

**BEHAVIOURAL ADJUSTMENT SEQUELAE IN  
CHILDREN BORN VERY PRETERM:  
MEASUREMENT ISSUES AND NEONATAL  
NEUROLOGICAL CORRELATES**

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THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE  
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**DOCTOR OF PHILOSOPHY**

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*Dedicated to Maa (Mum) and Deuta (Dad)*

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*Samudragupta Bora (PhD candidate) conceptualised the research aims presented in this paper with inputs from all the co-authors. Samudragupta performed the data analyses and wrote the manuscript draft. Samudragupta had 90% contribution to this paper.*

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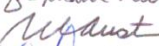
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## Abstract

**Background:** Children born very preterm are at an elevated risk of behavioural adjustment problems, particularly Attention-Deficit/Hyperactivity Disorder (ADHD) or inattention/hyperactivity difficulties. Importantly, these risks remain even after controlling for the effects of social risk factors correlated with very preterm birth. Behavioural outcomes in follow-up studies of children born very preterm are typically assessed using parent reports only. However, the extent to which behavioural problems are evident across multiple contexts (i.e., parent or teacher report) is not well known. Furthermore, the neonatal neuropathology underlying these behavioural difficulties in this population remains poorly understood.

**Aims:** Three research studies are undertaken primarily to examine: (1) the degree of agreement between parent and teacher reports of child behaviour adjustment, and the extent of situational (parent- or teacher-identified) and pervasive (parent- and teacher-identified) inattention/hyperactivity problems at ages 4, 6, and 9 years among children born very preterm and full-term; (2) to cross-validate the classification of children with situational and pervasive inattention/hyperactivity problems across the ages of 4 to 9, for a clinical diagnosis of ADHD at age 9 years; (3) to document risk of persistent ADHD symptoms between ages 4 and 9 years in children born very preterm, and to examine associations between qualitative measures of neonatal cerebral white matter injury/abnormality and quantitative volumetric measures of cerebral structural development, identified using magnetic resonance imaging (MRI) at term equivalent age, and children's later risks of persistent symptoms. Persistent ADHD symptoms were defined as behavioural inattention/hyperactivity problems shown at ages 4, 6, and 9, along with meeting the criteria for an ADHD clinical diagnosis at age 9 years.

**Methods:** As part of a prospective longitudinal study, a regional cohort of 110 very preterm ( $\leq 33$  weeks of gestation) and 113 full-term children born between 1998 and 2000 were studied from birth to age 9 years. At term equivalent age, all children born very preterm and 10 children born full-term underwent an MRI scan that was analysed using qualitative measures for cerebral white matter injury/abnormality,

and quantitative volumetric techniques with tissue segmentation and regional parcellation for cortical and subcortical grey matter, myelinated and unmyelinated white matter, and cerebrospinal fluid. At ages 4, 6 (corrected for the extent of prematurity), and 9 years (uncorrected), children were screened for behavioural adjustment problems including inattention/hyperactivity symptoms using the parent and teacher rated Strengths and Difficulties Questionnaire (SDQ). At age 9, the Development and Well-Being Assessment (DAWBA) structured psychiatric interview was also completed with primary caregiver and an independent clinical diagnosis of ADHD determined by a child psychiatrist blinded to child's perinatal history and group status.

**Results:** Agreement between parent and teacher reports regarding child behaviour adjustment was lower for children born very preterm than full-term (mean alternative chance-correlated coefficient,  $AC_1 = 0.63$  vs.  $0.80$ ). Across all assessment time-points, very preterm birth was associated with on average a 2-fold increased risk of behavioural inattention/hyperactivity problems. These elevated risks largely reflected high rates of situational symptoms (very preterm =  $22.3\% - 31.7\%$ ; full-term =  $10.9\% - 16.7\%$ ). In contrast, rates of pervasive symptoms were relatively modest (very preterm =  $6.8\% - 11.5\%$ ; full-term =  $4.7\% - 7.3\%$ ). Examination of the predictive validity of inattention/hyperactivity problems identified using parent and teacher reports showed that children exhibiting situational symptoms at ages 4 and 6 were much less likely than those exhibiting pervasive symptoms, for a subsequent clinical diagnosis of ADHD at age 9 years (very preterm =  $29\% - 47.8\%$  vs.  $66.7\% - 75\%$ ; full-term =  $13.3\% - 22.2\%$  vs.  $33.3\% - 40\%$ ). Furthermore, receiver operating characteristic curves fitted to the data showed that children born very preterm exhibiting inattention/hyperactivity problems at two or three time-points (area under curve,  $AUC = .909$ ) have better predictive validity for later ADHD diagnosis, compared to those exhibiting symptoms at age 4 ( $AUC = .794$ ) or 6 years ( $AUC = .813$ ) only. Children born very preterm were also at an elevated risk of persistent ADHD symptoms across the ages of 4 to 9 years, with the risk being 5-fold higher than their full-term peers ( $13.1\%$  vs.  $2.8\%$ ). Results also revealed possible associations between neonatal neuropathology and later risk of persistent ADHD symptoms. There were no significant linear associations between increasing severity of qualitative neonatal MRI measures of white matter injury/abnormality

and very preterm children's later risk of persistent ADHD symptoms. However, reduction in total cerebral tissue volumes and corresponding increase of cerebrospinal fluid (adjusted for intracranial volume) were significantly associated with increased risk of persistent symptoms in children born very preterm ( $p = .001$ ). In terms of regional tissue volumes, total cerebral tissues in the dorsal prefrontal region showed the largest volumetric reductions among all the subregions in children born very preterm exhibiting persistent ADHD symptoms, with 3.2 ml (7%) and 8.2 ml (16%) lower tissue volumes than children born very preterm and full-term without persistent symptoms, respectively.

**Conclusions:** Reliance on a single informant to examine child behaviour outcomes at a single time-point may lead to an under- or over-estimation of later ADHD risks. Combining reports from multiple informants and repeated assessments over time may provide better clinical prognostic validity. Children born very preterm are at an increased risk of behavioural inattention/hyperactivity problems during their early school years; although risks of more severe, pervasive problems are relatively modest compared with situational problems. Behavioural adjustment difficulties recognised as early as during preschool age using standardised behaviour screening tools can be a reliable indicator for identifying children born very preterm at risk of subsequent ADHD diagnosis. Finally, study findings suggest that increased risk of ADHD symptoms in children born very preterm can at least in part be accounted for by disturbances to neonatal cerebral growth and maturation.

# Chapter 1

## Very Preterm Birth: An Overview

### *As Premature Babies Grow, So Can Their Problems*

*It has been 11 years since Alex Martin was born, a 1-pound 2-ounce bundle of miniature bones and bright red skin, with fingers no bigger than matchsticks and legs so thin they might have fit inside his father's wedding band. His parents, Rick and Allison, waited four months to send birth announcements. "The doctors kept telling us we had to plan for his funeral," Mrs. Martin explained.*

*Today, Alex is a blond-haired, fair-skinned fifth grader with clear brown eyes, gold-rimmed glasses and a collection of what his mother calls labels: mild cerebral palsy, asthma, hyperactivity and Asperger's syndrome, a form of autism. At an age when most children have conquered fractions, Alex wrestles with addition. He learned to read about a year ago and is racing through the Hardy Boys series. But speaking is a challenge; words roll around like marbles in his mouth.*

*Alex cannot ride a bike. He still wears sneakers that fasten with Velcro, because his fingers cannot master the intricacies of laces. Often, he retreats into a private fantasy world . . .*

*(Excerpt from an article by Sheryl Gay Stolberg published in the New York Times, May 8, 2000)*

Preterm birth (< 37 completed weeks of gestation) is one of the primary causes of neonatal mortality accounting for 27% of neonatal deaths worldwide (Lawn, Gravett, Nunes, Rubens, & Stanton, 2010). Nonetheless, mortality rates among infants born preterm have considerably declined over the past 20 years with a large number of infants successfully resuscitated at very young gestational ages (Ananth & Vintzileos, 2006; Demissie et al., 2001; Lisonkova, Hutcheon, & Joseph, 2011). These gains in survival have largely resulted from advancements in antenatal, perinatal, and neonatal care practices, such as improved neonatal resuscitation

techniques, thermoregulation, increased use of antenatal corticosteroids, and surfactant therapy for accelerating foetal lung maturation (Bissinger & Annibale, 2010; Modanlou, Beharry, Padilla, & Iriye, 1996). However, despite substantial improvements in neonatal mortality, rates of perinatal brain injury and long-term morbidity in infants born preterm remain high (Saigal & Doyle, 2008; Volpe, 2003). Specifically, longitudinal follow-up research suggests that infants born preterm are at a higher risk of cerebral white matter pathology, neurosensory and motor function deficits, poorer cognitive outcomes, and neurobehavioural impairments, relative to their full-term peers; with an inverse relationship between gestational age at birth and morbidity risks (Saigal & Doyle, 2008; Volpe, 2003). Thus, the recent focus of research has largely shifted to reducing the long-term morbidities associated with preterm birth, with a strong emphasis on neonatal clinical and neurological markers for the early identification of those children born preterm likely to be at greatest risk of later developmental challenges.

### **1.1 Defining Preterm Birth**

Infants born preterm represent a heterogeneous population (Behrman & Butler, 2007). Precise definitions of preterm birth are necessary to understand the scientific literature addressing the mechanisms of preterm birth, neurodevelopmental follow-up, and intervention strategies for these infants (Behrman & Butler, 2007). The World Health Organization defines preterm birth as childbirth before 37 completed weeks of gestation (Beck et al., 2010). Childbirth before 33 weeks of gestation is defined as a very preterm birth (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; McCormick, Litt, Smith, & Zupancic, 2011). Extremely preterm birth is typically defined as childbirth before 28 weeks of gestation (P. J. Anderson et al., 2011; Marlow, Wolke, Bracewell, & Samara, 2005). Childbirth between 37 and 42 completed weeks of gestation is considered as a full-term birth (Zegers-Hochschild et al., 2009).

Prior to the 1990's, birth weight was predominantly used to assess the extent of prematurity rather than gestational age due to the difficulties associated with estimating the timing of natural conception (Behrman & Butler, 2007; Lawn et al., 2010). The World Health Organization defines a birth weight of less than 2,500 grams, irrespective of the gestational age, as low birth weight (Blanc & Wardlaw,



2005). Birth weight less than 1,500 grams is defined as a very low birth weight and less than 1,000 grams as an extremely low birth weight (Behrman & Butler, 2007). However, birth weight has been shown to be an unreliable estimate of preterm birth. This is due to the likelihood of including infants who were born at later gestational ages, but were characterised as low birth weight due to intrauterine growth restriction (Behrman & Butler, 2007; Lawn et al., 2010). These foetal growth restricted infants present a different developmental trajectory compared to infants born preterm with normal foetal development (Feldman & Eidelman, 2006; Ramenghi et al., 2011). However, with the increasing use of prenatal ultrasound in routine clinical practice, gestational age can be calculated more accurately and is now considered the most reliable index for evaluating and reporting the extent of prematurity (Behrman & Butler, 2007; Lawn et al., 2010).

Birth weight and gestational age at birth are generally highly correlated. For example, it is estimated that approximately two-thirds of infants with a low birth weight are born preterm and almost all infants with a very or extremely low birth weight are born very preterm (Kramer et al., 2001; Roberts & Lancaster, 1999; Stoll et al., 2010). Thus, for the purpose of this thesis and literature review, follow-up studies concerning infants with a birth weight of less than 1,500 grams and/or less than 33 weeks gestational age at birth will all be included to ensure comprehensive review of research concerned with the neurodevelopmental outcomes of infants born very preterm.

## **1.2 Prevalence of Preterm Birth**

Recent statistics published by the World Health Organization estimated the global prevalence of preterm birth to be approximately 9.6% of all live births representing 12.9 million infants (Beck et al., 2010). This rate varies across different world regions, with the highest prevalence reported in Africa (11.9%), followed by North America (10.6%), and the lowest prevalence (6.2%) in Europe (Beck et al., 2010). Table 1.1 (page 4) summarises the global and regional prevalence of preterm birth.

The prevalence of preterm birth in New Zealand has increased over the past 20 years compared to other high-income countries (Lawn et al., 2010). For example, between 1980 and 1999, the proportion of singleton infants born preterm in New

Zealand rose from 4.3% to 5.9%, representing a relative increase of 37.2% (Craig, Thompson, & Mitchell, 2002). Similarly, the proportion of infants born extremely preterm has increased from 0.3% in 1980 to 0.5% in 1999, representing a relative increase of 81.5% (Craig et al., 2002). Recent estimates also suggest similar trends (see Table 1.2, page 5), with approximately 0.8% and 0.5% of all live births in New Zealand between 2000 and 2010 being born within the gestational ages of 28 to 31 weeks and less than 28 weeks, respectively (Ministry of Health New Zealand).

**Table 1.1:** Global and Regional Prevalence of Preterm Birth

Region/Subregion	Preterm Birth Rate	
	%	95% CI
World total	9.6	9.1 – 10.1
More developed countries	7.5	7.3 – 7.8
Less developed countries	8.8	8.1 – 9.4
Least developed countries	12.5	11.7 – 13.3
Africa	11.9	11.1 – 12.6
Asia	9.1	8.3 – 9.8
Europe	6.2	5.8 – 6.7
Latin America & the Caribbean	8.1	7.5 – 8.8
North America	10.6	10.5 – 10.6
Oceania (Australia & New Zealand)	6.4	6.3 – 6.6

*Note.* From “The Worldwide Incidence of Preterm Birth: A Systematic Review of Maternal Mortality and Morbidity,” by S. Beck et al., 2010, *Bulletin of the World Health Organization*, 88(1), page 35. Reproduced with permission from the World Health Organization. CI = Confidence Interval.

**Table 1.2:** Prevalence of Preterm Birth in New Zealand

Year	Total Live Births	Preterm Birth Rate, <i>n</i> (%)		
		32 – 36 weeks	28 – 31 weeks	< 28 weeks
2000	55,782	3,430 (6.1)	442 (0.8)	282 (0.5)
2001	54,545	3,313 (6.1)	492 (0.9)	250 (0.5)
2002	53,733	3,265 (6.1)	436 (0.8)	303 (0.6)
2003	55,289	3,245 (5.9)	466 (0.8)	275 (0.5)
2004	55,943	3,337 (6.0)	410 (0.7)	250 (0.4)
2005 <sup>a</sup>	56,739	3,303 (5.8)	495 (0.9)	265 (0.5)
2006 <sup>a</sup>	58,635	3,502 (6.0)	470 (0.8)	257 (0.4)
2007 <sup>a</sup>	61,984	3,631 (5.9)	460 (0.7)	296 (0.5)
2008 <sup>a</sup>	62,015	3,695 (6.0)	492 (0.8)	300 (0.5)
2009 <sup>a</sup>	61,649	3,758 (6.1)	462 (0.7)	297 (0.5)
2010 <sup>a</sup>	62,096	3,654 (5.9)	487 (0.8)	293 (0.5)

*Note.* Reproduced from the *Reports on Maternity: Maternal and Newborn Information*. The New Zealand Health Information Service, Ministry of Health, New Zealand.

<sup>a</sup>Based on provisional data.

Recently published statistics suggest a disproportionate distribution of neonatal mortality rates globally for infants born preterm (Lawn et al., 2010). For example, preterm birth accounted for 13.5 neonatal deaths per 1,000 live births in Nigeria compared to 2 per 1,000 in the United Kingdom (Lawn et al., 2010). This discrepancy in mortality is primarily due to lack of sophisticated neonatal intensive care services in low- and middle-income countries (Lawn et al., 2010; Saigal & Doyle, 2008). Nonetheless, there is general consensus that survival rates of infants born very preterm have improved dramatically since the early 1990s, with the largest gains being in the survival of infants born below 26 weeks of gestation particularly in high-income countries (Lawn et al., 2010; Saigal & Doyle, 2008). Based on neonatal mortality data from France and England in 1997, survival rates till hospital discharge for infants born very preterm were estimated at 13.8% and 15.6% for those born at less than 26 weeks of gestation, 57.1% and 68% for those born at 26 to 28 weeks of gestation, and 85.8% and 91.5% for those born at 28 to 32 weeks of gestation, respectively (Draper, Zeitlin, Field, Manktelow, & Truffert, 2007).

Similarly, based on data from 9,575 infants born at 22 to 28 weeks gestational age between 2003 and 2007, the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported a 72% survival rate till discharge (Stoll et al., 2010). Specifically, 92% of infants born at 28 weeks, 72% of infants born at 25 weeks, and 23% of infants born at 23 weeks of gestation survived till discharge, respectively (Stoll et al., 2010).

Survival rates of infants born very preterm have also improved in New Zealand. For example, 84% ( $n = 554$ ) of infants born very preterm in 2004 survived to hospital discharge (Ministry of Health, New Zealand). In 2006, as reported by the Australian and New Zealand Neonatal Network, 78.7% ( $n = 833$ ) of infants born extremely preterm and 97% ( $n = 3,516$ ) of infants born very preterm admitted to a level III neonatal intensive care unit (NICU) in Australia and New Zealand survived till discharge (ANZNN, 2009). These findings indicate that we may be close to the threshold of viability for infants born at younger gestational ages. It now becomes imperative to prevent and minimise the developmental morbidities associated with very preterm birth.

