional problems scores in the combined sample

Block	Adjusted R2	Variable	beta	t-value	p-value
1	0.07				
		IQ	-.23	-2.64	.01
		Prematurity	.12	1.31	.19
2	0.10				
		IQ	.40	1.41	.16
		Prematurity	.12	1.42	.16
		Interaction	-.66	-2.32	.02

IQ significantly predicted emotional problems scores (β = -.23, $p<.01$), and the interaction between prematurity and IQ did significantly predict emotional problems scores (β = -.66, $p<.05$). The scatterplot in Figure 14 below illustrates that as expected, low IQ is associated with emotional problems in the PB group only.

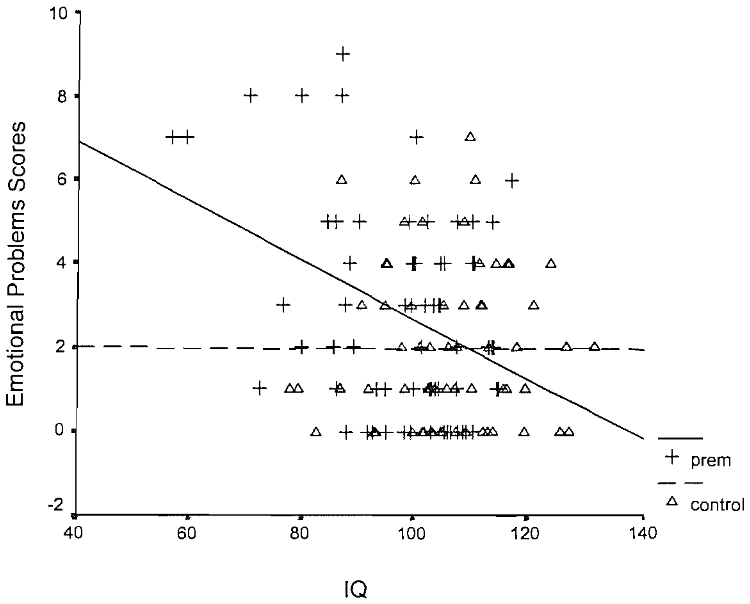


Figure 14: Scatterplot and regression line of IQ against emotion problems score, for premature and control cases for the total sample

Amongst the control group, there is no association between high or low IQ and emotional problems. For the PB children, low IQ is closely associated with higher levels of emotional problems.

8.3.3 Effects of age

Regression analysis were run to determine whether PB children exhibit different levels of behaviour problems across age. The results are summarised in Table 43 below.

Table 43: Regression of behaviour problems against age for the PB group.

	R2	beta	t	p
Total SDQ	.00	.12	.94	.35
Peer	.01	.16	1.33	.19
Emotion	.05	.24	2.05	.05
Hyperactivity	-.01	-.03	-.26	.79
Prosocial	-.01	-.03	-.03	.79

N = 71

An age related change was only significant for the emotional behaviour scores (β = .24, p<.05), with emotional behaviour problems increasing with age. This regression is illustrated in Figure 15 below.

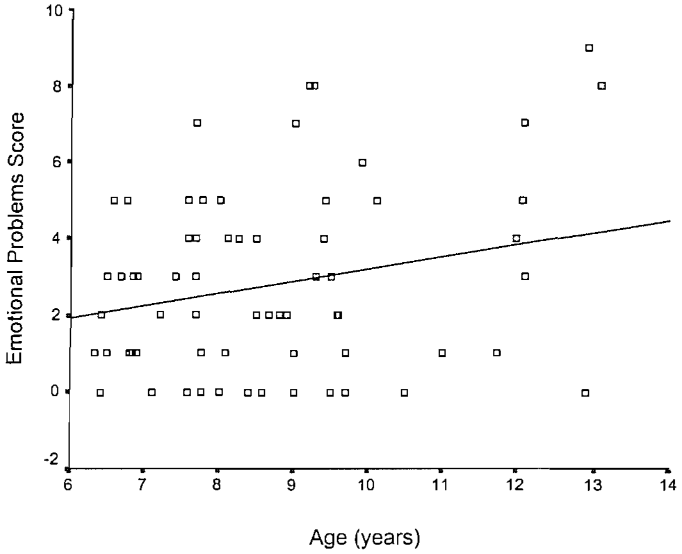


Figure 15: Scatterplot of Emotional Problem Score against age of the PB and TB cases of the total sample

It is clear from the spread of the data in the scatterplot that the significant regression analyses of age onto emotional behaviour score was not due to outliers. A score of 4 on the emotional behaviour subscale is considered borderline.

8.3.4 Between group differences on Memory and Digit Span for the extended PhD sample

As the 7 children who were assessed from the CHADS sample were older than 10 years of age, they were assessed using the RBMT-E version. As described in Section 4.2.2.5 the test is essentially comparable to the children's version. One difference is the scoring system, as a result of which the scores were not directly compared to those of the children from the original PB sample.

Scores on the RBMT – E fell in the normal range for 6 of the 7 adolescents assessed. The case whose scores fell into the borderline category missed the average category only by one point. Based on the overall memory scores, there was no indication of these adolescents having specific episodic memory difficulties. These results are in line with those of Study 1b.

The mean score on the digit span test for the combined sample was 9.17 (SD = 1.17), which did not differ significantly from the expected standard score of 10 in a one sample t-test $t_{(5)} = -1.75$, $p = 0.14$.

8.3.5 Replication of Study 2: Neonatal risk factors and cognitive outcome using the extended PhD sample

An additional 7 CHADS cases available for re-assessment as part of the PhD study were included in a re-analysis of the data from Study 2. The justification for this is based around the small sample sizes, which resulted from missing medical files, and children lost to follow-up (relevant only for the asthma and sleep disordered breathing questionnaire). With the additional cases added, the PB group consisted of 31 cases for whom all data were available. The mean gestational age for this group was 28.58 weeks (SD = 2.17), and mean birthweight 1230.25 (SD = 369.51).

The increased data set was analysed for neonatal factors which predict later cognitive outcome. Low and very low birthweight groups were not found to differ on IQ ($t_{(46)} = -1.09$, $p = .28$, $d = .35$). Groups did not differ on total behaviour score ($t_{(46)} = -.85$, $p = .40$, $d = .71$); or hyperactive behaviour score ($t_{(41)} = -.11$, $p = .17$, $d = .02$). MANOVA of EF scores showed no multivariate effect of birthweight ($F_{(2,40)} = 1.87$, $p = .17$), and neither of the main effects was significant. (Table 44)

Table 44: F ratios and effect sizes for univariate main effects of birth weight on tests of EF

Source		Mean Square	df	F	p	d
Multivariate						
	Birthweight (λ = .914)		2	1.87	.17	
Univariate						
Birthstatus	Cog Switch	7.77	1	0.56	0.45	0.07
	Inhibition	14.73	1	2.07	0.16	0.18
Error	Cog Switch	13.81	41			
	Inhibition	7.12	41			

A similar pattern of results was found for the analysis with long and short term ventilation as the independent variable, IQ: $t_{(46)}$ = -1.82, p = .08, d = .08; total behaviour score $t_{(46)}$ = 1.74, p = .09, d = 1.32; Hyperactive behaviour score $t_{(46)}$ = 1.88, p = .07, d = .21. The multivariate effect of ventilation on EF scores was not significant $F_{(2, 40)}$ = 1.71, p = .19 (Table 45).

Table 45: F ratios and effect sizes for univariate main effects of ventilation on tests of EF

Source		Mean Square	df	F	p	d
Multivariate						
	Ventilation (λ = .921)		2	1.71	0.19	
Univariate						
Birthstatus	Cog Switch	24.49	1	1.83	.18	0..58
	Inhibition	18.36	1	2.61	.11	0.18
Error	Cog Switch	13.40	41			
	Inhibition	7.03	41			

When the analysis was repeated for the long and short term oxygen therapy groups, a difference in IQ was not significant ($t_{(33)} = -0.27$, $p = .79$, $d = .08$), neither were differences in total behaviour score ($t_{(33)} = 0.63$, $p = .53$, $d = .47$); or hyperactive behaviour score ($t_{(33)} = 1.22$, $p = .23$, $d = .26$). However, the multivariate effect of oxygen therapy on EF scores was significant ($F_{(2,28)} = 3.77$, $p < .05$), and the univariate effect for inhibition was significant ($F_{(1,31)} = 7.00$, $p < .05$). The univariate effect for switching was not significant ($F_{(1, 31)} = 3.79$, $p = .06$), (Table 46).