### **1.3 Very Preterm Birth and the Developing Brain**

Very preterm birth has profound consequences for brain growth and maturation (Kinney, 2006; Perlman, 2001; Volpe, 2009). For example, the foetal brain at 20 weeks of gestation weighs 10% of the expected brain weight of a newborn infant at term equivalent age (Kinney, 2006). Between 20 and 32 weeks of gestation, brain weight increases linearly up to approximately 50% of brain weight at term (Kinney, 2006). Similarly, the cortical volume at 28 weeks of gestation is equivalent to 13% of the cortical volume at term, which increases up to 53% by 34 weeks of gestation (Kinney, 2006). Furthermore, there is a 5-fold increase in myelinated white matter volume between 35 and 41 weeks of gestation (Kinney, 2006).

Being born very preterm results in the loss of a safe intrauterine environment for the developing brain, thereby interrupting the normal trajectory of cerebral maturation (Mathur & Inder, 2009). Moreover, perinatal complications of very preterm birth such as hypoxia-ischaemia, bronchopulmonary dysplasia, suboptimal nutrition, inflammation and/or infection may have cumulative negative

consequences during critical periods of brain growth and maturation (Adams-Chapman & Stoll, 2006; Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Perlman, 2001; Wilkinson, Brosi, & Jiang, 2007).

Understanding of the neuropathological sequela of very preterm birth was limited until the mid-1980's by the need to rely on cranial ultrasound, which has poor spatial resolution and low sensitivity in detecting subtle neuropathologies (Maalouf et al., 2001; van Wezel-Meijler et al., 1999; Woodward, Anderson, Austin, Howard, & Inder, 2006). However, the advent of magnetic resonance imaging (MRI) has led to significant advances in clinical and research understanding of the neuropathologies associated with very preterm birth (Inder, Warfield, Wang, Huppi, & Volpe, 2005; Inder et al., 2003). Findings now suggest that the nature of neuropathology in infants born very preterm includes both: (1) perinatal cerebral injuries (i.e., direct injuries involving neuronal necrosis) such as periventricular leukomalacia and intraventricular haemorrhage, and (2) altered cerebral development and maturation as a consequence of cerebral injuries and/or clinical complications of premature birth (Inder et al., 2005; Inder et al., 2003; Mathur & Inder, 2009; Volpe, 2009).

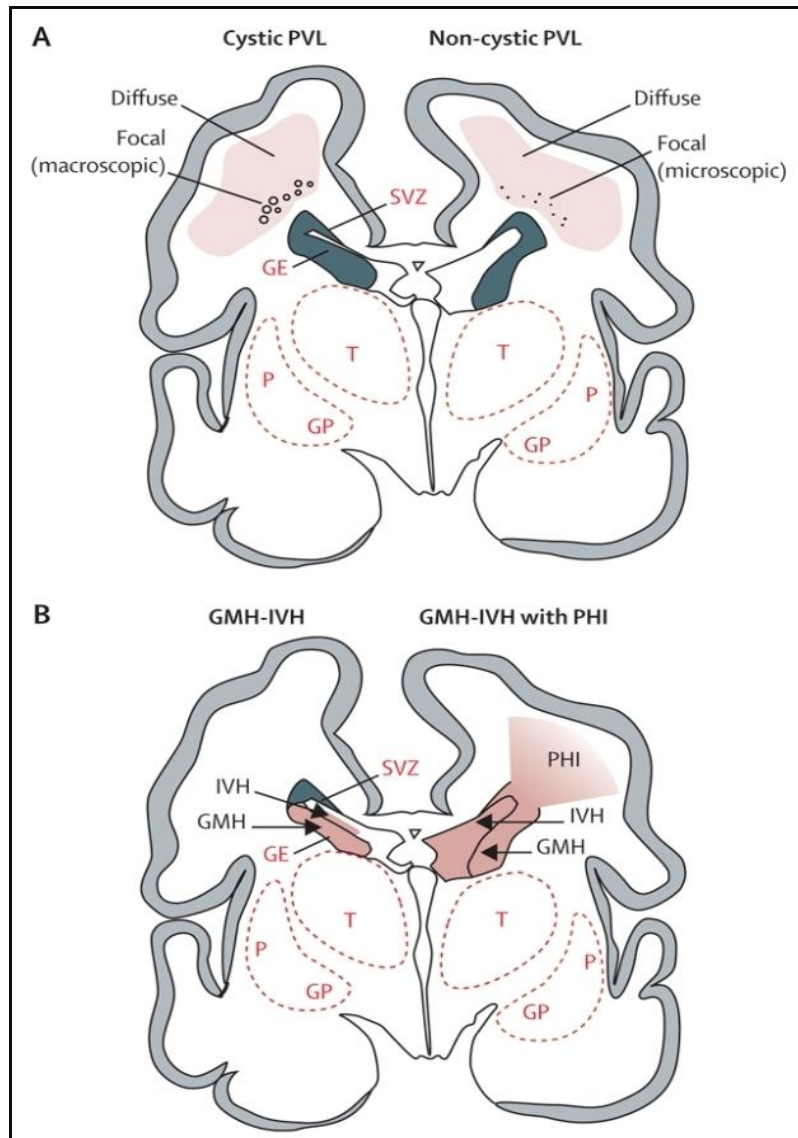
### **1.3.1 Perinatal Cerebral Injury**

Periventricular leukomalacia consists of a spectrum of cerebral white matter pathology, and is the characteristic pattern of perinatal cerebral injury in infants born very preterm (Back, 2006; Volpe, 2003, 2009). As illustrated in Figure 1.1A (page 9), the most serious form is cystic periventricular leukomalacia which manifests as focal necrotic lesions with subsequent cystic formations deep in the periventricular white matter (Volpe, 2009). This type of injury is easily identified using neonatal cranial ultrasound (Volpe, 2003, 2009). However, the incidence of cystic periventricular leukomalacia is decreasing, and now affects less than 5% of infants born very preterm (Volpe, 2003; Woodward et al., 2006). Recently, a less severe form of periventricular leukomalacia manifesting as more subtle, diffuse noncystic white matter injury has been recognised as the dominant form of cerebral white matter pathology in infants born very preterm (Volpe, 2003, 2009). This can be readily identified using neonatal MRI (Inder et al., 2003). For example, in a follow-up of a regional cohort of 100 infants born very preterm, 16 infants had noncystic white matter injury evident at term equivalent age while only 4 infants

had cystic injury (Inder et al., 2003). This diffuse injury is characterised primarily by the loss of premyelinating oligodendrocytes with prominent astrogliosis and microgliosis, resulting in hypomyelination and ventriculomegaly (Volpe, 2009). Recent follow-up research estimates 20% of infants born very preterm have moderate to severe white matter injury, and a further 50% have mild white matter injury (Inder et al., 2003; Woodward et al., 2006).

As illustrated in Figure 1.1B (page 9), germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH) represents another characteristic pattern of perinatal cerebral injury in infants born very preterm, and can be readily detected using cranial ultrasound (Ballabh, 2010; Boardman & Dyet, 2007). Nonetheless, the incidence has gone down from between 40% and 50% in the 1980s to between 20% and 25% in the 1990s, with rates varying widely across neonatal centres (Ballabh, 2010; Boardman & Dyet, 2007; Sheth, 1998). Furthermore, the severe GMH-IVH with periventricular haemorrhagic infarction only occurs in approximately 4% to 5% of infants born very preterm, although the incidence increases up to between 20% and 30% in infants born at 24 to 26 weeks of gestation and/or less than 750 grams birth weight (Volpe, 2009). GMH-IVH in infants born very preterm originates in the subependymal germinal matrix located ventrolateral to the lateral ventricles, an area which is highly vascularised with capillaries that are vulnerable to rupture in response to fluctuations in blood flow (Roland & Hill, 2003). Moreover, the germinal matrix capillaries are vascular end zones of arterial supply or “watershed areas” and are highly vulnerable to ischaemia (Roland & Hill, 2003). In the case of GMH-IVH with periventricular haemorrhagic infarction, the associated infarction with haemorrhage in the germinal matrix destroys the dorsal subventricular zone and the ventral ganglionic eminence along with premyelinating oligodendrocytes and axons, resulting in hypomyelination and impaired thalamic and cortical neuronal development (Volpe, 2005, 2009).

In summary, perinatal cerebral injury in infants born very preterm reflects direct disturbances in the structural integrity of cerebral white matter. Direct injury involving major neuronal necrosis in the cerebral cortical grey matter is atypical in infants born very preterm, although altered structural development of grey matter has been shown in association with white matter injury (Mathur & Inder, 2009).



**Figure 1.1:** Cystic and noncystic periventricular leukomalacia (PVL) and germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH) and GMH-IVH with periventricular haemorrhagic infarction (PHI).<sup>1</sup>

Coronal sections from the brain of a 28-week-old premature infant. The dorsal cerebral subventricular zone (SVZ), the ventral germinative epithelium of the ganglionic eminence (GE), thalamus (T), and putamen (P)/globus pallidus (GP) are shown. (A) The focal necrotic lesions in cystic PVL (small circles) are macroscopic in size and evolve to cysts. The focal necrotic lesions in noncystic PVL (black dots) are microscopic in size and evolve to glial scars. The diffuse component of both cystic and noncystic PVL (pink) is characterised by the cellular changes. (B) Haemorrhage (red) into the GE results in GMH, which could burst through the ependyma to cause an IVH (left). When the GHM-IVH is large, PHI might result (right).

<sup>1</sup>From "Brain Injury in Premature Infants: A Complex Amalgam of Destructive and Developmental Disturbances," by J.J. Volpe, 2009, *Lancet Neurology*, 8(1), page 110. Reproduced with permission from Elsevier.

### **1.3.2 Altered Cerebral Structural Development**

As illustrated in Figure 1.2 (page 12), perinatal injury to the cerebral white matter in infants born very preterm may also have secondary consequences for growth and maturation of various cerebral structures (Inder et al., 1999; Mathur & Inder, 2009; Volpe, 2009). For example, infants born very preterm with periventricular leukomalacia have been found to have a significant reduction of myelinated white matter volume at term equivalent age, compared to infants born very preterm without periventricular leukomalacia and infants born full-term (Inder et al., 1999). Furthermore, follow-up research shows lower white matter volume and fractional anisotropy in children born very preterm between 8.8 and 11.5 years of age compared to age-matched children born full-term (Yung et al., 2007). A similar trend was also evident among adolescents born very preterm (mean age = 15 years), with significantly smaller white matter volume in adolescence shown for those with periventricular haemorrhage and ventriculomegaly detected on neonatal cranial ultrasound compared to those without that injury (Nosarti et al., 2002). Thus, although myelination primarily occurs after postterm age, early white matter injury in infants born very preterm may have long-term disruptive consequences for the structural development of cerebral white matter tracts.

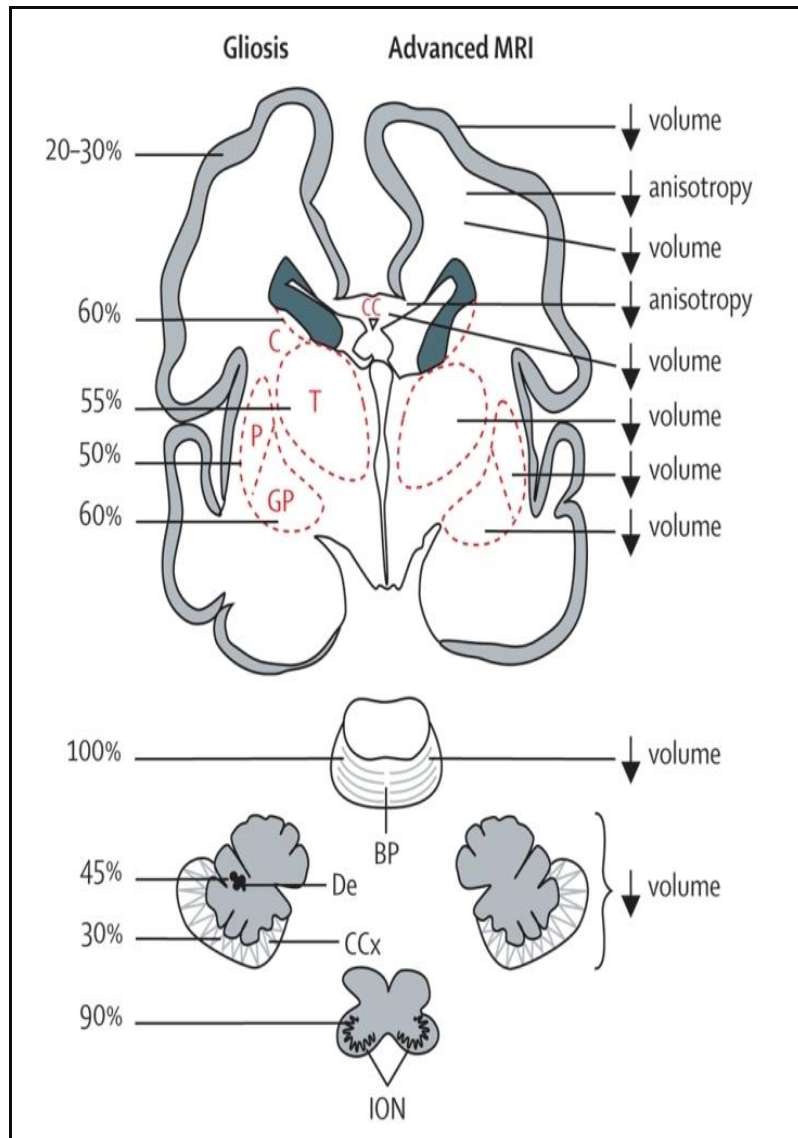
Altered grey matter development in association with perinatal cerebral white matter injury has also been well documented in infants born very preterm (Inder et al., 1999; Mathur & Inder, 2009). For example, infants born very preterm with periventricular leukomalacia were found to have reduced cortical grey matter volume at term equivalent age compared to infants born very preterm without periventricular leukomalacia and infants born full-term (Inder et al., 1999). Furthermore, infants born very preterm have been shown to have less mature gyration and reduced cortical surface area at term equivalent age relative to infants born full-term (Ajayi-Obe, Saeed, Cowan, Rutherford, & Edwards, 2000; Inder et al., 2003). Significant volumetric reduction of cortical grey matter has also been reported in 8-year-old children born very preterm compared to their full-term peers, with group differences persisting after excluding children with perinatal white matter injury (Lodygensky et al., 2005). Along with decreased cortical grey matter volume, infants born very preterm have been shown to have reduced subcortical grey matter volume (i.e., basal ganglia and thalamus), relative to infants



born full-term, at term equivalent as well as during school age (Inder et al., 2005; Kesler et al., 2004; Thompson et al., 2007).

Along with perinatal white matter injury, disruption of typical cerebral structural development in infants born very preterm has also been shown to be independently associated with perinatal complications of premature birth such as intrauterine growth restriction and bronchopulmonary dysplasia (Inder et al., 2005; Mathur & Inder, 2009; Thompson et al., 2007; Thompson et al., 2008). For example, prominent volumetric reduction of total cerebral tissues (- 10% to - 30%) has been shown; particularly cortical grey matter (- 11% to - 35%), subcortical grey matter (- 20%), and cerebellum (- 21%) in very preterm infants treated with postnatal dexamethasone therapy compared to untreated very preterm infants (Murphy et al., 2001; Parikh et al., 2007).

Impaired cerebral structural growth and maturation in infants born very preterm has also been demonstrated using brain metrics such as biparietal cerebral or transverse cerebellar diameters. Specifically, infants born at less than 30 weeks of gestation were shown to have reduced bifrontal cerebral (- 11.6%), biparietal cerebral (- 12%), and transverse cerebellar (- 8.7%) diameters at term equivalent age relative to infants born full-term (Nguyen The Tich et al., 2009). In conclusion, as recently described by Volpe, neuropathological sequelae of very preterm birth can be aptly summarised as a “. . . complex amalgam of primary destructive disease and secondary maturational and trophic disturbances” (Volpe, 2009, page 110).



**Figure 1.2:** Main neuronal/axonal structures affected in premature infants with periventricular leukomalacia.<sup>2</sup>

Coronal sections of the cerebrum, pons, cerebellum, and medulla (inferior olivary nuclei) are shown. The frequency of gliosis by neuropathological study and the major abnormalities detected by advanced MRI (volumetric and diffusion-based MRI) are shown. BP = basis pontis, C = caudate, CC = corpus callosum, CCx = cerebellar cortex, De = dentate, GP = globus pallidus, ION = inferior olivary nuclei, P = putamen, T = thalamus.

<sup>2</sup>From "Brain Injury in Premature Infants: A Complex Amalgam of Destructive and Developmental Disturbances," by J.J. Volpe, 2009, *Lancet Neurology*, 8(1), page 112. Reproduced with permission from Elsevier.

#### **1.4 Very Preterm Birth and Neurodevelopmental Outcomes**

Coupled with neurological risks, survivors of very preterm birth are highly vulnerable to a range of perinatal complications (described in Appendix A, page 137), and subsequent neurodevelopmental impairments (Saigal & Doyle, 2008). This increased susceptibility is largely due to the immaturity of body organs at birth, as well as the intensive interventions required in the NICU for survival (McCormick et al., 2011; Saigal & Doyle, 2008). Common clinical complications during perinatal and neonatal period in infants born very preterm include: respiratory distress syndrome and bronchopulmonary dysplasia, poor postnatal growth, necrotising enterocolitis, patent ductus arteriosus, early and late onset sepsis, and retinopathy of prematurity (McCormick et al., 2011; Randis, 2008; Saigal & Doyle, 2008). Long-term neurodevelopmental consequences following very preterm birth span across sensory, motor, cognitive, and behavioural domains (Saigal & Doyle, 2008; Woodward et al., 2009). Follow-up research suggests an inverse relationship between gestational age at birth and both incidence and severity of adverse neurodevelopmental outcomes (Saigal & Doyle, 2008; Woodward et al., 2009).