Table 46: F ratios and effect sizes for univariate main effects of oxygen therapy on tests of EF

Source		Mean Square	df	F	p	d
Multivariate						
	Oxygen (λ = .788)		2	3.77	.04	
Univariate						
Birthstatus	Cog Switch	54.20	1	3.79	.06	0.48
	Inhibition	39.61	1	7.00	.01	0.52
Error	Cog Switch	14.28	29			
	Inhibition	5.66	29			

8.3.6 Findings from parent report questionnaires using the extended PhD sample

The data for parent report questionnaires on asthma, sleep disordered breathing and DuPaul ADHD screener were combined for the original PhD sample and the additional 9 cases from the CHADS sample who agreed to complete questionnaires as part of the PhD project. These 9 cases were added to the PhD sample in order to make up for the loss of children to follow – up in the PhD sample.

8.3.6.1 Asthma

The asthma questionnaire was completed by parents, and asked for asthma related symptoms (e.g. has your child ever had asthma), and in the case of asthma symptoms, the severity of symptoms (e.g. wheezing at night causing the child to wake up). A score of “1” was assigned to those cases for whom some symptoms of asthma were noted either at present or in the past. Those cases who were reported never to have had asthma or related symptoms were assigned a score of “0”. Within the PB group 53% of children and adolescents were reported to have had asthma symptoms at some time, compared to 36% in the TB control group. Chi square analysis was carried out and the result showed that the difference was not significant $\chi^2_{(1)} = 1.48$, $p = 0.22$.

8.3.6.2 Sleep Disordered Breathing Questionnaire

The sleep disordered breathing questionnaire consisted of two parts. Part A contained questions relating to the quality of the child’s sleep and unusual sleep behaviour such as sleep walking. Part B consisted of questions relating to breathing during sleep, such as snoring, struggling to breathe while asleep and moming headaches. There was no difference in sleep related problems between TB and PB groups. Independent t-test analyses were not significant (Part A: $t_{(56)} = -1.10$, $p = .28$ $d = .46$; Part B: $t_{(55)} = .34$, $p = .74$; $d = .09$ Total Score: $t_{(53)} = -.77$, $p = .45$, $d = .28$). These results indicate that children and adolescents in the PB group did not present with more sleep related problems than children in the TB group.

8.3.6.3 AD/HD screening questionnaire

Scores were calculated for the total AD/HD scale, inattentive subscale and hyperactive subscale. These scores were then coded according to age and gender of the child, using the normative data presented in DuPaul (1998). A score above the 80^{th} percentile for age and gender was assigned a value of "1", the remaining scores were assigned "0". The sample size for this analysis was N = 52, 30 PB cases and 22 term cases. Chi-Square analysis was carried out to determine whether more children and adolescents in the prem group scored above the 80^{th} percentile compared to the term born group. For the AD/HD total score: $\chi^2_{(1)} = 0.31$, $p = .58$; Hyperactivity scaled score: $\chi^2_{(1)} = 0.12$, $p = .73$; Inattention scaled score: $\chi^2_{(1)} = 0.27$, $p = .60$. The prem group did not have a significantly higher frequency of scores above the 80^{th} percentile than the term group on the total AD/HD scale or the hyperactivity and inattention subscales.

8.4 Discussion

8.4.1 Re-analysis of the initial CHADS sample

The first part of the analysis compared the data obtained on the CHADS sample, to that of the present sample. Results were comparable to those obtained in Study 1. Differences in IQ between the TB and PB children of the CHADS sample were significant. No differences were found on behaviour, nor EF tests. EF tasks used in the CHADS study were taken from the CANTAB battery only. The results on EF tests from CANTAB used in Study 1 were also not found to differ between the TB and PB group.

8.4.1.2 Testing the association between IQ, prematurity and behaviour

In the CHADS sample, there was an association between IQ and hyperactive behaviour which was found to be stronger for the PB children than the TB children, though the regression was not significant, the pattern of results replicated results described in Study 3.

8.4.1.3 Testing the association between EF, prematurity and behaviour

For the regression of EF and prematurity on hyperactive behaviour no significant effect was observed. The effect sizes were smaller than those of Study 3. This may be due to the different EF measures used in the two analyses. In Study 3 the EF measure was the mean scores of the inhibition and cognitive switching tests of the TEACh. For the present study, the EF measure was the mean of the CANTAB Stockings of Cambridge and Intra-Extra Dimensional Shift tests. A stronger association between a measure of inhibition and hyperactive behaviour is expected than between a measure of planning and hyperactive behaviour.

8.4.1 Findings from the combined CHADS and PhD Sample.

8.4.1.1 Between group differences on IQ

The main findings of Study 1 and 3 were re-analysed using data from the CHADS sample (for both TB and PB which were collected during the CHADS study in 2000), and data from the PhD sample. As expected there was a large between groups effect of IQ, with the PB children achieving significantly lower scores on the total IQ score as well as the four subtests.

8.4.1.2 Between group differences on Behaviour

Between groups analysis of the behaviour scores (based on parental SDQ report) revealed a significant difference for emotional problems and prosocial behaviour problems. The PB children were reported to have more emotional problems than their TB peers, as well as better prosocial behaviour. The difference in prosocial behaviour is replicated from Study 1, where it was concluded that the elevated scores on the prosocial scale may represent parental desire to identify positive behavioural traits in their PB children (Goodman, 1994).

A difference in emotional problems was not found in Study 1, however in the combined sample, PB children had significantly higher emotional problems scores than TB children. This finding was not due to differences between the two cohorts, children in the CHADS sample did not have more emotional problems than children in the PhD sample, and nor was there a greater incidence of emotional problems amongst PB children from either group (the sample by prematurity interaction was not significant). It can therefore be concluded that the effect size for emotional problems amongst PB children is low, and a significant difference was therefore not found in either CHADS or

PhD sample, but the sample size in the combined sample was sufficient to identify a significant difference.

Huddy, Johnson and Hope (2001) report emotional problems for children born between 32 and 35 weeks gestational age, at 7 years of age. Parent report SDQ showed that 10% of PB children had borderline scores, and 10% had abnormal scores. The study did not include a control group, so differences to term born groups were not discussed. This is a lower rate of emotional problems compared to the present sample. However, children in the Huddy et al. study were of higher gestational age, and therefore at lower risk of psychological sequelae of prematurity.

Research studies commonly report only on hyperactive behaviour problems of PB children. Emotional difficulties are addressed less frequently. Although some studies report descriptive statistics of emotional problems, analyses are not carried out to compare the incidence of behaviour problems between PB and TB children. Hille et al. (2001) report behaviour problems for a group of PB children comparable to those in the present study on the basis of gestational age and birthweight. Children in Hille et al. had a median gestational age of 27 weeks, and median birthweight of 850 grams. The study compared behavioural outcome of PB children from four countries. Internalising problems (including somatic complaints and nervous / depressed symptoms) were only significantly higher in PB children than TB peers in the Dutch sample of children. In a study of 14 year old PB children born at less than 1500g, emotional problems (reported using the parent version of the Rutter Behavioural Questionnaires) were reported in 12% of PB children and 4% of TB children (Stevenson, Blackburn, & Pharoah, 1999, significance of these differences in frequencies were not reported). In an earlier study of the same cohort of children (Pharoah et al., 1994) 17% of PB children were reported to have emotional problems (again using the parent report of the Rutter Behavioural Questionnaire). The incidence of emotional behaviour problems remained fairly constant between the ages of 8 and 14 years in that sample of PB children. None of the studies addressed the incidence of emotional problems or discussed potential causes. Emotional problems amongst PB children are likely to be related to developmental delay, health problems (such as asthma), small stature and poor school achievement.

In the present study, an increase in emotional problems score with age was found. This suggests that emotional problems affect older PB children more than younger PB children. As emotional problems are recorded but not discussed in previous studies, it is not possible to compare this finding to previous reports. It is likely that the increase in emotional problems with age is related to the increasing demands placed on the child and the continuing difficulties faced by the child or adolescent. Pharoah et al. (2003) reported that PB adolescents achieve fewer GCSEs and lower points in these examinations, indicating that academic underachievement continues into adolescence. Furthermore, a recent study (Nadeau, Tessier, Lefebvre, & Robaey, 2004) has reported that PB children are at an increased risk for victimisation at school. Victimisation is associated with both short term and long term adjustment problems such as low self esteem, anxiety, and peer rejection. Nadeau et al. report that even in the absence of visible disabilities (including motoric and cognitive disability) PB children have several personal risk factors that are associated with victimisation. This argument is discussed further in Section 8.3.1.3 in view of the finding that emotional difficulties are associated with IQ in the PB group but not the TB group.