##### **1.4.1 Neurosensory Outcomes**

Typically, 1% to 2% of infants born very preterm and between 4% and 10% of infants born extremely preterm suffer from blindness or severe visual impairments (Behrman & Butler, 2007; McCormick et al., 2011; Saigal & Doyle, 2008). This risk is higher for less severe visual impairments such as myopia, hyperopia, and strabismus, with almost a quarter of infants born very preterm developing these impairments (Behrman & Butler, 2007; Marlow et al., 2005; Saigal & Doyle, 2008). In a recent follow-up of 11-year-old children born very preterm ( $N = 98$ ), 6% ( $n = 6$ ) of the children had visual acuity of less than 0.8, 12% ( $n = 12$ ) had strabismus, and between 14% and 46% had abnormal outcomes on visual-motor tests (Kok et al., 2007). Similar to visual functioning, the incidence of hearing impairments typically varies between 3% and 6% in infants born extremely preterm (Marlow et al., 2005; Saigal & Doyle, 2008). For example, in the population-based EPICure study of 6-year-old children born at less than 26 weeks of gestation ( $N = 241$ ), 4% ( $n = 10$ ) had mild hearing impairments, 3% ( $n = 7$ ) had sensorineural hearing loss corrected with hearing aids, and a further 3% ( $n = 7$ ) had profound sensorineural hearing loss that could not be corrected with hearing aids (Marlow et al., 2005).

### **1.4.2 Neuromotor Outcomes**

Infants born very preterm are also at an increased risk of impaired neuromotor functioning, with risks increasing with decreasing gestational age at birth (McCormick et al., 2011; Saigal & Doyle, 2008; Woodward et al., 2009). Specifically, the prevalence of cerebral palsy is estimated at 40 to 150 cases per 1,000 live births for infants born very preterm compared to 2 to 3 per 1,000 live births for infants born full-term (Robertson, Watt, & Yasui, 2007; Saigal & Doyle, 2008). While 6% to 9% of infants born very preterm are at risk of moderate to severe cerebral palsy, rates may increase up to between 16% and 28% for infants born extremely preterm (McCormick et al., 2011). In addition to cerebral palsy, infants born very preterm are at an elevated risk of minor neuromotor dysfunction, including motor delay, motor incoordination disorder, poor fine and gross motor skills, as well as sensorimotor integration difficulties (Behrman & Butler, 2007; de Kieviet, Piek, Aarnoudse-Moens, & Oosterlaan, 2009). As shown in a recent meta-analysis, children born very preterm without congenital abnormalities on average scored 0.6 to 0.9 standard deviations below children born full-term on standardised tests of motor development (de Kieviet et al., 2009).

### **1.4.3 Neurocognitive Outcomes**

Infants born very preterm are also at risk of poor intellectual and neurocognitive functioning compared to their full-term peers across all developmental stages (Behrman & Butler, 2007; Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Johnson, 2007). A meta-analysis of studies published between 1980 and 2001 concerning school-aged children born very preterm, reported a pooled weighted mean difference of 10.9 points for intelligence quotient (IQ) scores between very preterm and full-term control groups (Bhutta et al., 2002). All the 15 case-control studies included in the meta-analysis favoured the full-term control group, with the individual weighted mean difference in IQ scores ranging from 7.0 to 22.7 points (Bhutta et al., 2002). Typically, a linear relationship is evident between gestational age at birth and IQ scores, with follow-up research suggesting a downward shift of 1.5 to 2.5 IQ points per week of decrement in gestational age from 32 weeks (Behrman & Butler, 2007; Johnson, 2007).

In a recent population-based follow-up of 6-year-old children born extremely preterm (< 26 weeks of gestation;  $N = 241$ ), 41% ( $n = 99$ ) of children showed severe cognitive impairment (defined as  $> M - 2SD$ ) compared to 1% ( $n = 2$ ) of age- and sex-matched full-term classroom peers (Marlow et al., 2005). Furthermore, there was a mean difference of 24 points in the overall cognitive ability scores between the extremely preterm and full-term group, which lowered to 20 points after the exclusion of children with physical disability (Marlow et al., 2005). Children born extremely preterm were also characterised by poorer performance on specific cognitive subtests relative to their full-term peers, with a mean difference of 12% and 18% respectively, for sequential processing and simultaneous processing abilities (Marlow et al., 2005).

Along with global cognitive impairments, children born very preterm may also demonstrate domain-specific cognitive impairments (Marlow et al., 2005; Woodward, Clark, Pritchard, Anderson, & Inder, 2011). These findings are often independent of intellectual functioning abilities. For example, children born very preterm with normal IQ scores have been shown to perform poorly relative to children born full-term on tests of attention, memory, learning disabilities, and planning and problem solving (Behrman & Butler, 2007). These difficulties appear to persist with age. Specifically, children born very preterm were shown to have working memory deficits as early as 2 to 4 years of age (Woodward, Edgin, Thompson, & Inder, 2005). Within the same regional cohort, children born very preterm had poorer verbal and visuospatial working memory abilities at 6 years of age compared to children born full-term (Clark & Woodward, 2010). Similarly, in another follow-up of a large representative cohort, children born extremely preterm had higher rates of impairment in selective, sustained, shifting, and divided attention at 8 years of age relative to children born full-term (P. J. Anderson et al., 2011). Children born very preterm may also demonstrate speech and language impairments (Foster-Cohen, Friesen, Champion, & Woodward, 2010). For example, at age 4 years, children born very preterm were characterised by significantly poorer receptive and expressive language skills than children born full-term, with risks persisting after accounting for neurosensory impairments and social risk factors (Foster-Cohen et al., 2010).

#### **1.4.4 Neurobehavioural Outcomes**

In addition to risks of sensory, motor, and cognitive impairments, children born very preterm are also more likely to experience neurobehavioural impairments and increased emotional and behavioural difficulties compared to their full-term peers (Aarnoudse-Moens et al., 2009; Burnett et al., 2011). Neurobehavioural disturbances among very preterm survivors have been identified as early as term equivalent age (Brown, Doyle, Bear, & Inder, 2006). Findings from the Victorian Infant Brain Studies (VIBeS) demonstrate that infants born very preterm have significantly poorer self-regulation, inattention, and greater excitability at term age compared to infants born full-term, when assessed on the NICU Network Neurobehavioural Scale (Brown et al., 2006). These difficulties often persist throughout childhood. For example, in a meta-analysis of 16 case-control studies of school-aged children born very preterm (published between 1980 and 2001), 13 studies (81%) reported an increased risk of internalising or externalising behavioural problems following very preterm birth (Bhutta et al., 2002). In a more recent meta-analysis of 9 case-control studies of children born very preterm and/or with a very low birth weight (published between 1998 and 2008), 6 studies (69%) reported a higher prevalence of externalising behavioural problems in children born very preterm (Aarnoudse-Moens et al., 2009). However, there was no significant effect size for externalising behavioural problems when all the studies were pooled together, and a small combined effect size for internalising behavioural problems (Aarnoudse-Moens et al., 2009). Nonetheless, both meta-analyses suggested that Attention-Deficit/Hyperactivity Disorder (ADHD) or inattention/hyperactivity is the most common neurobehavioural impairment associated with very preterm birth (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002). Recently, a “preterm behavioural phenotype” has been identified which is characterised by behavioural inattention/hyperactivity, poor socio-emotional adjustment, and an elevated risk of internalising problems (Johnson et al., 2010b; Johnson & Marlow, 2011). Increased risk of these neurobehavioural impairments are evident even after taking into account the influence of social risks, neurosensory impairments, and cognitive deficits (Johnson & Marlow, 2011). Very preterm birth has also been recently identified as a potential risk factor for Autism Spectrum Disorder (Johnson & Marlow, 2011). In the EPICure study of 11-year-old children born extremely

preterm (< 26 weeks gestation), 15.8% ( $n = 29$ ) of children born extremely preterm compared to 2.9% ( $n = 4$ ) of their full-term peers were screened as positive for Autism Spectrum Disorder (Johnson et al., 2010a). Out of those who screened positive, 7.7% ( $n = 14$ ) of extremely preterm children but no full-term children were assigned a clinical diagnosis (Johnson et al., 2010a).

Thus, there is a growing body of scientific evidence to suggest that infants born very preterm are at an increased risk for a wide range of long-term neurodevelopmental impairments. These elevated risks can be recognised as early as term equivalent age and appear to persist through into the school years. Such findings highlight the need for appropriate follow-up and strategies for effective early intervention in order to optimise the developmental outcomes.

### **1.5 Thesis Outline**

This thesis primarily aims to examine the development of ADHD symptomatology in a regional cohort of children born very preterm. Three studies are undertaken to examine a range of issues concerning measurement of ADHD symptomatology in children born very preterm, and the possible associations between persistent ADHD symptoms and neonatal cerebral structural development and cerebral injury.

The thesis is organised into seven chapters. Following this chapter are six chapters, which are briefly outlined below.

Chapter 2 provides the conceptual framework for the research questions addressed in this thesis. The chapter is divided primarily into two sections: (1) a review of published studies concerning ADHD or behavioural inattention/hyperactivity in preschool- and school-aged children born very preterm, (2) a review of published studies concerned with the neurological factors associated with ADHD or behavioural inattention/hyperactivity in children born very preterm. Finally, research questions are formulated and specific aims and hypotheses for this thesis are presented.

Chapter 3 provides an overview of the research design of this thesis. Sample characteristics and the general data collection procedures have been briefly described in this chapter.

Chapters 4, 5, and 6 are presented as stand-alone chapters, each addressing a set of specific research aims as outlined in chapter 2. Each of these chapters includes a brief introduction, and then methods, results, and discussion.

Chapter 4 describes the behavioural adjustment outcomes of children born very preterm at age 6 years. Of particular interest was the degree of agreement between parent and teacher ratings of child behavioural adjustment problems, and the extent of situational (parent- or teacher-reported) and pervasive (parent- and teacher-reported) behavioural adjustment problems.

Chapter 5 describes the predictive validity of parent and teacher ratings of child behavioural inattention/hyperactivity at ages 4 and 6 in identifying children born very preterm at high risk of a subsequent ADHD psychiatric diagnosis at age 9 years. Of particular interest was to cross-validate the classification of children with situational and pervasive inattention/hyperactivity symptoms based on parent and teacher ratings of child behaviour across the ages of 4 to 9, for a clinical diagnosis of ADHD at age 9 years.

Chapter 6 describes the relationships between MRI measures of cerebral structural development and white matter injury at term equivalent age, and subsequent risk of persistent ADHD symptoms across the ages of 4 to 9 years in children born very preterm. Of particular interest was the association between neonatal cerebral structural development and later risk of persistent ADHD symptoms, over and above the influence of neonatal clinical and social risk factors.

Chapter 7 integrates the findings from the three research studies presented in chapters 4 to 6, discussing the strengths and limitations of the current research. Next, the findings are discussed in light of their clinical and theoretical relevance. Finally, the thesis concludes by highlighting the scope for further research concerning ADHD symptomatology in children born very preterm.



## Chapter 2

### **ADHD Symptomatology in Children Born Very Preterm: A Conceptual Framework**

The American Academy of Pediatrics Clinical Practice Guideline (2011) describes ADHD as a neurobehavioural disorder of childhood characterised by the symptoms of persistent inattention, hyperactivity, or impulsivity (Wolraich et al., 2011). These core symptoms should be manifested at a degree that is severe enough to be categorised as developmentally inappropriate for child's age and sex, as well as occurring across multiple contexts, and causing significant impairment to social or occupational functioning (Wolraich et al., 2011). Further details from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* criteria for the clinical diagnosis of ADHD and the subtypes are provided in Appendix B (pages 138 – 139).

Children born very preterm are widely recognised to be at an increased risk of ADHD (Bhutta et al., 2002). Follow-up studies suggest that school-aged children born very preterm are two to four times more likely than their full-term peers to meet the *DSM-III*, *DSM-III-R*, or *DSM-IV* diagnostic criteria for ADHD (Bhutta et al., 2002; Johnson & Marlow, 2011). However, the clinical manifestation of ADHD symptomatology in these children has been shown to be distinct from the general population (Johnson & Marlow, 2011). Specifically, unlike children born full-term, a male disadvantage for ADHD has not been found for children born very preterm (P. J. Anderson et al., 2011; Johnson & Marlow, 2011; Szatmari, 1993). Moreover, ADHD in children born very preterm has been recognised to be a more “pure” form of ADHD, since it is not typically associated with comorbid conduct and/or oppositional-defiant disorders (Johnson & Marlow, 2011; Szatmari, 1993). Regarding ADHD subtypes, follow-up studies have tended to report a predominance of the ADHD inattentive subtype in children born very preterm (Johnson et al., 2010b; Johnson & Marlow, 2011; Whitaker et al., 1997).

## **2.1 ADHD Symptomatology in Children Born Very Preterm: A Review**

This section provides a systematic overview of existing studies examining the risk of ADHD or behavioural inattention/hyperactivity in preschool- and school-aged children born very preterm. Table 2.1 (pages 21 – 22) provides a methodological summary of all the studies selected for inclusion in this review, including study sample characteristics, assessment measures, and prevalence.

### **2.1.1 Inclusion Criteria**

A MEDLINE/PubMed and PsycINFO electronic database search for original articles was undertaken for the period from January 1991 to December 2011 using various combinations of the following subject headings and keywords: *preterm birth, low birth weight, premature, attention deficit hyperactivity disorder, ADHD, attention, inattention, hyperactivity, impulsivity, hyperkinesis, and behaviour*. Studies were included in the current review if they met all of the following criteria.

- (1) Peer-reviewed English language publication.
- (2) Inclusion of an index group of children born very preterm and a comparison group of children born full-term.
- (3) Index group consisted of children born very preterm ( $\leq 33$  weeks gestation) and/or with a very low birth weight ( $\leq 1,500$  grams birth weight).
- (4) Both very preterm and full-term groups included children born after 1990 following widespread changes in neonatal resuscitation practices.
- (5) ADHD symptomatology or behavioural inattention/hyperactivity was assessed using standardised behavioural screening or clinical diagnostic tool.
- (6) ADHD symptomatology or behavioural inattention/hyperactivity was assessed at preschool age (3 – 5 years), school age (6 – 12 years), or both.
- (7) Studies primarily concerning children with a very low birth weight without any gestational data were excluded due to the possibility of including small-for-gestational age children.
- (8) Studies exclusively focusing on high-risk, medically selected, subgroups of children born very preterm were also excluded.

Fifteen studies met the above selection criteria. Out of these, six studies included preschool-aged children and the remainder examined outcomes at school age (see Table 2.1, pages 21 – 22).

Table 2.1: Summary of Studies of ADHD or Behavioural Inattention/Hyperactivity in Children Born Very Preterm												
Reference	Sample Characteristics						ADHD Diagnosis or Behavioural Inattention/Hyperactivity Screening				Results	
	Very Preterm			Full-Term			Age at Follow-up (Years)	Assessment Measure/s	Child Behaviour Informant	Prevalence (%)		Odds Ratio (95% Confidence Interval)
	Year Born	Sample Size	Gestational Age (Weeks)	Birth Weight (Grams)	Sample Size	Very Preterm				Full-Term		
Delobel-Ayoub et al., 2006	1997	1,205	24 – 32	–	441	3	SDQ	Parent	20	11	2.1 (1.5 – 2.9)	
Baron et al., 2011	2004 – 2006	60	26.0 ± 1.7	782.6 ± 149.3	90	3	BASC	Parent	No significant ( $p < .05$ ) group differences Hyperactivity, Effect size = 0.005 Attention problems, Effect size = 0.006			
Woodward et al., 2009	1998 – 2000	103	27.9 ± 2.3	1,061.6 ± 310.9	107	4	SDQ	Parent	24.3	11.2	–	
Hoff et al., 2004	1994 – 1995	94	27.5 ± 1.8	924.6 ± 168.7	72	5	CASQ	Parent	17.5	4.2	–	
Reijneveld et al., 2006	1992 – 1995	397	30.2 ± 1.9	1,268 ± 329	6,007	5	CBCL	Parent	4.2	1.3	3.4 (2.0 – 5.9)	
Delobel-Ayoub et al., 2009	1997	1,096	24 – 32	–	372	5	SDQ	Parent	18	9	2.1 (1.5 – 3.1)	
Samara et al., 2008	1995	224	≤ 25	–	162	6	SDQ; specific items from DSM, ICD, CBCL, Conners'	Parent and Teacher	Details on Pages 27 – 29			
Foulder-Hughes et al., 2003	1991 – 1992	280	≤ 32	–	210	7 – 8	CADS	Teacher	8.9	2.1	–	
Anderson et al., 2003	1991 – 1992	257	≤ 28	< 1,000	213	8	BASC	Parent and Teacher	Preterm children at an increased risk of hyperactivity (parent report, mean difference = 2.5) and attention problems (both parent and teacher reports, mean difference = 3.4 – 4.1)			

Note. Table 2.1 continued on following page. – = not reported; ± = Mean ± Standard Deviation.