8.3.1.3 Investigating the association between IQ, prematurity and emotional problems.

Regression analysis of IQ, prematurity and emotion problems showed a strong association between IQ and emotion problems in the PB group only. Low IQ was related to elevated emotional problems. This finding holds implications for conclusions drawn in Study 3. The analysis in Study 3 was aimed at identifying the relationship between hyperactive behaviour, IQ and EF. From the results it was not clear whether the associations between both IQ and EF with behaviour were a result of psychosocial factors, or due to shared components of brain insult. In other words, the cognitive function-behaviour association could be explained by attributing poor behaviour (especially lack of inhibitory control) to cognitive deficits with inhibition, such that the inhibition deficit is global and affects both cognitive and behavioural functioning. The alternative hypothesis was that poor cognitive performance can be attributable to poor behavioural outcome, via psychosocial processes. One such suggestion is that children with cognitive difficulties develop poor academic self-concept, and as a result develop behavioural difficulties (Gadeyne et al., 2004; Hinshaw, 1992). Given that emotional problems are also associated with low IQ in the PB children more than in the TB children supports the notion that PB children who have poor outcome may be affected by their often multiple learning and developmental problems and therefore present with more internalising problems.

Nadeau et al.'s (2004) study lends support to this argument. Prematurely born children at risk of cognitive and hyperactive behaviour problems may additionally be prone to emotional problems which result in part from victimisation associated with the primary cognitive and behavioural difficulties. In Study 3 it was suggested that the association between IQ and hyperactive behaviour problems in PB children was a result of poor academic self-concept leading to behavioural difficulties. Similarly the association between IQ and emotion problems was found only in the PB group, again suggesting a link between poor cognitive performance and behaviour which is specific to PB children. These findings point towards psychosocial causes of behaviour problems, which are strongly influenced by poor cognitive outcome.

A longitudinal analysis of child emotional and hyperactive behaviour problems from both teacher and parent report would help illuminate the findings and possible explanations. Further studies using detailed measures of emotional problems, and self-concept as well as other psychosocial factors are required to develop and test the findings of this study.

8.4.2 Replication of Study 2: Neonatal risk factors and cognitive outcome

When the analyses of Study 2 were repeated with the extra 7 cases the pattern of results did not change from those obtained in Study 2 except for the analysis using duration of ventilation as an independent variable. Low and very low birthweight groups did not differ on IQ, EF or behaviour. Furthermore, long term and short term ventilation groups did not differ on any of the three measures (though in Study 2 differences were significant for behaviour and EF). PB children who received long term oxygen (more than 28 days) did not differ from those who received short term oxygen therapy on IQ, behaviour or cognitive switching scores, however, they did achieve lower scores on the inhibition test.

8.4.2.1 Analysis of questionnaire data using the extended PhD sample

Including the additional 9 cases to the sample did not result in any significant changes to the results. PB children had a slightly higher rate of asthma symptoms than their TB peers, though this difference was not significant. There was no between group difference in terms of Sleep Disordered Breathing problems. None of the three scales, Total ADHD, Inattention or Hyperactivity of the DuPaul ADHD rating scale differed between PB and TB children.

8.5 Conclusions

The results of re-analysis of the findings of studies 1-3 using an extended sample did not highlight any inconsistencies to the findings of the first three studies, therefore the conclusions to these studies remain appropriate. However, an additional finding was made, which suggested that PB children had more emotional problems than their TB peers, and that these emotional problems increase with age. It was suggested that the age effect is due to an increase in academic and social demands, and the risk of victimisation, which are likely causes of internalising behaviour. As these data are cross-sectional, these conclusions are made with caution. Further longitudinal work would be necessary to establish the course of emotional problems in PB children over time. More importantly, PB children with low IQ had significantly more emotional problems than TB children, for whom there was no association between IQ and emotional problems. This finding lends support to the interpretation of the IQ – behaviour relationship investigated in Study 3 where the association between low cognitive score and behaviour problems in PB children was suggested to be strongly related to psychosocial factors (academic self-concept for instance), rather than cognitive inhibitory problems accounting for poor behaviour.

CHAPTER 9
General Discussion

This thesis concerns the cognitive and behavioural outcome of children born prematurely. Three aims were addressed: first to investigate differences between prematurely born and term born children on EF skills and behaviour; second, to investigate which neonatal risk factors are important in predicting cognitive outcome in prematurely born children; and third to investigate the relationship between IQ, EF and behaviour. The findings of the four studies are summarised in this chapter, and the overall findings of the thesis discussed. The potential limitations to the work are addressed, and a plan for future work outlined.

9.1 Summary of findings and interpretations

9.1.1 Cognitive outcome

As predicted in Hypothesis 1, prematurely born children achieved significantly lower IQ scores than their term born peers. IQ scores fell within the average range (90 – 110) for PB children, and the mean difference was 8 – 10 points which is less than one standard deviation from the population mean. This finding was consistent for both the PhD sample and the CHADS sample, as well as with published reports of general cognitive function (see Section 3.3.1).

In line with Hypothesis 2, prematurely born children achieved significantly lower scores than their peers on tests of everyday attention. In particular sustained attention, which requires maintaining attention to a monotonous task, and selective attention, which requires maintaining attention in the face of distracting stimuli were affected. The mean scores of the PB group fell within the 12th to 45th percentiles. By comparison, mean scores of TB children were at the 45th percentile. As expected, prematurely born children also performed significantly worse than their peers on two domains of Executive Function. Inhibition measured by a Go No-Go task and cognitive switching measured by a subtest of the TEA-Ch were two domains of EF in which PB children underperformed. Mean scores fell below one standard deviation of the population mean for these tests. However, the third domain of EF, working memory, was not found to be affected in PB children. Both a spatial working memory task and an auditory working memory task were administered, and PB children achieved appropriate scores that did not differ from those of the term born group. The impairment of cognitive switching was independent of PB children's lower IQ. Analysis of covariance revealed that between group differences remained for the test of cognitive switching but not for inhibition when IQ scores were covaried. The findings are discussed further in Section 9.2.1

Hypothesis 3 predicted that prematurely born children would present with more behaviour problems than their term born peers, a prediction which was not consistently supported. Prematurely born children did not have more hyperactive or inattentive behaviour problems. This finding was unexpected both in the light of previous research findings (see Section 3.3.4) and with respect to the children's cognitive profile. Given the children's inhibitory difficulties, some hyperactive or inattentive behaviour problems were expected. In Study 4, PB children showed more emotion problems than their term born peers, and these problems were found to be more prevalent amongst the older children. An unexpected finding was that PB children showed better prosocial behaviour than their term born peers. Such a finding has not been reported previously and a possible explanation is parental reporting bias (see Goodman, 1994). The relationship between cognitive outcome and behaviour is addressed in Section 9.2.2.

In line with the predictions of Hypothesis 4, prematurely born children's performance difficulties were observed on tasks requiring visuo-spatial skills, a finding which is supported by the literature summarised in Section 3.3.2. The group of prematurely born children assessed in the PhD studies showed mild to moderate difficulties with the visuo-spatial integration task (their score fell approximately 1 SD below the mean of the TB group.Tests of visuo-spatial skills were included in order to obtain a complete cognitive profile of the PB children in the PhD study. Visuo-spatial deficits were not, however, one of the primary areas of interest in this thesis and the findings were not considered in further depth.

Both episodic and semantic memory tests were included in the assessment battery. Hypothesis 4 predicted that PB children would not have semantic memory difficulties, a finding which was confirmed in Study 1. In Hypothesis 5 it was predicted that prematurely born children would have episodic memory difficulties. Children in the present study did not under-perform on tests of episodic memory, a finding which does not support reports of episodic memory difficulties in Isaacs et al. (2000). It was suggested that the reason for this discrepancy was that PB children in the Isaacs study were at higher hypoxic risk due to lower mean birthweight, and longer durations of respiratory assistance and oxygen therapy. It is likely therefore that the children in the present study were of relatively less biological risk and did not display the mild episodic memory difficulties that are reported in Isaacs et al. This possibility could not be tested in Study 2. Data were not consistently available for both neonatal respiratory insufficiency and RBMT scores in order to carry out the analysis with sufficient power.

9.1.2 Neonatal Risk Factors

Neonatal risk factors for the development of PB children were addressed in Study 2. Gestational age, birthweight, APGAR, IVH, and indices of respiratory insufficiency (duration of ventilation, duration of oxygen therapy) were included. Respiratory insufficiency indices were found to be the only neonatal risk factors that were significantly associated with cognitive outcome. When the PhD sample and the sub-sample of CHADS participants that were followed up were combined, duration of oxygen therapy exceeding 28 days in duration was the single best predictor of EF outcome. It was suggested that long term oxygen therapy is a marker for respiratory insufficiency and the associated long term risks to lung development as well as cognitive development. A likely explanation for this association is the risk of brain insult which is elevated amongst infants with respiratory insufficiency (e.g. Peterson et al., 2000). Neonatal respiratory insufficiency is suggested as an important marker for neonatal illness and vulnerability for brain insult, and therefore as a risk factor for cognitive outcome. The relationship between brain insult and cognitive outcome is discussed further in Section 9.2

9.2 Integration of findings

9.2.1 Executive Functions in Prematurely Born Children

Although EF make a central contribution to cognitive function overall, as well as to behavioural and attentional regulation, they have been studied relatively less than other cognitive functions in the prematurity outcome literature. Five studies have been identified which addressed EF formally in the assessments of prematurely born children. These studies report difficulties with Working Memory (Frisk & Whyte, 1994; Luciana et al., 1999), Inhibition (Harvey et al., 1999) and cognitive flexibility (Espy et al., 2002). PB children in the present study did have difficulty with inhibition and cognitive flexibility; however, they did not have difficulties with either spatial or auditory working memory.

The assessments of EF in PB children not only showed that these children have difficulties with EF, but also raised three further issues. Firstly, only two of the three EF dimensions were found to be affected in PB children. These results suggest a dissociation of EF, which is consistent with the fractionated models of EF (e.g. Lehto et al., 2003; Miyake et al., 2000). It is therefore proposed below that PB children are an example of a population with a common neuropsychological profile in whom EF are dissociated. The second issue is related to the relationship between EF, IQ and the impact of EF difficulties on academic related skills. Finally, the third issue raised is concerned with the traditional view of EF as prefrontal functions. Prematurely born children are usually affected by subcortical white matter damage in the periventricular region, while prefrontal damage has not been reported (Frisk & Whyte, 1994; Peterson et al., 2000; Stewart et al., 1999; Volpe et al., 1998). In Section 9.2.1.3 it is argued that PB children with sub-cortical white matter damage represent a population of patients with EF deficits in the absence of frontal lobe damage.

9.2.1.1 Fractionated models of EF

In Section 3.5.1 two approaches towards cognitive models of EF are introduced. A unitary model approach to EF is described by Barkley (1997) who places emphasis on the role of inhibition as the underlying component of EF. Barkley suggests that inhibitory control is required for uncompromised EF. In this view, a deficit in inhibitory control would also affect both the capacity for cognitive switching as well as working memory. However, the findings of Study 1 do not support such a model. Alternative models suggest a fractionation of EF dimensions based on cognitive models (Baddeley, 1996) and confirmatory factor analysis of EF tests (e.g. Lehto et al., 2003; Miyake et al., 2000) which typically include three dimensions covering inhibition, cognitive switching and working memory.

A fractionated approach to EF allows for a differentiation of function. Differentiation of functions are supported by confirmatory factor analyses of test performance as mentioned above, but also by the nature of the development of the biological substrates of EF. Jacobs et al. (1997), for instance, report a significant development of executive skills as well as a differentiation in the time course of development of dimensions of EF in typically developing children. Furthermore, Anderson (1998) summarises evidence in favour of a differentiation of function throughout development on the basis of the maturation of anterior, posterior and subcortical neural systems. The importance of considering other anatomical areas which contribute to executive skills is highlighted. So, for instance, the quality of neural transmission from posterior and subcortical areas to the frontal cortex is as important as the maturation of the frontal cortex itself. While testing the temporal pattern of the development of different dimensions of EF is problematic due to the biases associated with adapting EF tests for very young children, Welsh, Pennington and Groissier (1991) have suggested that the capacity to inhibit responses is the first EF to mature at around 6 years of age.

The differential developmental trajectory and dissociation of the three domains of EF may in part help explain why no working memory difficulties were apparent in the PB group assessed in Study 1. Compromise or insult to structures contributing to EF skills may have differential effects on outcome depending on the timing of the insult (Luciana, 2003). If brain insult associated with premature birth causes a delay or deficit in the maturation of EF, then it is likely that this delay or deficit would be expressed differentially for the three dimensions of EF. In those dimensions which mature earlier, the delay would be more obvious than in those dimensions which mature relatively later. According to Welsh et al. (1991) by 8 years of age (the mean age of children assessed in study 1), inhibitory control should have reached higher levels of functioning than working memory or cognitive flexibility. This would result in the capacity for a greater deviation from mean inhibition performance of typically developing children in the PB group, than for the other dimensions of EF which have reached lower levels of maturity at this age.

In order to evaluate the above argument, longitudinal assessment of EF in PB children and a group of typically developing term born children would be necessary. Alternative accounts for the dissociation of EF difficulties observed in Study 1 could draw on the anatomical correlates of the EF. However, in the absence of imaging data, it is not appropriate to speculate about possible brain damage and its localization with respect to the complexity of associating EF dimensions with anatomical correlates. Finally working memory deficits may have been too subtle in the group of PB children assessed in Study 1 to be identified by the CANTAB measure. It is possible that the present group of PB children were higher functioning than those tested, for instance, in Luciana et al. (1999) for whom working memory difficulties on the CANTAB were found. Again this question would be most appropriately addressed using imaging data in order to evaluate and compare the actual extent and location of brain damage associated with premature birth.

9.2.1.2 The relationship between EF, IQ and implications for academic achievement

In Chapter 7 the relationship between EF and IQ was discussed, both in adult and developmental neuropsychology. In Section 7.2, different views about the developmental trajectories of EF and IQ and their relationship were presented. Many developmental neuropsychologists argue that IQ and EF cannot be completely dissociated in a developmental context (Duncan, 1995; Russell, 1999). They suggest that IQ and EF are related, in that EF are necessary to some degree, in order to obtain the skills tested in IQ tests. Berg and Sternberg (1985) suggest that inhibition in particular is a driving force for IQ development. This theory supports the finding of Study 1 where the PB groups inhibition deficits were not found to be independent of the groups lower IQ scores. This finding not only agrees with the notion that IQ and EF are associated in development, but also suggests that some EF dimensions are linked to IQ, while some are independent of IQ. In terms of academic achievement, EF skills have recently been linked with mathematical abilities. Bull and Scerif (2001), for instance, reported that all three dimensions of EF uniquely predict variance of mathematical ability (using standardised tests and achievement measures) in 7 year old children. Recently Bull (2004) assessed preschool children on tasks covering the three EF dimensions, and investigated whether EF performance around age 4 would predict mathematics ability at ages 5 and 6, at the beginning and the end of the first year of school. The results showed that working memory, cognitive switching and inhibition significantly contributed to the variance in basic mathematical abilities. Such findings highlight the importance of EF skills for the performance on basic mathematical skills early during schooling.

Espy (2004) has investigated the relationship between EF abilities in 2-5 year old PB children and TB children with their mathematics performance on the Woodcock-Johnson mathematics proficiency test. The results of regression analyses showed that PB and TB children seemed to use different strategies for simple mathematical problems. While there was a significant association between inhibitory control and mathematics in the TB group, this was not the case for the PB group. Espy suggests that although PB and TB groups achieved similar mathematics proficiency scores, TB children relied on inhibitory control skills, while PB children did not. The PB children may therefore be relying on other skills such as primary verbal and visuo-spatial strategies. It is likely that these children's inhibitory deficits have direct impact on longer term academic mathematics performance. Using alternative strategies may introduce extra processing load, and processing time, which would result in children being less accurate and perhaps requiring more time to complete mathematics problems at school. This would help explain the common finding that PB children have more difficulties with mathematics than their TB peers. Furthermore, the use of alternative strategies may result in children falling behind at the early stages of mathematics training which would have longer term implications for their performance. Landerl, Bevan and Butterworth (2004) report that 8 – 9 year old children with dyscalculia (a specific mathematical disorder) achieve average and above average scores on tests of working memory. Clearly the relationship between EF skills and mathematics ability in school age children of all ages is complex, and will not be further discussed here. It is important to note however, that EF deficits do have an impact on academic achievement, and that early identification of EF deficits in PB children may give rise to the opportunities for appropriate interventions at pre- and primary school ages.