Reference	Sample Characteristics					ADHD Diagnosis or Behavioural Inattention/Hyperactivity Screening				Results	
	Year Born	Very Preterm		Full-Term	Age at Follow-up (Years)	Assessment Measure/s	Child Behaviour Informant	Prevalence (%)		Odds Ratio (95% Confidence Interval)	
		Sample Size	Gestational Age (Weeks)					Birth Weight (Grams)	Sample Size		Very Preterm
Hack et al., 2009	1992 – 1995	219	26.4 ± 2.0	810 ± 124	176	8	CSI-4	Parent	17	5	4.2 (1.9 – 9.1)
Anderson et al., 2011	1997	189	26.5 ± 2.0	833 ± 164	173	8	CADS	Parent	44	25	1.8 (1.1 – 3.1)
Larrouque et al., 2011	1997	1,387	24 – 32	–	319	8	SDQ	Parent	17	11	–
Shum et al., 2008	1992 – 1995	45	26.4 ± 1.9	838.2 ± 151.7	49	7 – 9	ADHD RS	Parent and Teacher	18.2 (Parent) 0 (Teacher)	4.1 (Parent) 2.6 (Teacher)	–
Farooqi et al., 2007	1990 – 1992	83	24.6 ± 0.7	765 ± 111	86	11	CBCL/TRF	Parent and Teacher	30 (Parent) 24 (Teacher)	9 (Parent) 7 (Teacher)	3.5 (1.4 – 8.5) 3.4 (1.3 – 9.4)
Johnson et al., 2011	1995	183	≤ 25	–	138	11	DAWBA	Parent and Teacher	11.5	2.9	4.3 (1.5 – 13.0)

Note – – = not reported; ± = Mean ± Standard Deviation.

Abbreviations:  
SDQ = Strengths and Difficulties Questionnaire  
BASC = Behaviour Assessment System for Children  
CASQ = Conners' Abbreviated Symptom Questionnaire  
CBCL = Child Behaviour Checklist  
TRF = Teacher Report Form  
CADS = Conners' ADHD/DSM-IV Scales  
CSI-4 = Child Symptom Inventory  
ADHD RS = ADHD Rating Scale-IV  
DAWBA = Development and Well Being Assessment

### 2.1.2 ADHD Symptomatology at Preschool Age

Although it is difficult to diagnose ADHD in preschoolers, follow-up studies have consistently reported higher rates of behavioural inattention/hyperactivity in preschool-aged children born very preterm relative to their full-term peers (see Table 2.1, page 21). For example, in the population-based Etude Epidémiologique sur les Petits Ages Gestationnels (EPIPAGE) study, 3-year-old children born very preterm were rated by their parents as having more behavioural difficulties on the Strengths and Difficulties Questionnaire (SDQ) than children born full-term (Delobel-Ayoub et al., 2006). Furthermore, inattention/hyperactivity was the most frequently reported behavioural problem, with children born very preterm having a 2-fold increased risk relative to their full-term peers (Delobel-Ayoub et al., 2006). There was also a trend for later risk to increase with decreasing gestational age at birth, with children born between 24 and 28 weeks of gestation being at a greater risk of inattention/hyperactivity than very preterm children born at later gestational ages (Delobel-Ayoub et al., 2006). These increased risks remained even after adjustment for the effects of child sex, neurodevelopmental delay and/or poor child health at age 3 years, and family social risk (Delobel-Ayoub et al., 2006). Within the same cohort, these between-group differences were also evident at age 5 years, with the odds for inattention/hyperactivity being 2-fold higher for children born very preterm than children born full-term, suggesting continuities in attentional problems (Delobel-Ayoub et al., 2009). Although the EPIPAGE study did not correct for gestational age at birth at each of their cross-sectional follow-up, research findings do indicate that inattention/hyperactivity difficulties in children born very preterm emerge early and can be detected using standardised behavioural screening tools. Moreover, findings show that association between very preterm birth and inattentive/hyperactive behaviour cannot be entirely explained by the effects of social and clinical risk factors correlated with very preterm birth.

In contrast to the findings of the EPIPAGE follow-up, a recent study of a much smaller sample of children born very preterm ( $N = 60$ ) and full-term ( $N = 90$ ) at 3 years corrected age found no significant between-group differences on Attention problems and Hyperactivity subscales from the parent rated Behaviour Assessment Scales for Children-2 (BASC-2) (Baron, Erickson, Ahronovich, Baker, & Litman, 2011). However, these findings may have limited generalisability due to being a

single-centre cohort study, based on a small sample of children born very preterm with limited statistical power (Vohr et al., 2004). It should also be noted that the recruitment of the very preterm sample was quite low (32.7%) which further restricts the generalisability, although no significant differences in neonatal clinical characteristics were found between those recruited and not recruited in the study (Baron et al., 2011). Nonetheless, this is of concern as it has been shown that children born very preterm who are difficult to follow-up (defined as failure to attend scheduled assessments, family relocations, child being with foster parents, and/or change of names) may have poorer neurodevelopmental outcomes than those followed-up easily (Tin, Fritz, Wariyar, & Hey, 1998).

Consistent with the findings of the EPIPAGE follow-up, a prospective longitudinal study of a regional cohort of children born very preterm ( $N = 103$ ) and full-term ( $N = 107$ ) in Christchurch, New Zealand, found inattention/hyperactivity to be the most common behavioural impairment amongst preschoolers born very preterm (Woodward et al., 2009). The sample of children born very preterm was divided into two groups (i.e., very preterm and extremely preterm) based on their gestational age at birth. Findings showed that at corrected age 4 years, 37.2% ( $n = 16$ ) of children born extremely preterm and 15% ( $n = 9$ ) of children born very preterm were rated by their parents as being in the clinical range on the SDQ inattention/hyperactivity subscale, defined as a score above the 90th percentile for the full-term group (Woodward et al., 2009). Methodological strengths of this follow-up study included the high sample recruitment (92% of all eligible very preterm infants recruited at birth) and retention rates (98% follow-up to age 4 years), as well as the inclusion of a regionally representative full-term comparison group matched to the very preterm group for sex, birth date, and place of birth (Woodward et al., 2009).

A longitudinal follow-up from The Netherlands based on data from three regional cohorts of children born very preterm ( $N = 397$ ) and two national cohorts of children born full-term ( $N = 6,007$ ) reported similar findings as the above study from New Zealand (Reijneveld et al., 2006). At age 5 years, behavioural adjustment was assessed using the parent reported Child Behaviour Checklist (CBCL). Results showed that children born very preterm had significantly higher mean total

behaviour problems scores (Reijneveld et al., 2006). Examination of children's scores on the eight syndrome subscales showed that the largest mean difference between the two groups was for attentional problems (Reijneveld et al., 2006). Evaluation of the proportion of scores within the clinical range also revealed the highest prevalence for attention problems, with children born very preterm having odds that were 3-fold higher than children born full-term (Reijneveld et al., 2006). The authors also noted that these between-group differences may be an underestimate as the control group consisted of a population-based cohort that likely included some children born preterm (Reijneveld et al., 2006).

Likewise, a follow-up of preschool-aged children born extremely preterm in Denmark reported an increased risk of inattentive/hyperactive behaviour problems amongst these children compared to their full-term peers (Hoff, Hansen, Munck, & Mortensen, 2004). Specifically, at age 5 years, a national cohort of children born extremely preterm ( $N = 197$ ) and a full-term comparison group ( $N = 72$ ) were assessed using the parent reported Conners' Abbreviated Symptom Questionnaire (Hoff et al., 2004). Compared to 4.2% of children born full-term, 17.5% of children born extremely preterm obtained scores within the clinical range for inattention/hyperactivity; with risks increasing up to 46.7% for extremely preterm children with neurosensory disability and 23.5% for those with intellectual impairment (Hoff et al., 2004).

In conclusion, despite inconsistencies across studies in respect to: (1) age at follow-up, (2) correcting a child's age for prematurity, (3) measures used to assess child behaviour, and (4) controlling for potential confounders; follow-up research has consistently demonstrated ADHD symptomatology as the most common neurobehavioural morbidity amongst preschool-aged children born very preterm. This elevated risk persists even after taking into account family social risk and/or excluding children with moderate to severe neurodevelopmental impairment. Furthermore, an inverse relationship exists between gestational age at birth and subsequent risk of ADHD symptomatology, with children born at less than 28 weeks of gestation being at a higher risk of inattention/hyperactivity problems during preschool years than those born between 28 and 33 weeks of gestation.

However, it is important to note that follow-up research during the preschool years has almost exclusively been based on parent report of child behaviour. This may be of concern as parents of children born very preterm may anticipate developmental problems due to their earlier neonatal experiences and may potentially over-report the extent of child behavioural difficulties (Allen et al., 2004). Nonetheless, these findings tend to suggest that ADHD symptomatology in children born very preterm can be easily recognised even prior to school entry. While early identification of ADHD and associated symptoms is crucial for appropriate intervention and follow-up, it highlights the importance for further follow-up as these children very often encounter pressures of the school environment which may exacerbate existing behavioural difficulties. The school years also provide an opportunity to assess whether children born very preterm manifest behavioural inattention/hyperactivity across multiple contexts, including home and school. Thus, it will be important to evaluate the degree of change and continuity, and the extent to which the children exhibiting behavioural inattention/hyperactivity during preschool years may do so consistently over time.

### **2.1.3 ADHD Symptomatology at School Age<sup>3</sup>**

ADHD is one of the most frequently studied neurobehavioural impairments in school-aged children born very preterm, with findings being generally consistent to those reported during the preschool years. Specifically, there is clear evidence on increased risk of ADHD or inattention/hyperactivity in school-aged children born very preterm across multiple studies and countries (see Table 2.1, pages 21 – 22). For example, in a meta-analysis of 7 case-control studies of school-aged children born very preterm (published between 1980 and 2001), the pooled relative risk for an ADHD diagnosis based on *DSM-III*, *DSM-III-R*, or *DSM-IV* criteria was 2.6 (95% confidence interval, CI: 1.8 – 3.8) when compared to children born full-term (Bhutta et al., 2002). Similarly, in a more recent meta-analysis of 9 case-control studies published between 1998 and 2008, attentional difficulties were reported as the most prevalent behaviour problem (Aarnoudse-Moens et al., 2009). Moreover, based on combined effect sizes, children born very preterm obtained scores that on

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<sup>3</sup>Shum et al. (2008) is excluded in subsection 2.1.3 (pages 26 – 31) due to inconsistent results reported in text (page 108) and corresponding table (Table 3), as well as limited generalisability of the study design.



average were 0.4 and 0.6 standard deviations higher than children born full-term on parent and teacher ratings of child attention problems, respectively (Aarnoudse-Moens et al., 2009). Although all the studies included in these meta-analyses did not meet the current inclusion criteria, a similar pattern of findings were seen in the studies reviewed for this thesis (see Table 2.1). These studies are discussed below.

In the population-based EPICure study, all children born extremely preterm (< 26 weeks of gestation) in the United Kingdom and Ireland during 1995 were followed-up at age 6 years (Samara, Marlow, & Wolke, 2008). Excluding deaths, retention to age 6 was 78% ( $N = 241$ ). An age- and sex-matched full-term comparison group ( $N = 162$ ) of classroom peers was also recruited (Samara et al., 2008). At age 6, behavioural outcomes, including attentional problems, were assessed using the parent and teacher rated SDQ, supplemented by items from the CBCL, Conners' rating scales, *DSM-IV*, and the *International Classification of Diseases, 10th Revision (ICD-10)* to assess attention problems and overactivity/impulsivity (Samara et al., 2008). The novelty as well as the strength of the 6-year EPICure follow-up was the emphasis on pervasive behaviour problems, defined as a score greater than the 90th percentile of the full-term group on both of the parent and teacher scales. Based on parent report alone, children born extremely preterm had a 4-fold increased risk of exceeding the cut-point for ADHD symptomatology relative to their full-term peers. Specifically, 48% ( $n = 107$ ) of children born extremely preterm compared to 17.7% ( $n = 26$ ) of children born full-term were classified as in the clinical range on the SDQ inattention/hyperactivity subscale (Samara et al., 2008). Furthermore, 47.3% ( $n = 106$ ) and 32.6% ( $n = 73$ ) of children born extremely preterm were rated by their parents as above the clinical cut-point scores on the additional measures of attention problems and overactivity/impulsivity, respectively (Samara et al., 2008). Teacher reports revealed a similar pattern of results. An important distinction and a methodological strength of this study was the use of a stringent pervasive problems criterion, defined as agreement between parent and teacher reports regarding child behaviour difficulties. When this definition was used, compared to 8.8% ( $n = 13$ ) of children born full-term, 30.6% ( $n = 60$ ) of children born extremely preterm exhibited pervasive inattention/hyperactivity difficulties (odds ratio, OR: 4.5; 95% CI: 2.4 – 8.7) on the SDQ inattention/hyperactivity subscale (Samara et al., 2008). Furthermore, the odds for clinically significant pervasive attention and

overactivity/impulsivity problems were 3.5 and 6.9 times higher for children born extremely preterm than full-term (Samara et al., 2008). While between-group differences for inattention/hyperactivity and overactivity/impulsivity were accounted for by cognitive abilities, group differences for attention problems were only partially explained and risks persisted after adjustment for cognitive abilities (Samara et al., 2008).

The EPICure study further followed-up (retention: 71%,  $N = 219$ ) their population-based cohort of children born extremely preterm at age 11 years (Johnson et al., 2010b). Children were diagnosed for ADHD using the Development and Well Being Assessment (DAWBA). The DAWBA is a structured psychiatric interview completed by the parents and a corresponding questionnaire completed by child's class teacher and is used to determine whether children meet the *DSM-IV* diagnostic criteria for ADHD and other psychiatric disorders (Johnson et al., 2010b). Results showed that ADHD was the most prevalent (11.5%,  $n = 21$ ) *DSM-IV* psychiatric disorder found among 11-year-old children born extremely preterm, with their odds being 4-fold higher than that of their full-term peers (Johnson et al., 2010b). Unlike children born full-term, increased risk of ADHD in children born extremely preterm primarily reflected the ADHD inattentive (7.1%,  $n = 13$ ) than ADHD combined (4.4%,  $n = 8$ ) subtype (Johnson et al., 2010b). Furthermore, extremely preterm children with cognitive impairment had a 5-fold (20.8% vs. 5.4%) increased risk of ADHD compared to those without cognitive impairment (Johnson et al., 2010b). These between-group differences persisted after exclusion of extremely preterm children with neurosensory impairment. However, after excluding children born extremely preterm with either neurosensory or cognitive impairment, these between-group differences were no longer significant (Johnson et al., 2010b).

Methodological strengths of the EPICure follow-up studies at ages 6 and 11 years included: (1) national cohort of children born extremely preterm; (2) the use of multiple informants to report on child behaviour; (3) the use of a more stringent pervasive classification of behavioural difficulties at age 6, based on agreement between parent and teacher reports; (4) psychiatric diagnostic evaluation of child behaviour at age 11; and (5) control for the potential effects of neurosensory and cognitive impairment. However, one of the major limitations of these two follow-up

evaluations included the selective dropout of children with cerebral palsy, cognitive impairment, as well as those belonging to higher social risk families (Johnson et al., 2010b). Nonetheless, findings from these studies suggest that school-aged children born at less than 26 weeks of gestation also appear to be at an elevated risk of ADHD, with much of this risk reflecting attentional difficulties and to a lesser extent hyperactivity/impulsivity. Associations between extremely preterm birth and ADHD were mediated by cognitive functioning, which may at least in part explain the low comorbidity between ADHD and conduct disorders in this high-risk population (Johnson et al., 2010b).

Similarly, another follow-up study from the United Kingdom has reported an increased prevalence of *DSM-IV* ADHD symptoms in 7- to 8-year old children born very preterm (Foulder-Hughes & Cooke, 2003). ADHD symptomatology was assessed using the Connors' Teacher Rating Scale (Foulder-Hughes & Cooke, 2003). Results showed that compared to 2.1% ( $n = 3$ ) of children born full-term, 8.9% ( $n = 18$ ) of children born very preterm screened positive for ADHD (Foulder-Hughes & Cooke, 2003). These between-group differences persisted even after excluding children with intellectual functioning deficits defined as an intelligence quotient (IQ) less than 70 (Foulder-Hughes & Cooke, 2003).

At age 8 years, three longitudinal follow-up studies (retention: 90% – 94%) examined the risk of ADHD in children born extremely preterm relative to children born full-term (P. J. Anderson et al., 2011; P. J. Anderson & Doyle, 2003; Hack et al., 2009). Two of the three studies assessed ADHD symptoms using parent rated standardised screening questionnaires of child behaviour (P. J. Anderson et al., 2011; Hack et al., 2009). The third study assessed ADHD symptomatology using the parent and teacher rated BASC (P. J. Anderson & Doyle, 2003). Irrespective of the different measures of child behaviour, all studies consistently found that 8-year-old children born extremely preterm were significantly more likely to experience inattention/hyperactivity, with the odds for extremely preterm children being 1.8 to 4.2 times higher than children born full-term (P. J. Anderson et al., 2011; Hack et al., 2009). These, between-group differences persisted after exclusion of children with neurosensory deficits, moderate to severe cerebral palsy, and severe cognitive delay (P. J. Anderson et al., 2011).

In the population-based EPIPAGE study (described previously, see subsection 2.1.2, page 23), children born very preterm ( $N = 1,387$ ) were also followed-up at age 8 years (Larroque et al., 2011). Using the inattention/hyperactivity subscale from the parent rated SDQ, 17% ( $n = 239$ ) of children born very preterm scored above the clinical cut-point compared to 11% ( $n = 35$ ) of children born full-term (Larroque et al., 2011). Consistent with the results reported for this cohort at ages 3 and 5 years, children born between 24 and 28 weeks of gestation were at higher risk (19%,  $n = 62$ ) of behavioural inattention/hyperactivity at age 8 than those born between 29 and 32 weeks of gestation (Larroque et al., 2011).