9.2.1.3 Prefrontal and Subcortical involvement in Executive Functions

Executive dysfunction may be related either to damage of the prefrontal cortex, or to association fibres that run between prefrontal and subcortical areas. In order to determine why PB children should have EF difficulties it is necessary to identify locations where damage is likely to have occurred. Earliest imaging of infant brains has shown that neonatal brain damage associated with premature birth most often occurs as a result of intraventricular haemorrhage and periventricular leukomalacia in PB children (Huppi et al., 1996; Inder et al., 1999). While hypoxic damage to other brain areas is likely, the damage to the periventricular region is the most obvious. Brain imaging studies of older PB children have reported smaller brain volumes overall in PB children, as well as abnormalities of the hippocampal system, and there are no reports of frontal lobe or prefrontal abnormalities (Frisk and Whyte, 1994; Peterson et al., 2000; Steward et al., 1999). Given this evidence of the nature and location of damage to the PB child's brain, executive dysfunction resulting from prefrontal injury is unlikely. The Executive Function difficulties of PB children are therefore more likely to be the result of subcortical damage, that has disrupted fronto-striatal connections or affected the fronto-caudate axis by damage to the caudate nucleus (basal ganglia see Fig. 16). As illustrated in Figure 15, the caudate nucleus lies close to the wall of the lateral cerebral ventricles, and periventricular damage is therefore likely to affect the caudate nucleus.

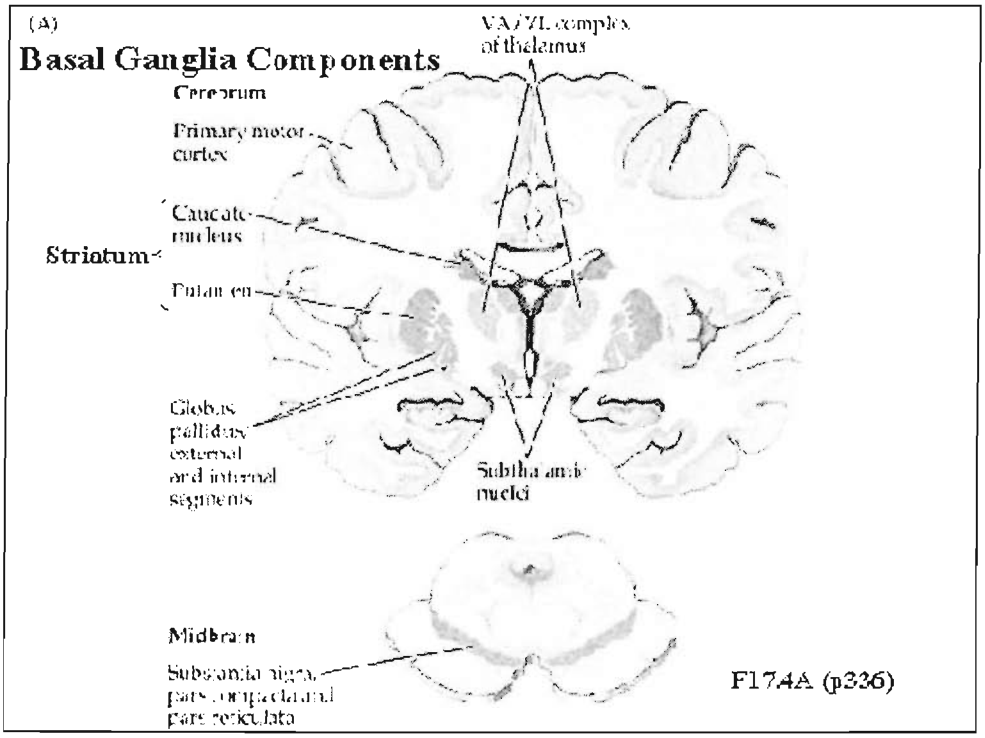


Figure 16: Coronal section of the cerebrum illustrating the location of the basal ganglia relative to the cerebral ventricles.
(http://aids.hallym.ac.kr/d/kns/tutor/medical/unified/basalganglia/bgimg005.gif, retrieved 27. 08. 2004)

Although often associated with an important function of the Prefrontal Cortex, Executive Functions also rely on intact connections with and functioning of subcortical structures, particularly the striatum (see Section 5.2.2). As Figure 15 illustrates, the striatum consists of the caudate nucleus which lies adjacent to the lateral ventricles, and the putamen. Robbins (1998) presents evidence for the requirement of intact basal ganglia, specifically striatum, for set shifting tasks, backing the suggestion made in this thesis, that Executive Deficits in PB children may be a result of damage to the caudate nucleus. Future imaging work targeted at identifying subcortical white matter damage especially around the lateral ventricles, and associating this with EF performance, would further test the suggestion that caudate damage is responsible for EF deficit in PB children.

9.2.2 Behaviour in Prematurely Born Children

Based on previous reports of behavioural outcome amongst PB children, and these children's EF profile, hyperactive and inattentive behaviour problems were expected. However, PB children in the PhD study did not have significantly higher ratings than their TB peers on hyperactive or inattentive behaviour problems, nor were more PB children rated as within the borderline or abnormal ranges. This finding was consistent for both the PhD and the CHADS sample. In terms of prosocial behaviour, PB children from both samples were rated significantly higher than their TB peers. It was suggested that this finding may relate to a parental desire to identify positive behavioural traits in their high risk children (Goodman, 1994).

In the analysis of the combined CHADS and PhD samples, significantly more emotional problems were found amongst PB children, and these problems were observed to increase with age. It was suggested that this age-related increase of emotional problems amongst PB children is related to the increasing academic and social demands, which may make PB children's developmental delay and difficulties more apparent. A recent study addressing victimisation in prematurely born children (Nadeau et al., 2004) supports this suggestion, and highlights this as an important area for future investigation.

9.2.2.1 The relationship between EF, IQ and behaviour

In Study 3 the relationship between IQ, EF and behaviour was studied. The main finding was that hyperactive behaviour scores were negatively related to IQ scores in PB children only. An interaction effect by which lower IQ scores were associated with higher hyperactive behaviour problem scores in the PB group was found. The association between EF and behaviour was the same for both groups, with decreases in EF scores associated with a slight increase in hyperactive behaviour problems. Structural Equation Modelling in which both EF and IQ were entered as predictors of hyperactive behaviour problems revealed that prematurity did not moderate the relationship between IQ and hyperactive behaviour in this model. The results suggested that there is a trend by which low IQ is associated with hyperactive behaviour only in the PB children. Possible explanations of this trend refer to Goodman et al. (1995) who found that children with low average IQ were more likely to present with hyperactive behavioural style than children with average IQ. The authors suggest that low IQ is a marker or cause of behaviour problems amongst normally developing children. The reverse explanation by which hyperactive behavioural style may contribute to poor learning and therefore lower IQ was rejected. In Study 3 of this thesis it was therefore concluded that poor cognitive function and associated academic difficulties may result in behavioural difficulties in PB children, who because of their prematurity are already at an increased risk for behaviour problems.

In study 4 the relationship between IQ and behaviour was revisited using the combined CHADS and PhD samples. In these analyses, the association between IQ and hyperactive behaviour amongst PB children was replicated.

Furthermore, the relationship between IQ and emotional problems was investigated, to further explore the finding of elevated emotion problems amongst PB children. There was a strong negative association between emotion problems and IQ within the PB group only. The interaction between IQ and prematurity was significant, and amongst PB children, lower IQ significantly predicted increased emotional problems. This finding is consistent with the earlier suggestion that low IQ was a marker for or cause of hyperactive behaviour problems, specific to PB children due to their elevated risk of behaviour problems and difficulties in other developmental areas. These results suggest that both internalising and externalising problems are features of prematurely born children's behavioural profiles. Furthermore, the IQ - emotional problems link also supports the interpretation of the age related increase of emotional problems in the PB group. It was suggested that emotional problems increase with age amongst PB children due to the increased demands children are faced with academically and socially, which may progressively highlight their difficulties associated with low IQ. Those children with the greatest cognitive disadvantage would be expected to also have the highest levels of emotional problems. Hyperactive behaviour may be prevalent amongst younger PB children, while emotional difficulties increase with age. Further longitudinal work is needed to explore the temporal pattern of behavioural difficulties amongst PB children. The findings are important in the light of a recent study exploring the relationship between maternal warmth and behaviour (AD/HD symptoms) in low birthweight twins (Tully, Arsenault, Caspi, Moffitt, & Morgan, 2004). Tully et al. found that behavioural difficulties but not cognitive difficulties in low birthweight children may be moderated by maternal warmth. Such a moderation effect may provide the opportunity for interventions targeted at the parenting of PB children to minimise behavioural difficulties associated with poor cognitive outcome.