At age 11 years, a Swedish national prospective follow-up study of a cohort of 83 children born extremely preterm (< 26 weeks of gestation) and 86 children born full-term assessed attention problems and ADHD symptomatology using both the parent and teacher rated CBCL (Farooqi, Hagglof, Sedin, Gothefors, & Serenius, 2007). According to both parent and teacher ratings, children born extremely preterm were significantly more likely than their full-term peers to obtain scores within the clinical range, defined as a score greater than 90th percentile of the full-term group. Specifically, between 24% and 30% of children born extremely preterm scored above the attention problems clinical-cut point, with the odds being 3-fold higher than children born full-term after controlling for the effects of child sex, chronic medical illness, maternal mental health, family functioning, and a range of social risk factors (Farooqi et al., 2007). Furthermore, based on parent and teacher reports, children born extremely preterm were also at an increased risk of an ADHD *DSM-IV-R* diagnosis (Farooqi et al., 2007). Methodological strengths of this longitudinal study included the nationally representative sample of children born extremely preterm, high sample retention (97%), and the use of multiple informants to assess child behaviour.

Taken together, it is estimated that between 9% and 17% of children born very preterm and between 17% and 48% of children born extremely preterm are at risk of ADHD or behavioural inattention/hyperactivity problems during their school years. Moreover, inattentive symptoms appear to be somewhat more common than behavioural hyperactivity/impulsivity. Although these estimates are predominantly based on parent reports, follow-up research using teacher reports of child behaviour

suggest generally similar rates. When a pervasive criterion of child behaviour difficulties is used (i.e., meet cut-off criteria on both parent and teacher rated scales), findings suggest that between 15% and 33% of children born at less than 26 weeks of gestation compared to between 5% and 9% of children born full-term are at risk for pervasive inattention/hyperactivity problems. While follow-up research has primarily relied on child behaviour screening measures or *DSM*-based questionnaires, school-aged children born very preterm have also been shown to be at an elevated risk of obtaining a clinical diagnosis of ADHD based on blinded diagnostic psychiatric evaluations. Relative to their full-term peers, the high prevalence of ADHD symptomatology in school-aged children born very preterm persists after accounting for social risks, neurosensory impairments, and cognitive deficits. This is of concern as behavioural inattention/hyperactivity during school age may compromise the child's typical cognitive development and likely to interfere with academic achievement, along with other repercussions of poor mental health (P. J. Anderson et al., 2011; Hille et al., 1994).

## **2.2 Neonatal Predictors of ADHD Symptomatology**

Children born very preterm have often been described as a “double hazard population” (Escalona, 1982; Nadeau, Tessier, Boivin, Lefebvre, & Robaey, 2003). This is due to their increased susceptibility to both biological and social risks that may adversely impact neurodevelopmental outcomes (Escalona, 1982; Nadeau et al., 2003). For example, biologically, infants born very preterm are at a higher risk of perinatal complications particularly affecting the brain and the lungs than infants born full-term, with potential impact on neurodevelopmental outcomes (Nadeau et al., 2003; Woodward et al., 2006). In terms of social risks, very preterm birth has been linked with social disadvantages including: lower socioeconomic status, single parenthood, early motherhood, and minority ethnic status (Nadeau et al., 2003). Thus, in order to understand the impact of very preterm birth on developmental outcomes, it is important to consider the role of both biological and social risks in the evolution of later risk (Nadeau et al., 2003).

As shown in Table 2.1 (pages 21 – 22), a considerable number of studies have reported a higher prevalence of ADHD or behavioural inattention/hyperactivity in children born very preterm compared to those born full-term. However, much less

effort has been directed towards identifying potential neonatal risk factors that may help explain associations between very preterm birth and later risk of ADHD symptomatology. For example, of the 15 studies previously reviewed, only 4 studies examined the contribution of neonatal biological and social risk factors to subsequent ADHD risk (P. J. Anderson et al., 2011; Delobel-Ayoub et al., 2006; Hack et al., 2009; Reijneveld et al., 2006). Unlike the general population, weak associations between social background characteristics and risk of ADHD have generally been found in contemporary cohorts of children born very preterm (Delobel-Ayoub et al., 2006; Johnson, 2007; Johnson & Marlow, 2011). In contrast, ADHD symptomatology in these children has been shown to be strongly associated with a range of perinatal and neonatal complications, including gestational age at birth, low birth weight, intrauterine growth restriction, and perinatal brain injury (Johnson, 2007; Johnson & Marlow, 2011). Studies examining these neonatal clinical predictors of later ADHD or behavioural inattention/hyperactivity risks in children born very preterm are briefly reviewed below.

As previously noted, an inverse relationship has been observed between gestational age at birth and later risk of ADHD (Lindstrom, Lindblad, & Hjern, 2011). In the population-based EPIPAGE study (described in subsections 2.1.2, page 23; 2.1.3, page 30), at ages 3 and 8 years, children born between 24 and 28 weeks of gestation had a higher risk of behavioural inattention/hyperactivity (19% – 24% vs. 17% – 18%) than those born between 29 and 32 weeks of gestation (Delobel-Ayoub et al., 2006; Larroque et al., 2011). Similarly, in a regional cohort of children born in Christchurch, New Zealand (described in subsection 2.1.2, page 24), 37% of children born extremely preterm relative to 15% of children born very preterm exhibited inattention/hyperactivity difficulties at age 4 years (Woodward et al., 2009). This gestational age gradient effect was also demonstrated in a Swedish national cohort of children born between 1987 and 2000 (Lindstrom et al., 2011).<sup>4</sup> In this retrospective study, perinatal variables were examined for children aged 6 to 19 years ( $N = 7,506$ ) who were registered with the national health database of ADHD medication prescription in 2006 (Lindstrom et al., 2011). Results showed an inverse

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<sup>4</sup>Lindstrom et al. (2011) was not reviewed in subsection 2.1.3 (pages 26 – 31) as the index group included children aged 6 to 19 years, born at  $\geq 33$  weeks of gestation; outcome measure was based on prescribed medication; and the inclusion of sample born prior to the 1990.

relationship between gestational age at birth and the odds of later ADHD risk (Lindstrom et al., 2011). Specifically, after controlling for a range of perinatal clinical and social risk factors, the odds of ADHD were 2.1 (95% CI: 1.4 – 2.7) for those born between 23 and 28 weeks, 1.6 (95% CI: 1.4 – 1.7) for those born 29 and 32 weeks, and 1.4 (95% CI: 1.2 – 1.7) for those born between 33 and 34 weeks of gestation compared to children born at 39 to 41 weeks of gestation (Lindstrom et al., 2011).

Along with gestational age at birth, birth weight is also an important neonatal predictor of the development of subsequent ADHD symptoms (Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011; Mick, Biederman, Prince, Fischer, & Faraone, 2002). Specifically, after controlling for genetic and social risk factors, children diagnosed with ADHD ( $N = 252$ ; mean age = 11.2 years) were shown to be at a 3-fold higher risk of being born with a low birth weight relative to children with no ADHD diagnosis ( $N = 231$ ; mean age = 12.2 years) (Mick et al., 2002). Moreover, it was estimated that 13.8% of all cases of ADHD may be accounted for by low birth weight (Mick et al., 2002). Recently, associations between low birth weight and ADHD were found at ages 3, 7, 10, and 12 years in a national follow-up in The Netherlands (Groen-Blokhuis et al., 2011).<sup>5</sup> This study was based on data from 14,789 twins born between 1986 and 2003 (Groen-Blokhuis et al., 2011). Results showed that children with a birth weight between 1,500 and 2,000 grams obtained on average, scores that were 0.2 to 0.4 standard deviations higher on the attention problems scale than children with a birth weight between 3,000 and 3,500 grams (Groen-Blokhuis et al., 2011). Furthermore, within monozygotic, dizygotic, and unrelated birth weight discordant pairs, children with a lower birth weight scored 0.1 to 0.2 standard deviations higher on the attention problems and hyperactivity scales than children with a higher birth weight in a pair, across all the assessment time-points (Groen-Blokhuis et al., 2011). Similar to gestational age at birth, an inverse relationship has been proposed between birth weight and ADHD, with the risk of ADHD increasing with decreasing birth weight (Groen-Blokhuis et al., 2011). Although a causal association has been suggested between birth weight and risk of ADHD, it is not clear whether this association generalises to children born very or

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<sup>5</sup>Groen-Blokhuis et al. (2011) was not reviewed in subsections 2.1.2 (pages 23 – 26) and 2.1.3 (pages 26 – 31) as the index group included children born at  $\geq 33$  weeks of gestation and/or with a birth weight of  $\geq 1,500$  grams, sample consisted of twin births only, and the inclusion of sample born prior to the 1990.

extremely preterm, who are generally subject to severe perinatal complications than more mature preterm infants. However, as there is a considerable overlap between birth weight and gestational age, it is very likely that birth weight will have a similar role in placing children born very preterm at risk for ADHD.

Intrauterine growth restriction has also been identified as a potential risk factor for ADHD symptomatology in children born very preterm (Guellec et al., 2011; Lindstrom et al., 2011). For example, in the population-based EPIPAGE study (described in subsection 2.1.2, page 23), within the very preterm group, children born small-for-gestational age<sup>6</sup> were at an increased risk of behavioural inattention/hyperactivity at age 5 years (23.5% vs. 15%) compared to children born appropriate-for-gestational age<sup>7</sup> (Guellec et al., 2011). These between-group differences remained after statistical control for the effects of child sex, antenatal corticosteroid exposure, and social risk (Guellec et al., 2011). However, within the same cohort, there were no significant between-group differences (19.1% vs. 21.7%) in the incidence of inattention/hyperactivity problems between small- and appropriate-for-gestational age children born between 24 and 28 weeks of gestation (Guellec et al., 2011). Thus, the findings from this study are not very conclusive.

Other neonatal clinical complications associated with very preterm birth that may increase the risk of ADHD symptomatology include repeated exposure to antenatal corticosteroids, artificial ventilation, and necrotising enterocolitis (Crowther et al., 2007; Reijneveld et al., 2006; Taylor, Klein, Schatschneider, & Hack, 1998). For example, in a Dutch sample of children born very preterm, children requiring artificial ventilation for at least one week during the neonatal period obtained higher attention problems scale scores at age 5 years compared to the rest of the children (Reijneveld et al., 2006). Similarly, in a follow-up of a sample of children born very preterm and/or with a very low birth weight ( $N = 133$ ), those with necrotising enterocolitis were perceived by their parents as showing higher mean levels of hyperactivity at early school age than those without necrotising enterocolitis, after adjusting for child sex, age, and social risks (Taylor et al., 1998).

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<sup>6</sup>Small-for-gestational age = birth weight for gestational age at < 10th percentile.

<sup>7</sup>Appropriate-for-gestational age = birth weight for gestational age at  $\geq$  20th percentile.



Although a range of perinatal complications have been shown to be associated with later risk of ADHD or behavioural inattention/hyperactivity difficulties in children born very preterm, only small to moderate amount of variances are independently explained by these factors. Moreover, the underlying pathophysiological mechanisms or causal pathways have not yet been clearly specified. However, existing research does suggest the possibility of these relationships being associated with neurological abnormalities such as perinatal cerebral injury and/or alterations in cerebral structural development as a consequence of white matter injury and/or complications following premature birth (Boardman et al., 2007; Qiu et al., 2012; Thompson, et al., 2007).

### **2.3 Neurological Mechanisms Associated with ADHD Symptomatology in Children Born Very Preterm: A Review**

Over the last decade, it has been increasingly recognised that perinatal cerebral injury and/or altered cerebral growth and maturation during the neonatal period may help explain a range of neurodevelopmental impairments in infants born very preterm (Mathur & Inder, 2009; Volpe, 2009; Woodward et al., 2006; Woodward et al., 2005). Perinatal cerebral injury in infants born very preterm has been primarily characterised by lesions in the cerebral white matter (Mathur & Inder, 2009; Volpe, 2003). Specifically, four types of lesions are the most common: (1) germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH), (2) GMH-IVH with periventricular haemorrhagic infarction, (3) cystic periventricular leukomalacia, and (4) noncystic periventricular leukomalacia or diffuse white matter injury (Volpe, 2003, 2005, 2009).

GMH-IVH involves unilateral or bilateral haemorrhage in the germinal matrix tissue, representing a spectrum of lesions, and classified based on the extent of haemorrhage as evident on cranial ultrasound (Tortorolo, Luciano, Papacci, & Tonelli, 1999; Volpe, 2008). Based on Volpe's GMH-IVH grading scheme, grade I corresponds to haemorrhage confined within the germinal matrix; grade II involves extension of haemorrhage into the ventricles, filling 10% to 50% of the ventricular space; and grade III refers to extension of haemorrhage into the ventricles, filling greater than 50% of the ventricular space along with ventricular dilatation (Tortorolo et al., 1999; Volpe, 2008).

GMH-IVH with periventricular haemorrhagic infarction, although often considered synonymous with grade IV GMH-IVH based on Papile classification, may not always be an extension of a large GMH-IVH (Tortorolo et al., 1999). As per Volpe's classification, this is regarded as a distinct form of injury involving extensive damage to the periventricular white matter (Inder & Volpe, 2000; Tortorolo et al., 1999). Specifically, GMH-IVH with periventricular haemorrhagic infarction is characterised by unilateral or strikingly asymmetric venous haemorrhagic necrosis in the deep periventricular white matter (Volpe, 2009).

In contrast to haemorrhagic lesions, periventricular leukomalacia typically represents bilateral and predominantly symmetric arterial necrosis in the periventricular white matter (Inder & Volpe, 2000). While cystic periventricular leukomalacia involves focal necrosis in the deep periventricular white matter, noncystic white matter injury involves diffuse injury to the glial cells in the central cerebral white matter (Inder & Volpe, 2000; Volpe, 2003).

In addition to perinatal cerebral injury, infants born very preterm are also at an elevated risk of atypical cerebral structural growth and maturation. For example, infants born very preterm have been shown to have volumetric reductions of cerebral cortical and subcortical grey matter, myelinated white matter, and concomitant increase of cerebrospinal fluid volume relative to infants born full-term, at term equivalent age through to adolescence. (Inder et al., 1999; Inder et al., 2005). Along with loss of global cerebral tissue volumes, infants born very preterm have been found to have region-specific neuroanatomical alterations, including volumetric reductions of cerebral tissues in the parieto-occipital, sensorimotor, orbitofrontal, and premotor regions (Thompson et al., 2007; Woodward et al., 2005).

This section provides a systematic overview of existing studies concerned with the neurological factors associated with ADHD or behavioural inattention/hyperactivity problems in children born very preterm. Given the paucity of published research, all studies of children born preterm (< 37 weeks of gestation) were included despite the primary focus of this thesis being very preterm birth.

### 2.3.1 Inclusion Criteria

A MEDLINE/PubMed and PsycINFO electronic database search for original articles was undertaken for the period from January 1981 to December 2011 using various combinations of the following subject headings and keywords: *preterm birth, low birth weight, ADHD, attention, inattention, hyperactivity, impulsivity, behaviour, brain, cerebral, neurological, intraventricular haemorrhage, periventricular leukomalacia, brain volume, encephalopathy, MRI, ultrasound, and diffusion tensor imaging*. Studies were included in the current review if they met all of the following criteria.

- (1) Peer-reviewed English language publication.
- (2) Index group consisted of children born preterm (< 37 weeks of gestation) and/or with a low birth weight (< 2,500 grams birth weight).
- (3) ADHD symptomatology or behavioural inattention/hyperactivity was assessed between the ages of 3 and 18 years.
- (4) Neural correlates of ADHD symptomatology or inattention/hyperactivity were assessed using structural neuroimaging methods.

Twelve studies met these selection criteria. Of those selected, five studies examined associations between perinatal cerebral injury and later risks of ADHD symptomatology (see Table 2.2, page 38), and the remainder examined alterations in cerebral growth and maturation in relation to ADHD symptomatology in children born preterm (see Table 2.3, page 42).

Reference	Sample Characteristics						Neonatal Neural Correlates of ADHD Symptomatology		
	Year Born	Sample Size	Gestational Age (Weeks)	Birth Weight (Grams)	Age at Follow-up (Years)	Assessment Measure	Results		
Fawer et al., 1991	1982 – 1984	81	31.2 ± 1.7	1,501.3 ± 353.7	5	Ultrasound	Small focal periventricular leukomalacia associated with a higher incidence (37.5%)		
Whitaker et al., 1997	1984 – 1987	564	96% born preterm	501 – 2,000	6	Ultrasound	Parenchymal lesion and/or ventricular enlargement associated with a higher incidence (31.3%)		
O'Callaghan et al., 1997	1977 – 1986	55	27.0 ± 1.5	870 ± 96	10.7 ± 2.6	Ultrasound	Grade III or IV intraventricular haemorrhage associated with a higher incidence (28%)		
Indredavik et al., 2010	1986 – 1988	65	29.0 ± 2.4	1,180 ± 242	14	Ultrasound	Intraventricular haemorrhage associated with a 7 to 8-fold higher risk		
Whitaker et al., 2011	1984 – 1987	458	96% born preterm	501 – 2,000	16	Ultrasound	Parenchymal lesion and/or ventricular enlargement associated with a higher incidence (9.5% – 23.8%)		

Note. ± = Mean ± Standard Deviation.

### **2.3.2 Perinatal Cerebral Injury and ADHD Symptomatology**

Research concerning neonatal neural correlates of ADHD in children born preterm has demonstrated associations between perinatal cerebral injury and later risks of ADHD (see Table 2.2, page 38). For example, in a longitudinal follow-up of infants born preterm ( $\leq 34$  weeks of gestation;  $N = 81$ ), neuropathology as detected using neonatal cranial ultrasound was shown to be associated with subsequent ADHD symptomatology assessed using an adapted version of child behavioural checklist completed by parents along with observation of child behaviour during follow-up assessments (Fawer & Calame, 1991). Specifically, infants born preterm with small focal periventricular leukomalacia were at an increased risk of ADHD at age 5 years (37.5% vs. 14.3% – 17.6%) compared to infants born preterm with isolated periventricular haemorrhage or those without ultrasound evidence of perinatal cerebral injury (Fawer & Calame, 1991). While these results may have restricted generalisability due to being a single-centre cohort study, findings do highlight the potential role of perinatal cerebral white matter injury in placing children born preterm at risk of ADHD symptomatology.

Consistent with the above findings, follow-up of a large regional cohort of infants born preterm and/or with a birth weight of less than 2,000 grams has shown perinatal cerebral white matter injury to be predictive of ADHD diagnosis at early school age through to adolescence (Whitaker et al., 2011). In this study, 1,105 infants had a neonatal cranial ultrasound which was screened for cerebral injury by two radiologists blinded to the child's perinatal complications. Cerebral injury was classified as: (1) isolated germinal matrix haemorrhage and/or intraventricular haemorrhage (GMH/IVH) or (2) parenchymal lesion and/or ventricular enlargement (PL/VE) with or without GMH-IVH (Whitaker et al., 2011). Follow-up at age 6 years had a retention rate of 76% ( $N = 685$ ) of their original sample out of which 564 children had a valid psychiatric assessment using the Diagnostic Interview Schedule for Children (DISC-2.1P) completed by parents (Whitaker et al., 1997). At age 6, ADHD was the most prevalent psychiatric disorder found in children born preterm (15.6%), with children with perinatal PL/VE having 2.7 times the odds of ADHD than those without cerebral injury (Whitaker et al., 1997). However, there were no significant differences between children with perinatal GMH/IVH and those without cerebral injury (Whitaker et al., 1997). Furthermore, associations between

PL/VE and ADHD were significant (OR: 3.4; 95% CI: 1.3 – 8.7) after accounting for clinical and social risk factors (Whitaker et al., 1997). A further follow-up of the cohort at age 16 years had a retention rate of 72.9% ( $N = 628$ ) out of which 458 adolescents had a valid psychiatric assessment using the DISC-IVP completed by parents (Whitaker et al., 2011). Similar to the findings at the previous follow-up, adolescents with perinatal PL/VE were at an elevated risk of ADHD than those with GMH/IVH or those without cerebral injury. The odds for diagnosis of current ADHD inattentive subtype were 7.6-fold higher for those with perinatal PL/VE than those without cerebral injury (Whitaker et al., 2011). Moreover, although not statistically significant, adolescents with perinatal PL/VE showed higher prevalence of lifetime ADHD inattentive (23.8%) and hyperactive/impulsive subtypes (9.5%) compared to those with GMH/IVH or those without cerebral injury (Whitaker et al., 2011). These findings were also robust to the adjustment of a range of social and clinical risks (Whitaker et al., 2011). Methodological strengths of this longitudinal study included: regional cohort of children born preterm followed-up from birth to adolescence, good sample retention rates over time, a rigorous protocol for identifying perinatal cerebral injuries, and the diagnosis of ADHD using a structured psychiatric diagnostic interview (Whitaker et al., 2011).

Furthermore, two other prospective follow-up studies have shown associations between perinatal GMH-IVH and subsequent risk of ADHD in children born very preterm (Indredavik et al., 2010; O'Callaghan & Harvey, 1997). Specifically, in a follow-up of 55 school-aged children born very preterm, ADHD symptomatology was assessed using the DuPaul ADHD rating scale completed by parents and child's class teacher. Results showed that based on either parent or teacher reports, 28% ( $n = 4$ ) of children exhibiting ADHD symptomatology relative to 2% ( $n = 1$ ) of children without ADHD symptomatology at school age had evidence of grade III or IV GMH-IVH on neonatal cranial ultrasound (O'Callaghan & Harvey, 1997). Similarly, another prospective follow-up of 65 infants born very preterm has demonstrated GMH-IVH as a risk factor for *DSM-IV* ADHD diagnosis at age 14 by a blinded child psychiatrist based on semi-structured interview with parent and adolescent (Indredavik et al., 2010). Results from this study showed that after controlling for the effects of child sex, family socioeconomic status, and maternal mental health, the odds for behavioural inattention symptoms in very preterm adolescents with perinatal GMH-

IVH were 7.5-fold higher than those without that injury (Indredavik et al., 2010). There was also a tendency ( $p = .08$ ) suggesting possible associations between perinatal GMH-IVH and hyperactivity symptoms in very preterm adolescents, with the odds for diagnosis of behavioural hyperactivity being 7-fold higher for those with GMH-IVH than those without that injury (Indredavik et al., 2010). While these associations within the very preterm cohort were significant for those born appropriate-for-gestational age, no significant associations were evident for those born small-for-gestational age (Indredavik et al., 2010).

A comprehensive interpretation of the findings described above is difficult due to: (1) differing research designs, (2) limitations in sampling and retention, (3) control for potential confounders, and (4) differences in classification and grading of perinatal cerebral injuries. Nonetheless, taken together, these findings do highlight the importance of severe perinatal cerebral white matter injuries such as GMH-IVH with ventriculomegaly or periventricular haemorrhagic infarction as potential early markers of later ADHD risks. However, with significant advances in neuroprotective strategies, the incidence of these severe cerebral injuries in contemporary cohorts of infants born very preterm is declining. Recently, noncystic diffuse white matter injury has been shown to be the emerging characteristic pattern of perinatal cerebral injury in the infants born very preterm, and may be an early marker of long-term cognitive and behavioural difficulties in these infants. Research to date has not specifically examined associations between these more common diffuse white matter injuries and the risk of ADHD. This may be due to the fact that existing research has relied on cranial ultrasound as the primary neuroimaging modality which has poor sensitivity in detecting this subtle form of injury compared to MRI. Thus, it is important to examine the associations between perinatal diffuse cerebral white matter injury as detected using MRI and subsequent risk of ADHD symptomatology in infants born very preterm.

<b>Table 2.3: Summary of Studies of Cerebral Structural Correlates of ADHD or Behavioural Inattention/Hyperactivity in Children Born Very Preterm</b>									
Reference	Sample Characteristics						Cerebral Structural Correlates of ADHD Symptomatology		
	Very Preterm			Full-Term			Assessment Measure	Results	
	Year Born	Sample Size	Gestational Age (Weeks)	Birth Weight (Grams)	Age at Follow-up (Years)	Sample Size			
Krägeloh-Mann et al., 1999	1986 – 1989	19	30.2 ± 2.3	1,428 ± 548	5.5 – 7.2	56	MRI	Mild periventricular lesion in the parieto-occipital area associated with a higher prevalence	
Nagy et al., 2003	1988 – 1993	9	28.6 ± 1.1	≤ 1,500	11	10	DTI	Lower fractional anisotropy in the posterior corpus callosum and bilateral internal capsule, relative to the full-term group	
Nosarti et al., 2005	1979 – 1980	66	29.6 ± 1.9	1,288 ± 273	14	50	MRI	Reduction of left caudate nucleus volume associated with a higher prevalence of hyperactivity in preterm males only	
Indredavik et al., 2005	1986 – 1988	55	29.0 ± 2.7	1,189 ± 244	14 – 15	120	MRI	Reduction of white matter volume and thinning of the corpus callosum associated with a higher prevalence	
Skranes et al., 2007	1986 – 1988	34	29.3 ± 2.7	1,218 ± 229	15	47	DTI	Lower fractional anisotropy in 6 anatomical regions associated with a higher prevalence. Strongest associations in the external capsule, inferior, and middle fascicles on the left side	
Cooke et al., 1999	1980 – 1981	86	28.6 ± 1.7	1,103 ± 203	15 – 17	8	MRI	No significant associations between quantitative cerebral measurements and risk of ADHD at ages 12 to 13 years	
Abernethy et al., 2002	1980 – 1981	86	28.6 ± 1.7	1,103 ± 203	15 – 17	8	MRI	Reduction of bilateral hippocampus volumes associated with a higher prevalence at ages 12 to 13 years	

Note. ± = Mean ± Standard Deviation; MRI = Magnetic Resonance Imaging; DTI = Diffusion Tensor Imaging.



### 2.3.3 Cerebral Structural Development and ADHD Symptomatology

As described previously in subsection 1.3.2 (pages 10 – 12), impaired cerebral structural growth and maturation following perinatal cerebral injury has been shown in children born very preterm. Thus, it is speculated that the neonatal neurological markers of ADHD symptomatology in these children as described above may be associated with altered cerebral structural development, particularly the thalamocortical circuitry previously shown to be involved in the development of ADHD (Abernethy, Palaniappan, & Cooke, 2002; Whitaker et al., 2011). Follow-up research concerned with alterations in cerebral structural development in relation to ADHD symptomatology following very preterm birth has primarily focused on adolescents (see Table 2.3, page 42). For example, in a prospective follow-up of infants born very preterm ( $N = 66$ ), associations between caudate nuclei volumes and behavioural hyperactivity as assessed using the Rutter Behavioural Scale were examined at age 14 years (Nosarti, Allin, Frangou, Rifkin, & Murray, 2005). The caudate nucleus, a neuroanatomical structure implicated in ADHD in the general population, is particularly vulnerable to injury and prone to poor postnatal structural development in infants born very preterm due to its periventricular location (Nosarti et al., 2005). Results showed that adolescents who were born very preterm had reduced bilateral caudate nucleus volume relative to their full-term peers (left: - 7.3%; right: - 4.6%), although these differences were not statistically significant (Nosarti et al., 2005). Furthermore, an inverse relationship was found between left caudate nucleus volume and hyperactivity symptoms scores in very preterm males only ( $r = -.43$ ;  $p = .02$ ), with volumetric decrease of left caudate nucleus after adjustment for the total brain volume being associated with higher hyperactivity scores (Nosarti et al., 2005). These results were not confounded by the sex differences in neuroanatomy as no significant group differences were evident between male and female caudate nucleus volumes in this study sample (Nosarti et al., 2005). No significant associations were found between hyperactivity scores and total grey matter and bilateral hippocampal volumes, and the size of the lateral ventricles, after adjusting for the total brain volume (Nosarti et al., 2005).

In contrast, another longitudinal follow-up study of infants born very preterm ( $N = 86$ ) found no significant differences in caudate nuclei volumes at ages 15 to 16 years, between very preterm children with and without ADHD symptomatology at ages 12

to 13 years assessed using the parent and teacher rated Rutter Behavioural Scale and Connors' Hyperactivity Scale. (Abernethy et al., 2002). However, those with ADHD symptomatology had significantly lower bilateral hippocampal volumes compared to those without ADHD symptomatology ( $M \pm SD$ , mm<sup>3</sup>, left: 2,325  $\pm$  467 vs. 2,636  $\pm$  438; right: 2,266  $\pm$  435 vs. 2,500  $\pm$  400;  $p \leq .03$ ) (Abernethy et al., 2002). No significant differences in terms of linear and area measurements of the corpus callosum (overall, anterior, middle, and posterior) as well as the bilateral cerebral hemispheres were found between those with and without ADHD symptomatology (Cooke & Abernethy, 1999).

Coupled with the above findings using quantitative MRI, more advanced MRI techniques such as diffusion tensor imaging have further revealed microstructural alterations in the integrity of cerebral white matter in children born very preterm at risk of ADHD (see Table 2.3, page 42). Diffusion tensor imaging allows to measure the level of diffusivity of water molecules within the white matter and to compute fractional anisotropy values reflecting directional organisation of the white matter tracts (Nagy et al., 2003). Specifically, at age 11 years, compared to children born full-term ( $N = 10$ ), children born very preterm exhibiting inattentive/hyperactive behaviour ( $N = 9$ ) had significantly lower fractional anisotropy values in the posterior corpus callosum and bilateral internal capsule (anterior and posterior) suggesting altered development of these tracts (Nagy et al., 2003). The authors noted that the lower fractional anisotropy values in the posterior corpus callosum may at least in part be accounted for by volumetric differences in cerebral white matter within that cluster between the very preterm and full-term sample (Nagy et al., 2003). However, lower fractional anisotropy in the internal capsules could not be accounted for by differences in white matter volumes (Nagy et al., 2003). It should also be noted that none of the children in the very preterm sample had evidence of perinatal periventricular leukomalacia and/or GMH-IVH on cranial ultrasound (Nagy et al., 2003). Thus, it has been speculated that these lower fractional anisotropy values in very preterm children with attentional impairments may indicate impaired cerebral structural maturational process, and in particular poor myelination and altered axonal growth (Nagy et al., 2003). However, there was no evidence of disruption of organisation of the axonal pathways (Nagy et al., 2003).

Similarly, in another diffusion tensor imaging study of 14-year-old adolescents who were born very preterm ( $N = 34$ ), lower fractional anisotropy values were reported for those at risk of ADHD than those without risk of ADHD as assessed by a blinded child psychiatrist based on semi-structured interview with parent and adolescent (Skranes et al., 2007). Specifically, lower fractional anisotropies were found in the left posterior internal capsule, left external capsule, bilateral inferior fasciculus, right superior fasciculus, and the left middle fasciculus (Skranes et al., 2007). Out of these six anatomical regions, the strongest associations were shown in the external capsule, inferior fasciculus, and middle fasciculus, all on the left hemisphere (Skranes et al., 2007). The authors have speculated that the reduced fractional anisotropy values in relation to ADHD symptomatology evident within this sample may be reflecting poor structural maturation and organisational disturbances in white matter as a consequence of perinatal white matter injury.

Two other prospective longitudinal follow-up of infants born very preterm have also shown associations between abnormal MRI findings and ADHD symptomatology (Indredavik, Skranes et al., 2005; Krageloh-Mann et al., 1999). Direct comparisons of these results with the findings reported above may not be very feasible due to the qualitative evaluation of MRI scans. Nonetheless, results from these studies are generally consistent with the above findings and suggest cerebral white matter pathology as being associated with risk of ADHD. Specifically, in a follow-up of 55 infants born very preterm, those with an elevated risk of ADHD at age 14 years, showed significant reduction of white matter volume and thinning of the corpus callosum, based on qualitative evaluation of MRI scans by two radiologists blinded to the child's perinatal history including any previous MRI results (Indredavik, Skranes et al., 2005). These findings were unchanged after adjustment for the effects of child sex and family socioeconomic status (Indredavik, Skranes et al., 2005).

Similarly, associations between cerebral white matter abnormality and ADHD risk at age 5 years were shown in a follow-up of 19 infants born preterm (27 – 34 weeks of gestation) (Krageloh-Mann et al., 1999). Results showed that 37% ( $n = 7$ ) of children born preterm relative to 2% ( $n = 1$ ) of their full-term peers were at an increased risk of ADHD as diagnosed by a psychologist using parent and teacher ratings of child behaviour on Conners' scales (Krageloh-Mann et al., 1999). Within the preterm

group, those with abnormal MRI findings at age 5 years had significantly higher risk of ADHD symptomatology than those with normal MRI findings (Krageloh-Mann et al., 1999). Specifically two children born preterm showing ADHD symptomatology had bilateral periventricular lesion in the parieto-occipital region, and two other cases showed extensive reduction of white matter volume in the left occipital region (Krageloh-Mann et al., 1999). However, out of these four cases, only one case had evidence of perinatal periventricular leukomalacia on cranial ultrasound (Krageloh-Mann et al., 1999). This may, in part be reflecting the fact that poor postnatal cerebral development even without obvious evidence of perinatal cerebral injury may be responsible for the development of ADHD in this high-risk population.

Taken together, there has been some evidence, based on quantitative and qualitative MRI, and diffusion tensor imaging findings, suggesting that impaired cerebral growth and maturation, particularly cerebral white matter may be associated with the development of ADHD symptomatology in children born very preterm. However, further research is needed to improve the understanding of the neuropathological mechanisms that place children born very preterm at an increased risk of ADHD. The above findings coupled with the perinatal cerebral injury findings (described in subsection 2.3.2, pages 38 – 41) help to develop a conceptual pathway model to explain the potential pathophysiological mechanisms underlying the development and higher incidence of ADHD or behavioural inattention/hyperactivity following very preterm birth.