9.3 Conclusions

The findings suggest that amongst PB children, those with more severe neonatal respiratory insufficiency are at elevated risk for cognitive difficulties. It is proposed that damage to the caudate head of the basal ganglia and thereby the fronto-striatal connections may be mediating the relationship between neonatal respiratory illness and cognitive outcome. Subcortical white matter damage is likely to be responsible for EF deficits, which in turn may additionally impact general cognitive functioning as measured by IQ. Furthermore, behavioural difficulties are proposed to be a result of cognitive difficulties rather than a direct result of brain insult. These proposed relationships are elaborated in the discussion of possible future work (Section 9.6) and are summarised in the Structural Equation Model in Figure 16.

9.5 Limitations

Limitations of individual studies have previously been addressed in Section 5.5.1 and Section 6.4.2. In this section limitations are evaluated, and possibilities for the remediation of these limitations in future studies are discussed.

9.5.1 Sample and sampling characteristics

The children who participated in the studies reported in this thesis were considered representative of very prematurely born children described in other studies (see Section 5.2.1). The group was heterogeneous with respect to birthweight, gestational age and severity of neonatal illness. Due to the relatively small sample size, it was not possible to categorize children according to birthweight or gestational age bands and run analyses on these subgroups with sufficient power. Furthermore, children in both premature and term born groups were lost to follow up between the two assessments, although every effort was made to retain participating families. Both at initial recruitment and at the time of the second assessment measures such as those described in Edwards et al. (2002) were taken to maximise the participation rate. While a loss of participants was expected, larger original sample sizes ensure that after loss to follow-up numbers are sufficiently high to retain statistical power. Future studies would benefit from longer and more rigorous recruitment periods, which were not feasible in the time frame of a PhD. In the present studies, the number of participants was also restricted by the availability of prematurely born children in the Southampton area. Inclusion of a second region would likely double the number of available participants. Participants in the control group were recruited from local schools. Schools in the area of the University of Southampton are oversubscribed for participation in University projects, and are therefore restricted in the amount of cooperation offered. Future studies would benefit from coordination of research proposals to schools in the area, a scheme which is currently being introduced.

The concern that the two groups may not be representative of the respective populations was raised in Section 5.5.1. It was considered possible that the prematurely born group was "high-functioning" and over-represented PB children with only minor learning and behaviour difficulties. The term born control group on the other hand may have over-represented children with minor learning and behaviour problems. If this was the case however, the bias would diminish any between group effects, rather than produce false positives. The results are therefore considered conservative. Furthermore, in a study by Goodman and Yude (1996) the demographics of easy and hard to recruit families affected by hemiplegia are compared. The findings suggest that the demographics and characteristics of easy and hard to recruit subjects are similar. The same may be true for samples of families with prematurely born children, in which case sampling characteristics in the present studies are unlikely to have significantly affected the findings.

9.5.3 Issues relating to the assessment of EF

Executive Functions were assessed using standardised tools, and according to the assessment schedule detailed in the test manuals. While such an assessment can provide an accurate account of a child's EF ability, it may not reflect the child's performance in a classroom situation. The testing situation can be considered artificial in that the child experiences one to one attention, and may be more motivated to perform well on account of the session being a one-off event. In a classroom situation on the other hand, children are more easily distracted by others around them, they do not often experience one to one tuition, and other psychosocial factors relating to their school experience may interfere with their learning and attention. It is therefore possible, that EF measured in an assessment are not comparable to a child's performance and ability in a naturalistic setting. This issue is particularly important as children with better EF skills tend to be those that are less likely to be distracted. A difficulty with EF tasks during an assessment may therefore be a marker for even more serious difficulties in a more demanding classroom situation. In order to gain an impression of “everyday” executive functioning of a child, the inclusion of an observational element may be beneficial to the accuracy of an assessment. Lawrence et al. (2002) have assessed EF in naturalistic settings in children with AD/HD. The methodology involved the children playing a videogame which relied on motor control and visuo-spatial integration, response inhibition and other EF skills. In addition, children took part in a visit to the zoo, where they were asked to follow routes round the zoo and complete certain tasks along the way. The routes varied in length and the number of distracting animal exhibits, and visual and auditory distracters. The authors suggest that cognitive deficits associated with AD/HD may be context dependent, and that AD/HD is associated with some but not all forms of behavioural inhibition difficulties. Similarly, PB children may present with differing EF deficits depending on the context of the assessment situation. This example is important with respect to the assessment issues in developmental neuropsychology, and should be considered for future studies.

9.5.4 Issues relating to the assessment of behaviour

In the present study, behaviour was assessed using parent report questionnaires. Although both caregivers and teachers may give reliable report on children’s inhibitory difficulty (Bishop et al., 2003), some researchers have suggested that teacher ratings compared to parental ratings may be somewhat lower for behavioural difficulties (Youngstrom et al., 2000). Discrepancies between informants indicate the need for both parental and teacher ratings. As discussed in Section 5.3.3 parental bias may account for the lower than expected rate of behavioural difficulties in the PB children as well as the elevated scores in the prosocial behaviour scale. Goodman (1994) showed that parents of children with a chronic illness or disability may be more motivated to identify positive character traits in their children. Furthermore, parents of prematurely born children may expect a certain level of behavioural difficulty in their child, and may therefore set a lower expectation than they would for a term born child. Future studies should include a teacher report of the SDQ particularly as behaviours at school may differ from those at home. It may also be conclusive to ask parents to rate their expectations of their child's development and compare their performance to a TB, typically developing sibling or peer.

In addition to the SDQ, the DuPaul AD/HD rating scale was used to assess children's behavioural profiles. The DuPaul scale was chosen as it relates to AD/HD type behavioural symptoms, which are divided into hyperactive and inattentive behaviours. As discussed above, parental rating bias may have contributed to the finding that PB children did not differ from their TB peers on AD/HD related behaviours. Future studies using the DuPaul AD/HD screener would benefit from the teacher report of a child's behaviour in addition to the parental report. Without this teacher data, the DuPaul questionnaire data did not contribute to the findings of the study over and above the data obtained from the SDQ.

9.5.5 Design and methodology limitations

The inclusion of imaging data would have been a great advantage to the studies and the interpretations of results reported in this thesis. Magnetic resonance imaging (MRI) would have provided information on the extent of white matter damage in the PB participants. In Study 1, children with white matter damage would be expected to perform worse across all assessment measures than their PB peers with no brain damage. Furthermore, in Study 2 the relationship between respiratory insufficiency and later white matter damage could be investigated. It would be expected that those PB children with the most severe respiratory insufficiency would also be at greatest risk of white matter damage. In the investigation of the relationship between cognitive function and behaviour, SEM analysis could be used in order to determine the extent to which brain damage affects both cognitive and behavioural outcome. It would therefore provide a clearer picture about the relative influences of psychosocial factors and biological risk on behavioural outcome. This is discussed further in Section 9.6.

In larger scale studies, the psychologists carrying out assessments are often blinded to the prematurity status of participants. This was not possible in the present research, as both the recruitment and assessment of participants was necessarily carried out by the author. While knowledge of a participants' prematurity status may be considered problematic in terms of maintaining objectivity, the assessments used in the present studies are standardised assessment tools and rely on responses from the participant that are recorded as either incorrect or correct. Failure of a particular task does not allow for subjective interpretation. Although blinding is preferable for future studies, researchers' knowledge of prematurity status was not considered problematic for the present studies.

As discussed in Section 5.2.1 the socioeconomic status (SES) of the PB child's family as well as other environmental factors may moderate the relationship between biological risk and behavioural outcome. Since SES may be an important protective factor against adverse behavioural and possibly cognitive outcome, it would be beneficial to measure family SES more accurately than in the present studies. However, this information was not obtained in an effort to avoid asking personal and possibly intrusive information from parents who may already have reservations about participating in research. Furthermore a similar method using postcodes as an indication of SES has been reported previously (Moffitt et al., 2002). Using this method has the advantage of avoiding potentially intrusive questions asking parents to report household income and highest level of education.