#### **2.4 Conceptual Model of Development of ADHD Symptomatology**

Being born very preterm results in a range of perinatal complications due to immaturity of body organs at birth (see Appendix A, page 137). These complications may have consequences for perinatal cerebral injury (Volpe, 2009). For example, the primary pathogenetic mechanisms of periventricular leukomalacia in infants born very preterm involve hypoxia-ischaemia and/or inflammation/infection, which in turn may lead to excitotoxicity and free radical attack thereby causing injury to the premyelinating oligodendrocytes (Khwaja & Volpe, 2008). Perinatal complications of very preterm birth may also have disruptive consequences for cerebral structural development, either in association with or without perinatal cerebral injury (Boardman et al., 2007; Inder et al., 1999), For example, associations between

perinatal complications and global cerebral development at term equivalent age were examined in a cohort of 89 infants born very preterm without focal parenchymal lesion or posthaemorrhagic ventricular dilatation evident on cranial ultrasound and/or MRI scan (Boardman et al., 2007). Results showed that requirement for supplementary oxygen at 28 postnatal days was significantly associated with volumetric reduction of cerebral tissues at term equivalent age relative to those without that complication (Boardman et al., 2007). However, there was no significant association between global cerebral tissue volume and diffuse white matter injury (Boardman et al., 2007). Similarly, infants born very preterm treated with postnatal dexamethasone therapy were reported to have significantly lower (- 10.2%) global cerebral tissue volume compared to very preterm infants unexposed to postnatal dexamethasone, after adjustment for bronchopulmonary dysplasia, birth weight, and postmenstrual age at MRI (Murphy et al., 2001). Thus, it is clear that specific perinatal complications or a combination of various clinical complications following very preterm birth may have consequences for perinatal cerebral injury and/or disruption of typical cerebral growth and maturation.

Perinatal cerebral injury may have disruptive consequences for cerebral structural development, interrupting the development of both grey and white matter structures in infants born very preterm (described in subsection 1.3.2, pages 10 – 12). Many of these affected cerebral structures overlap with the structures implicated in ADHD in the general population. For example, ADHD symptomatology in the general population has been shown to be associated with structural alterations of the corpus callosum, caudate nucleus, amygdala, hippocampus, and lateral ventricles (Schrimsher, Billingsley, Jackson, & Moore, 2002; Seidman, Valera, & Makris, 2005). Thinning of the corpus callosum is one of the most common cerebral injuries evident in infants born very preterm (Inder et al., 2003; Skranes et al., 2007). Furthermore, poor postnatal growth trajectory of corpus callosum in infants born very preterm has been demonstrated, with an average growth rate of less than half the expected rate from birth to term equivalent age (N. G. Anderson, Laurent, Cook, Woodward, & Inder, 2005). Similarly, significant reductions of hippocampal and caudate nuclei volumes have been shown in infants born very preterm relative to their full-term peers, at term equivalent age as well as during early school age and adolescence (Abernethy et al., 2002; Thompson et al., 2008).

Cerebral structural alterations in the frontostriatal circuitry has also been shown in infants born very preterm which may be associated with the elevated risk of ADHD symptomatology in this high-risk population (Peterson et al., 2003; Thompson et al., 2007; Woodward et al., 2005).

## **2.5 Limitations of Existing Studies**

As describe previously, ADHD and its associated symptoms represent one of the most common adverse neurobehavioural outcome following very preterm birth. While this is a robust finding, several methodological and clinical issues necessitate further research. The first issue concerns the measurement accuracy of reported child behavioural difficulties. This is because existing follow-up research of very preterm survivors have mostly relied on parent report of child behaviour. This is of concern as parents of children born very preterm may potentially over-report the extent of child behavioural difficulties due to their earlier neonatal experiences. Even when teacher report of child behaviour is obtained along with parent report, these are typically described independently. This approach makes it difficult to ascertain the extent of agreement between parent and teacher reports regarding the nature and extent of child's problems, limiting the clinical utility of research findings. For example, of the 15 studies previously reviewed concerning risk of ADHD in children born very preterm (see Table 2.1, pages 21 – 22), 66.7% ( $n = 10$ ) of the studies utilised single informant report of child behaviour only (9/10 based on parent report). Of the remaining five studies utilising parent and teacher reports, three studies reported the results separately for each informant; one study considered agreement between parent and teacher reports to examine pervasive child behaviour problems, and another study for a clinical diagnosis of ADHD. This issue of measurement accuracy of behavioural difficulties in children born very preterm will be further addressed in chapter 4 (pages 59 – 73).

Another related issue that has been largely neglected by existing research concerns the predictive validity of current screening measures of ADHD symptomatology in identifying those children born very preterm likely to meet the clinical criteria for a diagnosis of ADHD. This is crucial as existing follow-up studies have almost exclusively relied on behavioural screening measures for identifying and reporting the risks of ADHD in these children. For example, of the 15 studies included in the

current literature review examining the risk of ADHD in children born very preterm (see Table 2.1, pages 21 – 22), only 1 study assessed child behaviour using a psychiatric diagnostic interview. This issue regarding the predictive validity of parent and teacher rated screening measures of inattention/hyperactivity for a clinical diagnosis of ADHD in children born very preterm will be further addressed in chapter 5 (pages 74 – 90).

A further limitation of existing research concerns the extent to which the children exhibiting behavioural inattention/hyperactivity do so consistently over time. As most of the existing findings are cross-sectional in nature, limited information is provided about the emergence of symptoms over time or the persistent nature of these behavioural difficulties. A related issue concerns the neurological correlates of ADHD symptomatology in children born very preterm. Specifically, follow-up research to date has not examined associations between perinatal diffuse cerebral white matter injury and subsequent risk of ADHD in these children. For example, all the studies previously reviewed (see Table 2.2, page 38), have exclusively relied on cranial ultrasound to identify perinatal cerebral injuries, which has less sensitivity and specificity than MRI in detecting this subtle, diffuse, but more common injury. In addition, although atypical cerebral growth and maturation in relation to ADHD symptomatology has been shown among adolescents who were born very preterm (see Table 2.3, page 42); existing research has not examined cerebral structural development in relation to risk of ADHD at an early developmental stage. This is important in order to aid the understanding of the pathogenesis of ADHD in these children, particularly to specify the timing of any such cerebral alterations. These issues regarding neonatal neural correlates of ADHD symptomatology in children born very preterm will be further addressed in chapter 6 (pages 91 – 114).

## **2.6 Research Aims**

This thesis primarily aims to examine the development of ADHD symptomatology following very preterm birth. Three research studies are undertaken as part of a prospective longitudinal follow-up study of a regional cohort of children born very preterm and full-term in Christchurch, New Zealand. The specific research aims and hypotheses for these studies are as follows:

(1) *Aim:* To describe the behavioural adjustment outcomes of children born very preterm relative to children born full-term at age 6 years, based on parent and teacher ratings of child behaviour.

*Hypotheses:*

1.1 Children born very preterm will be at an increased risk of behavioural adjustment problems compared to children born full-term.

1.2 Agreement between parent and teacher reports of child behavioural adjustment will be lower for children born very preterm than full-term.

1.3 Children born very preterm will be at an increased risk of situational (parent- or teacher-reported) and pervasive (parent- and teacher-reported) behavioural adjustment problems compared to children born full-term. However, the prevalence of pervasive problems will be relatively lower than situational problems.

(2) *Aim:* To assess in each study sample, the predictive validity of situational and pervasive behavioural inattention/hyperactivity symptoms across the ages of 4 to 9, for a clinical diagnosis of ADHD at age 9 years.

*Hypotheses:*

2.1 Children born very preterm will be at an increased risk of situational and pervasive inattention/hyperactivity problems at ages 4, 6, and 9 years, compared to children born full-term. However, the prevalence of pervasive symptoms will be relatively lower than situational symptoms across all the three assessment time-points.

2.2 Predictive validity of pervasive behavioural inattention/hyperactivity symptoms at ages 4 and 6 will be higher than situational symptoms, for an ADHD clinical diagnosis at age 9 years. Moreover, behavioural inattention/hyperactivity symptoms at more than one assessment time-point across the ages of 4 to 9 will have good sensitivity and specificity for a clinical diagnosis of ADHD at age 9 years.

(3) *Aim:* To examine the relationships between neonatal neuropathologies detected using MRI at term equivalent age and the subsequent risk of persistent ADHD symptoms across the ages of 4 to 9 years. Persistent ADHD symptoms are defined as behavioural inattention/hyperactivity symptoms



across all the three assessment time-points with an ADHD clinical diagnosis at age 9 years.

*Hypotheses:*

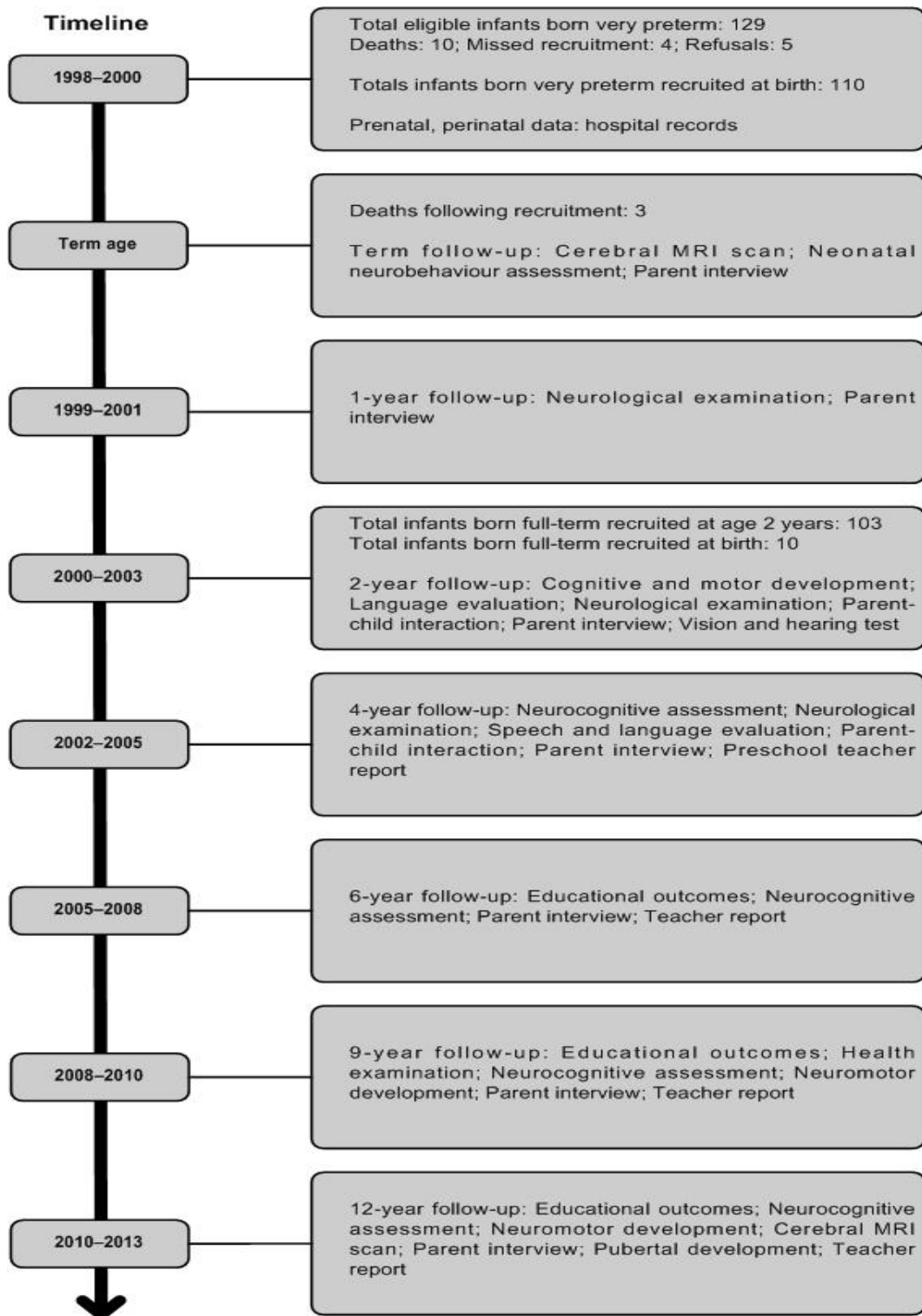
- 3.1 Children born very preterm will be at an increased risk of persistent ADHD symptoms compared to children born full-term.
- 3.2 Children born very preterm with moderate to severe neonatal cerebral white matter injury and/or abnormality based on qualitative evaluation of MRI scan will be at an increased risk of persistent ADHD symptoms, compared to children born very preterm with none or mild neonatal cerebral white matter abnormality.
- 3.3 Children born very preterm exhibiting persistent ADHD symptoms will demonstrate impaired neonatal cerebral structural growth and maturation (defined as loss of global and regional cerebral tissue volumes, based on quantitative evaluation of MRI scan), compared to children born very preterm and a subsample of children born full-term without persistent ADHD symptoms.
- 3.4 Neonatal cerebral structural growth and maturation will be an independent predictor of subsequent risk of persistent ADHD symptoms in children born very preterm, after accounting for the effects of neonatal cerebral white matter abnormalities, perinatal complications, and social risk factors.

## Chapter 3

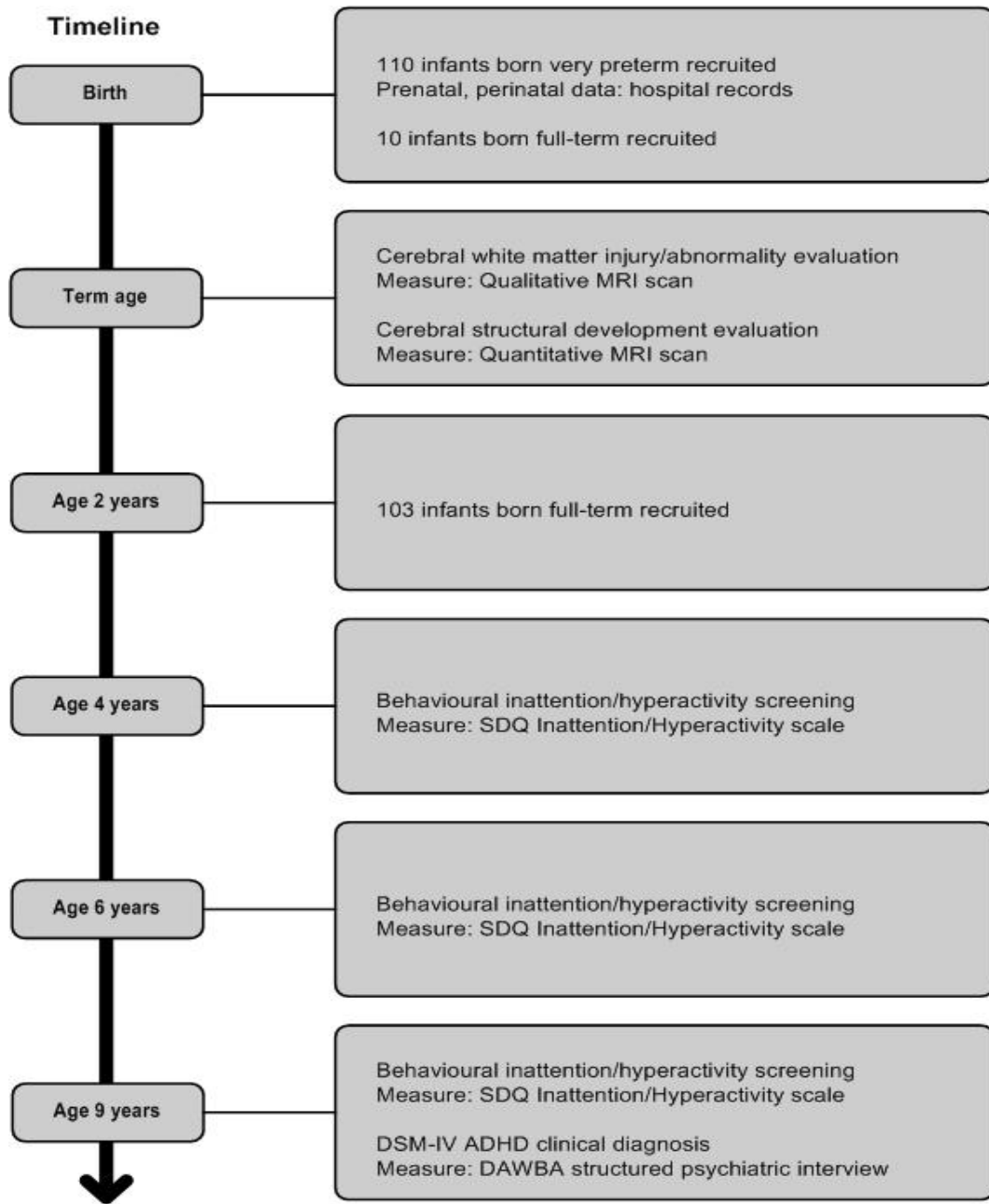
### Research Design

Data for this thesis were drawn from The Canterbury Preterm Study, a prospective longitudinal follow-up study of the neurodevelopment of infants born very preterm from birth to age 12 years. A regionally representative cohort of infants born very preterm ( $\leq 33$  weeks of gestation;  $N = 110$ ) was recruited at birth alongside a small group ( $N = 10$ ) of infants born full-term (38 – 41 weeks of gestation). At age 2 years, a larger control group of infants born full-term ( $N = 103$ ), matched to the very preterm group for sex, birth date, and place of birth was recruited. Infants born very preterm were initially followed-up at term equivalent and age 1 year. Thereafter, neurodevelopmental follow-up of both very preterm and full-term groups were completed at ages 2, 4, 6, and 9 years. 12 year follow-up of the cohort is currently in progress. An overview of the research design of this follow-up study is provided in Figure 3.1 (page 53). The author of this thesis was specifically involved with the 9 year follow-up assessments and was primarily responsible for the administration and scoring of various neuropsychological tests, along with overseeing the DAWBA structured psychiatric interview completed with parents by the research nurse.