Finally, a study of development and outcome after premature birth should ideally be longitudinal in design. An investigation in the time frame of a PhD is necessarily restricted to cross-sectional designs, or longitudinal work with the longest feasible follow-up period of around 18 months. A longitudinal design of 2 or more years allows for the analysis of developmental competencies across age, which is particularly important when addressing the possibilities that children grow into or out of their difficulties. A longitudinal design would also help to determine whether the EF difficulties experienced by many PB children are due to a developmental delay, or whether they should be considered a cognitive deficit. This difference would inform intervention programmes both for the timing and the nature of the interventions offered. Behavioural changes throughout childhood are expected, and a longitudinal study design would illuminate whether certain childhood events such as entering school, or starting secondary school have implications for children's internalising or externalising behaviours. The finding that emotional difficulties increase with age in PB children (Study 4) would be more accurately investigated in a longitudinal rather than cross-sectional study design.

9.6 Future Directions

On the basis of the findings of the four studies described in this thesis, a research plan for future work was devised. This future work should incorporate the issues raised in the thesis, and improve some of the design limitations identified. In order to resolve some of the limitations addressed in Section 9.5.3 such as the lab based assessment of EF, these issues would need to be addressed in designated studies. The proposed project presented here will not attempt to incorporate all such issues. Instead, the aim is to integrate information on PB children's biological or neonatal risk, with the actual sustained brain damage evident on brain imaging and cognitive and behavioural outcomes. To this end, a longitudinal study is proposed in which neonatal risk, white matter damage, cognitive outcome, behavioural outcome and protective factors are assessed. In order to integrate these variables and to estimate the relative impact of each of the predictive variables on the outcome measures a structured equation model is proposed (Figure 17).

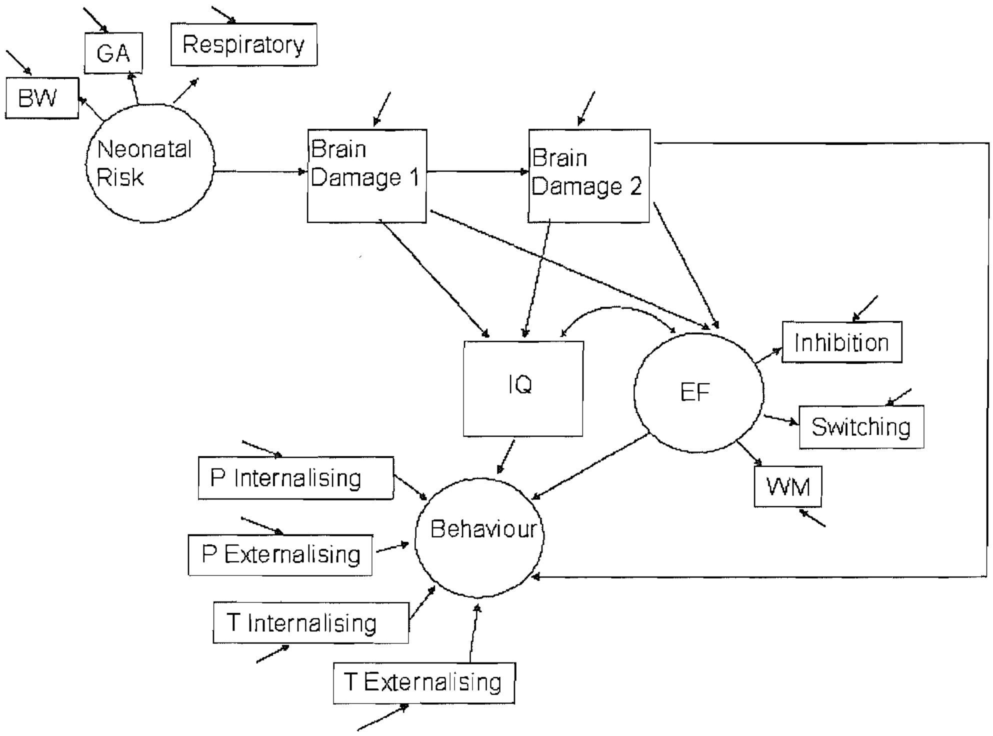


Figure 17: Proposed Path model of neonatal risk, brain damage cognitive and behavioural outcome and protective factors.

This model includes four latent variables each with a number of measured indicator variables, and two measured variables. The first latent variable is “Neonatal Risk”, which is indicated using birthweight, gestational age and respiratory insufficiency variables. Neonatal risk predicts the measured variable “Brain Damage 1” which is an indication of white matter damage at the time the child is discharged from the neonatal unit. For most children this will be at around full term gestational age (40 weeks). A second measured variable “Brain Damage 2” is a measure of white matter damage at 6 - 8 years of age. This measure will provide an indication of whether any brain damage evident at the time of discharge from hospital has remained, developed into more serious damage or indeed improved. Both variables “Brain Damage 1” and “Brain Damage 2” predict the latent variable “Executive Function” measured by tests of inhibition, cognitive switching and working memory, and also predict the measured variable IQ, which is the full scale IQ. The latent variable "Behaviour" is measured by both parent and teacher report of behaviours and covers internalising and externalising behaviours. The moderating effects of protective factors such as early care (e.g. Kangaroo Care), socioeconomic status, and maternal warmth on the relationship between cognitive outcome and behaviour, could be tested using multiple group SEM analyses.

9.1 Predictions

On the basis of findings in this thesis and of previous studies described in Chapters 3 and 4, it is predicted that neonatal risk is a significant predictor of brain damage at both time of hospital discharge (Brain Damage 1), and during middle childhood (Brain Damage 2). Brain damage in middle childhood is thought to significantly predict cognitive outcome, however, brain damage is not thought to significantly predict behavioural outcome at these ages. Cognitive outcome measured as both IQ and EF is thought to predict behaviour at both ages, and this relationship is predicted to be moderated by protective factors.

9.7 Summary and conclusions

In this thesis very prematurely born children were found to have a low average IQ and a specific deficit with Executive Functions. The children's behavioural profile showed a tendency towards hyperactive behavioural style and internalising problems, both of which were associated with poor cognitive outcome. Respiratory insufficiency was considered an important marker for cognitive and behavioural outcome, and should be considered as a risk factor for developmental difficulties alongside birthweight and gestational age.

The results of this thesis have inspired future work which should incorporate several predictors and outcome measures. A structural equation model was proposed which is expected to show that neonatal risk factors affect cognitive outcome via white matter damage, and that this brain damage predicts cognitive outcome which in turn is negatively related to behavioural problems. The relationship between cognitive outcome and behaviour is expected to be moderated by protective factors such as higher SES and parental warmth.

APPENDIX A: Strengths and Difficulties Questionnaire
Including Scoring and interpretation guidelines (retrieved from www.sdqinfo.com 5.12.2004)

Strengths and Difficulties Questionnaire

P4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name .... Male/Female

Date of Birth ....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes - minor difficulties	Yes - definite difficulties	Yes - severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature .... Date ....

Mother/Father/Other (please specify:)

Thank you very much for your help

Scoring the Informant-Rated Strengths and Difficulties Questionnaire

The 25 items in the SDQ comprise 5 scales of 5 items each. It is usually easiest to score all 5 scales first before working out the total difficulties score. Somewhat True is always scored as 1, but the scoring of Not True and Certainly True varies with the item, as shown below scale by scale. For each of the 5 scales the score can range from 0 to 10 if all 5 items were completed. Scale score can be prorated if at least 3 items were completed.

Emotional Symptoms Scale	Not True	Somewhat True	Certainly True
Often complains of headaches, stomach-aches ...	0	1	2
Many worries, often seems worried	0	1	2
Often unhappy, downhearted or tearful	0	1	2
Nervous or clingy in new situations ...	0	1	2
Many fears, easily scared	0	1	2

Conduct Problems Scale	Not True	Somewhat True	Certainly True
Often has temper tantrums or hot tempers	0	1	2
Generally obedient, usually does what ..	2	1	0
Often fights with other children or bullies them	0	1	2
Often lies or cheats	0	1	2
Steals from home, school or elsewhere	0	1	2

Hyperactivity Scale	Not True	Somewhat True	Certainly True
Restless, overactive, cannot stay still for long	0	1	2
Constantly fidgeting or squirming	0	1	2
Easily distracted, concentration wanders	0	1	2
Thinks things out before acting	2	1	0
Sees tasks through to the end, good attention span	2	1	0

Peer Problems Scale	Not True	Somewhat True	Certainly True
Rather solitary, tends to play alone	0	1	2
Has at least one good friend	2	1	0
Generally liked by other children	2	1	0
Picked on or bullied by other children	0	1	2
Gets on better with adults than with other children	0	1	2

Prosocial Scale	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	0	1	2
Shares readily with other children	0	1	2
Helpful if someone is hurt, upset of feeling ill	0	1	2
Kind to younger children	0	1	2
Often volunteers to help others	0	1	2

The Total Difficulties Score:

is generated by summing the scores from all the scales except the prosocial scale. The resultant score can range from 0 to 40 (and is counted as missing if one of the component scores is missing).

Interpreting Symptom Scores and Defining "Caseness" from Symptom Scores

Although SDQ scores can often be used as continuous variables, it is sometimes convenient to classify scores as normal, borderline and abnormal. Using the bandings shown below, an abnormal score on one or both of the total difficulties scores can be used to identify likely "cases" with mental health disorders. This is clearly only a rough-and ready method for detecting disorders – combining information from SDQ symptom and impact scores from multiple informants is better, but still far from perfect. Approximately 10% of a community sample scores in the abnormal band on any given score, with a further 10% scoring in the borderline band. The exact proportions vary according to country, age and gender – normative SDQ data are available from the web site. You may want to adjust banding and caseness criteria for these characteristics, setting the threshold higher when avoiding false positives is of paramount importance, and setting the threshold lower when avoiding false negatives is more important.

	Normal	Borderline	Abnormal
Parent Completed			
Total Difficulties Score	0 - 13	14 - 16	17 - 40
Emotional Symptoms Score	0 - 3	4	5 - 10
Conduct Problems Score	0 - 2	3	4 - 10
Hyperactivity Score	0 - 5	6	7 - 10
Peer Problems Score	0 - 2	3	4 - 10
Prosocial Behaviour Score	6 - 10	5	0 - 4
Teacher Completed			
Total Difficulties Score	0 - 11	12 - 15	16 - 40
Emotional Symptoms Score	0 - 4	5	6 - 10
Conduct Problems Score	0 - 2	3	4 - 10
Hyperactivity Score	0 - 5	6	7 - 10
Peer Problems Score	0 - 3	4	5 - 10
Prosocial Behaviour Score	6 - 10	5	0 - 4

Generating and Interpreting Impact Scores

When using a version of the SDQ that includes an "Impact Supplement", the items on overall distress and social impairment can be summed to generate an impact score that ranges from 0 to 10 for the parent-completed version and from 0-6 for the teacher-completed version.

	Not at all	Only a little	Quite a lot	A great deal
Parent report				
Difficulties upset or distress child	0	0	1	2
Interfere with HOME LIFE	0	0	1	2
Interfere with FRIENDSHIPS	0	0	1	2
Interfere with CLASSROOM LEARNING	0	0	1	2
Interfere with LEISURE ACTIVITIES	0	0	1	2
Teacher report				
Difficulties upset or distress child	0	0	1	2
Interfere with PEER RELATIONSHIPS	0	0	1	2
Interfere with CLASSROOM LEARNING	0	0	1	2

Responses to the questions on chronicity and burden to others are not included in the impact score. When respondents have answered "no" to the first question on the impact supplement (i.e. when they do not perceive the child as having any emotional or behavioural difficulties), they are not asked to complete the questions on resultant distress or impairment; the impact score is automatically scored zero in these circumstances.

Although the impact scores can be used as continuous variables, it is sometimes convenient to classify them as normal, borderline or abnormal: a total impact score of 2 or more is abnormal; a score of 1 is borderline; and a score of 0 is normal.

APPENDIX B: DuPaul ADHD questionnaire

APPENDIX C: Sleep Disordered Breathing Questionnaire

Sleep Disordered Breathing Questionnaire (Gozal 1998)

Regarding your child's room, does he/she...
Sleep alone [ ] Share with 1 [ ] Share with 2 [ ] Share with 3 [ ]
Share with >3 [ ]

Do any of his/her siblings snore?
Yes [ ] No [ ]

Does your child have ADHD? Or is your child hyperactive?
Yes [ ] No [ ]

On average, how long does your child sleep at night?
4-5 hour [ ] 6-7 hour [ ] 8-9 hours [ ] 10-11 hours [ ]
more than 11 hours [ ]

At what time does your child go to bed?
7-8 pm [ ] 8-9 pm [ ] 9-10 pm [ ] 10-11pm [ ] after 11pm [ ]

At what time does your child wake up?
5-6am [ ] 6-6.30 am [ ] 6.30 – 7am [ ] 7-7.30 am [ ]
after 7.30 am [ ]

Explanation of choices:
Never = never in past 6 months, **Rarely** = once a week, **Occasionally** = 2 times a week, **Frequently** = 3-4 times a week, **Almost always** = more than 4 times a week.

1. Have you seen or heard your child having nightmares that he/she does not remember the next day?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

2. Has he/she expressed fear of sleeping in the dark?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

3. Is your child easy to wake up in the morning?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

4. Does your child go to bed willingly?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

5. Is your child a restless sleeper?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

6. Have you seen your child smiling during sleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

7. Does he/she wake up at night?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

8. Have you heard your child talking in his/her sleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

9. Have you observed him/her sleep walking?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

10. While asleep, does he/she ever sit up in bed?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

11. Does he/she grind his/her teeth during sleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

12. Have you heard your child laugh during sleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

13. Has your child told you about having a frightening dream?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

14. Have you observed repetitive actions such as rocking or head banging during sleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

15. Does he/she have problems with bed wetting?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

16. Have you observed your child having a nightmare during which he/she appeared extremely afraid or terrified?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

17. Have you looked in on your child and discovered he/she was crying while asleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

18. Has he/she told you about having a pleasant dream?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

Part 2

1. Does your child stop breathing during sleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

2. Does your child struggle to breathe while asleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

3. Do you ever shake your child to make him/her breathe again?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

4. Do your child's lips ever turn blue or purple while asleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

5. Are you ever concerned about your child's breathing while asleep?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

6. How often does your child snore?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

7. How loud is the snore?
Very quiet [ ] Quiet [ ] Moderately loud [ ] Loud [ ]
Very loud [ ]

8. How often does your child have a sore throat?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

9. Does your child complain of morning headaches?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

10. Is your child a daytime mouth breather?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

11. Is your child sleepy during daytime?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

12. Does your child fall asleep during school?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

13. Does your child fall asleep while watching television?
Never [ ] Rarely [ ] Occasionally [ ] Frequently [ ]
Almost always [ ]

Thank You very much for your help.

APPENDIX D: Asthma questionnaire

Asthma questionnaire (Asher et al 1995)

Part 1: Asthma

1. Has your child ever had wheezing or whistling in the chest at any time in the past?
Yes[ ] No [ ]

IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 6

2. Has your child ever had wheezing or whistling in the chest <u>in the last 12 months?</u>
Yes[ ] No [ ]

IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 6

3. How many attacks of wheezing has your child had <u>in the last 12 months?</u>
None [ ] 1 to 3 [ ] 4 to 12 [ ] More than 12 [ ]

4. <u>In the last 12 months</u>, how often, on average, has your child's sleep been disturbed due to wheezing?
Never woke wheezing [ ] Less than one night per week [ ]
One or more nights per week [ ]

5. <u>In the last 12 months</u>, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?
Yes [ ] No [ ]

6. Has your child <u>ever</u> had asthma?
Yes [ ] No [ ]

7. <u>In the last 12 months</u>, has your child's chest sounded wheezy during or after exercise?
Yes [ ] No [ ]

8. <u>In the last 12 months</u>, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?
Yes [ ] No [ ]

APPENDIX E: Correlation matrices used for SEM analysis (Study 3, Chapter 7)

Table a: Correlation matrix of IQ, Inhibition, Cognitive switching and hyperactive behaviour for the term born group

	IQ	Hyperactivity	Switching	Inhibition
IQ	1.000			
Hyperactivity	.056	1.000		
Switching	.178	-.075	1.000	
Inhibition	-.001	-.172	.199	1.000

Table b: Correlation matrix of IQ, Inhibition, Cognitive switching and hyperactive behaviour for the prematurely born group

	IQ	Hyperactivity	Switching	Inhibition
IQ	1.000			
Hyperactivity	-.383	1.000		
Switching	.159	-.356	1.000	
Inhibition	.293	-.211	.387	1.000

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