As described previously, the primary focus of this thesis was the development of ADHD symptomatology or behavioural inattention/hyperactivity between ages 4 and 9 years in this cohort of children born very preterm. Of particular interest was to examine a range of measurement issues relating to the assessment of child inattention/hyperactivity problems using parent and teacher ratings, and to develop an effective strategy to optimise the use of parent and teacher ratings of child behaviour in order to reliably evaluate the extent of problems shown by these children. A second major focus was to identify the extent to which qualitative and quantitative volumetric MRI measures of neonatal cerebral injury and development correlated with later risk of ADHD symptoms in this cohort of children born very preterm. A general overview of the research design of the studies in this thesis is provided in Figure 3.2 (page 54).



**Figure 3.1:** Overview of The Canterbury Preterm Study research design.



**Figure 3.2:** Overview of the thesis study research design.

### 3.1 Sample Characteristics

The sample included two groups of infants. A descriptive profile of the neonatal clinical and social background characteristics of the two study groups is provided in Table 3.1 (page 57). The first group consisted of a regionally representative cohort of 129 infants born very preterm ( $\leq 33$  weeks of gestation) who were consecutively admitted to the level III NICU of Christchurch Women's Hospital, New Zealand, between November 1998 and December 2000. This unit is the sole provider of neonatal intensive care services for the greater Canterbury region. Infants with congenital anomalies, foetal alcohol syndrome, and/or non-English speaking parents were excluded. In total, excluding deaths ( $n = 10$ ), 92.4% ( $n = 110$ ) of all eligible infants were recruited at birth. Reasons for nonparticipation included refusals (4.2%) and missed recruitment (3.4%). There were no significant differences in perinatal characteristics between recruited and nonrecruited infants ( $p > .05$ ).

The second group consisted of 113 infants born full-term (38 – 41 weeks of gestation) who were recruited at age 2 years, with 10 of these infants recruited at birth. These full-term comparison infants were identified from hospital birth records ( $N = 7,200$  live births) over the same birth period as the very preterm group. For each very preterm infant, a full-term infant was identified by alternately selecting the second previous or the second next infant of the same sex in the delivery register. Consistent with the very preterm group, infants born full-term with congenital anomalies, foetal alcohol syndrome, and/or non-English speaking parents were excluded. In total, 62% of all eligible infants were recruited at age 2 years. Reasons for nonparticipation included: unable to trace (47%), refusals (12.5%), moved overseas (12.5%), or agreed but could not attend within the 2-week assessment window (28%). Infants born full-term recruited or not recruited did not differ significantly in terms of gestational age at birth, birth weight, sex, family type, minority ethnicity, and family socioeconomic status ( $p > .05$ ). A comparison of the socioeconomic profile of families in the full-term group with regional census data (Statistics New Zealand, 2001) indicated that these families were representative of the region from which they were recruited.

In terms of perinatal clinical characteristics of the two study groups, as shown in Table 3.1 (page 57), in line with sample selection criteria, infants born very preterm

and full-term differed significantly in gestational age and birth weight ( $p < .001$ ). Furthermore, there were significant between-group differences in the proportions of multiple births, with a third of infants in the very preterm group compared to 3.6% in the full-term group being twin births ( $p < .001$ ). There were also significant between-group differences in terms of intrauterine growth restriction, defined as a birth weight more than 2 standard deviations below the mean for gestational age and sex ( $p = .003$ ). Specifically, 10.3% of infants born very preterm relative to 0.9% of infants born full-term were characterised by intrauterine growth restriction. As both groups were matched on sex, a similar male to female ratio was evident, with 50% of the sample in each group being male.

As shown in Table 3.1, infants in the very preterm group experienced a range of perinatal complications. For example, 34.6% of these infants had bronchopulmonary dysplasia, requiring supplementary oxygen at 36 weeks; 6.5% of infants had a diagnosis of necrotising enterocolitis; and 43.9% of infants suffered from patent ductus arteriosus. In addition, 84.1% of infants born very preterm were administered antenatal corticosteroids. However, rates of postnatal corticosteroid (dexamethasone) use were low (5.6%). The incidence of severe neuronal injuries detected using cranial ultrasound was also low, with 10% of infants born very preterm having cystic periventricular leukomalacia and/or grade III or IV intraventricular haemorrhage.

Table 3.1 further describes the social background characteristics of the two study groups. As shown, infants in the very preterm group were significantly more likely to be born into lower socioeconomic status families than infants in the full-term group ( $p = .001$ ). Furthermore, very preterm infants were significantly more likely than full-term infants to be born to mothers who were not a high school graduate (39.3% vs. 19.1%). However, no significant between-group differences were evident in terms of maternal age, family type, and minority ethnicity ( $p > .05$ ).

**Table 3.1:** Neonatal Clinical and Social Characteristics of the Sample

<b>Measure</b>	<b>Very Preterm (<i>N</i> = 107)</b>	<b>Full-Term (<i>N</i> = 110)</b>	<b><i>p</i></b>
<b>Infant clinical characteristics</b>			
Gestational age at birth, <i>M</i> ± <i>SD</i> , weeks	27.8 ± 2.4	39.5 ± 1.2	< .001
Birth weight, <i>M</i> ± <i>SD</i> , grams	1,061.6 ± 314.2	3,579.5 ± 409.3	< .001
Male sex, %	50.5	53.6	.64
Twin birth, %	33.6	3.6	< .001
Intrauterine growth restriction <sup>a</sup> , %	10.3	0.9	.003
Oxygen therapy at 36 weeks, %	34.6	–	
Antenatal corticosteroid use, %	84.1	–	
Postnatal dexamethasone use, %	5.6	–	
Necrotising enterocolitis, %	6.5	–	
Patent ductus arteriosus, %	43.9	–	
Intraventricular haemorrhage grade III or IV <sup>b</sup> , %	5.6	–	
Cystic periventricular leukomalacia, %	5.6	–	
<b>Social background characteristics</b>			
Maternal age, <i>M</i> ± <i>SD</i> , years	30.7 ± 5.4	31.0 ± 4.4	.62
Mother not a high school graduate, %	39.3	19.1	.001
Single parenthood, %	17.8	11.8	.22
Minority ethnicity, %	14.0	11.8	.63
Family socioeconomic status <sup>c</sup>			
Professional/managerial, %	26.2	35.5	
Technical/skilled, %	43.0	54.5	
Semiskilled/unskilled/unemployed, %	30.8	10.0	.001

<sup>a</sup>Birth weight more than 2 standard deviations below the mean for gestational age.

<sup>b</sup>Based on Papile classification.

<sup>c</sup>Assessed using the Elley-Irving Socioeconomic Index (Elley & Irving, 2003).

### **3.2 General Procedures**

As illustrated in Figure 3.1 (page 53), a range of neurodevelopmental data were collected during the follow-up assessments of all the study children. During the neonatal period, extensive perinatal data were collected from the medical records and the hospital database for all study children. A serial cranial ultrasound through the anterior fontanel was performed within the first 48 hours of life, at age 5 to 7 days, and then at age 4 to 6 weeks. More frequent ultrasound was performed if an abnormality was detected. All scans were graded for the presence and extent of cystic periventricular leukomalacia and intraventricular haemorrhage. Parents were also interviewed about their family social circumstances by a research nurse.

All infants born very preterm underwent an MRI scan at term equivalent age (estimated based on prenatal ultrasound at 18 to 22 weeks of gestation). Ten infants born full-term also underwent an MRI scan on the week of their due date. All scans were assessed qualitatively for cerebral grey and white matter injury and/or abnormality using a standardised scoring system. Scans were also analysed using quantitative techniques to determine the global and regional volumes of different cerebral tissue subtypes. The protocols followed for acquisition of MRI data and postacquisition processing are described in detail in section 6.1 (pages 92 – 97).

As part of this follow-up study, all infants born very preterm and full-term attended subsequent neurodevelopmental assessments at ages 2, 4, 6 (corrected for prematurity), and at age 9 years (uncorrected). These comprehensive assessments were carried out by a multidisciplinary team, usually within a 2-week window of the child's birth date or the expected date of delivery (when an age correction was applied). Upon arrival at the research unit, each child's parent or guardian was provided with a brief description of the study procedures. Any concerns raised by the parent or the child were addressed prior to the signing of the consent form. All efforts were made to ensure that standard protocols for the administration of the test measures were followed. Child assessment procedures and measures specific to this thesis are described in detail in subsequent chapters (see section 4.1, pages 61 – 63; section 5.1, pages 76 – 79; section 6.1, pages 92 – 97). The research protocols were approved by the Canterbury Regional Ethics Committee (Reference: CTY/02/10/174; CTY/04/11/212; URA/07/13/EXP; URA/10/05/040).



## Chapter 4

### **Behavioural Adjustment Sequelae in Children Born Very Preterm at Early School Age<sup>8</sup>**

In the last decade, it has been increasingly recognised that children born very preterm are at an elevated risk of behavioural adjustment problems (Bhutta et al., 2002; Johnson & Marlow, 2011). Specifically, follow-up studies show school-aged children born very preterm are two to four times more likely to meet the *DSM-IV* criteria for ADHD than their full-term peers (Bhutta et al., 2002; Johnson et al., 2010b). More recent studies show that adjustment difficulties may also extend to internalising problems, such as anxiety, depression, and social maladjustment (Farooqi et al., 2007; Johnson et al., 2010b). Importantly, these risks remain even after social factors and severe neurodevelopmental impairment have been taken into account (Conrad, Richman, Lindgren, & Nopoulos, 2010; Farooqi et al., 2007; Johnson et al., 2010b).

While it is helpful to highlight the potential longer-term mental health consequences of very preterm birth, most existing studies have relied on parental reports of child behavioural adjustment (Delobel-Ayoub et al., 2009; Hack et al., 2009; Hille et al., 2001). This stands in contrast to *DSM-IV* and *ICD-10* recommendations that diagnostic information be collected from multiple report sources. The use of a single informant, particularly parents, raises concerns about the measurement accuracy of reported behavioural adjustment outcomes for a number of reasons. First, it is likely that parents of children born very preterm may be more sensitive to later problems given their earlier neonatal experiences (Allen et al., 2004; Perrin, West, & Culley, 1989). Second, parents of children born very preterm have been shown to be more vulnerable to depression, anxiety, and parenting stress (Singer et al., 1999; Treyvaud et al., 2010), with such difficulties potentially compromising their capacity to objectively assess their child's behavioural state (Najman et al., 2001).

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<sup>8</sup>From "Emotional and Behavioural Adjustment of Children Born Very Preterm at Early School Age," by S. Bora et al., 2011, *Journal of Paediatrics and Child Health*, 47(12), pages 863 – 869. Reproduced with permission from John Wiley and Sons.

Several studies have sought to address this problem by obtaining both parent and teacher reports of very preterm children's behavioural adjustment. However, these studies have typically reported rates of later adjustment problems separately for parents and teachers (P. J. Anderson & Doyle, 2003; Conrad et al., 2010; Farooqi et al., 2007), making it difficult to ascertain the degree of inter-informant agreement regarding the nature and extent of child behaviour problems. It has also given rise to considerable variability in reported prevalence across studies.

An alternative, and potentially more valid measurement approach, is to combine parent and teacher reports to assess the extent of child situational and pervasive behavioural adjustment problems (Achenbach, McConaughy, & Howell, 1987; Youngstrom, Loeber, & Stouthamer-Loeber, 2000). A situational problem is defined on the basis of either a parent- or teacher-identified problem, whereas a pervasive problem requires parent and teacher agreement that a clinically significant problem exists. This latter approach has the advantage of minimising the effects of report source bias. Mainstream child psychiatric research has also shown that diagnoses based on multiple informants have better sensitivity and specificity than those based on a single informant (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000), and that children with pervasive behavioural problems are subject to more severe and persistent impairments (Ablow et al., 1999; Rutter & Sandberg, 1985). However, despite these findings, very little is known about the extent of parent and teacher agreement or the prevalence of pervasive internalising and externalising problems in representative samples of children born very preterm. One exception is a study of 6-year-old children born extremely preterm (< 26 weeks of gestation) in the United Kingdom and Ireland (Samara et al., 2008). Findings from this study showed that in this high-risk group, the odds for clinically relevant pervasive behaviour problems were two to nine times higher than children born full-term, with the risks of behavioural inattention/hyperactivity, peer relations, and emotional problems the greatest. Whether these risks generalise to all children born very preterm remain unclear. Thus, the specific aims of this study are as follows:

- (1) To examine the extent to which children born very preterm are at an increased risk of behavioural adjustment problems relative to their full-term peers at age 6 years.

- (2) To assess in each study group, the degree of agreement between parent and teacher reports of child behavioural adjustment problems.
- (3) To compare the prevalence of situational and pervasive behavioural adjustment problems in children born very preterm and full-term.

## **4.1 Methods**

### **4.1.1 Sample**

The study sample consisted of a regionally representative cohort of 110 infants born very preterm and 113 infants born full-term, who were being followed-up as part of a prospective longitudinal study. Neonatal clinical characteristics and family backgrounds of the two study groups have been described previously in section 3.1 (pages 55 – 57). Sample retention to age 6 years was 97.2% ( $n = 104$ ; 3 deaths, 3 refusals) for the very preterm group and 96% ( $n = 108$ ; 4 untraced, 1 refusal) for the full-term group. There were no significant differences between children lost to follow-up at age 6 years and the remainder of the sample in terms of neonatal clinical and social background characteristics ( $p > .05$ ).

### **4.1.2 Procedure**

Within 2 weeks of their child's sixth birthday (corrected for the extent of prematurity), study families attended a comprehensive neurodevelopmental assessment that included questioning each child's parent and classroom teacher about their home and school behaviour. In New Zealand, no information about preterm birth status is collected or recorded in a child's school records. Teachers were not informed about the children's group status.

### **4.1.3 Measures**

The primary measures used to assess child behavioural adjustment were the parent and teacher versions of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997). The SDQ is a 25-item behavioural screening questionnaire, consisting of five subscales assessing child emotional symptoms, conduct problems, inattention/hyperactivity, peer relationship problems, and prosocial behaviour. As shown in Appendix C (pages 140 – 141), each subscale contains five items, with the responses scored on a 3-point Likert scale ranging from not true (0) to certainly true

(2). With the exception of the prosocial subscale, higher scores indicate poorer adjustment. An overall behavioural difficulties score was also created by summing across all the subscales except prosocial behaviour. The SDQ is one of the most widely used behavioural screening measures in epidemiological research and clinical practice, and has been shown to have good concurrent and predictive validity (Goodman, 1997, 2001; Mathai, Anderson, & Bourne, 2004; Vostanis, 2006). For example, the SDQ correlates highly with other popular measures of child behaviour, including the Child Behaviour Check List (CBCL), and has been shown to be comparable in distinguishing clinical and community samples (Goodman & Scott, 1999; Hawes & Dadds, 2004; Mathai et al., 2004). Similarly, studies have demonstrated moderate to high level of agreement between diagnoses generated by the SDQ and clinical diagnoses based on standardised semi-structured interview or by independent clinicians (Hawes & Dadds, 2004; Mathai et al., 2004). Furthermore, the SDQ has also been demonstrated to have moderate to strong internal reliability and good test-retest reliability (Hawes & Dadds, 2004).

For this study, a clinically significant problem was defined as a subscale score greater than 90th percentile of the score distribution of the full-term group. Using this criterion, children were then classified as having no, a situational or pervasive problem for each adjustment outcome. To meet the criteria for a situational problem, children had to exceed the cut-point on either the parent or teacher SDQ measures. To meet the more stringent criteria for a pervasive problem, both parent and teacher scores had to fall within the clinical range (> 90th percentile). To minimise data loss for those children with missing parent (very preterm:  $n = 4$ ; full-term:  $n = 1$ ) or teacher data (very preterm:  $n = 7$ ; full-term:  $n = 3$ ), these children were classified as having no clinically significant pervasive problems at age 6 years, unless clear difficulties (i.e., exceeded the SDQ clinical cut-points across both parent and teacher ratings) were evident at both of their previous (age 4) and subsequent (age 9) assessments on the same measure.

#### **4.1.4 Data Analysis**

Data analysis was conducted in four stages. First, between-group differences in parent- and teacher-reported child behavioural adjustment scores were examined using the independent-samples *t*-test. Second, between-group differences in the

proportions of children with scores within the clinical range were examined using the chi-square test for independence or Fisher's exact test as appropriate, with odds ratios (OR) and 95% confidence intervals (CI) also reported. Third, inter-rater agreement between parents and teachers was then assessed using the alternative chance-correlated coefficient ( $AC_1$ ) (Gwet, 2001, 2002). This statistic provides a more accurate measure of agreement than the Kappa statistic when base rates are low, allowing adjustment for chance agreement.  $AC_1$  values greater than 0.75 indicate good agreement between raters, while values between 0.40 and 0.75 indicate moderate agreement between raters that are above chance. Finally, multinomial logistic regression analysis was used to examine rates of situational and pervasive behavioural adjustment problems in each study group.

## **4.2 Results**

### **4.2.1 Prevalence of Parent- and Teacher-Reported Child Behavioural Adjustment Problems**

Table 4.1 (pages 65 – 67) shows the behavioural adjustment scores of children born very preterm and full-term as rated by their parents and teachers at age 6 years. Also shown for each group are the proportions of children whose scores placed them within the clinical range on each measure. Based on parent report, children born very preterm were significantly more likely than children born full-term to obtain higher mean scores on the emotional symptoms [ $t(174.7) = 3.4, p = .001$ ], inattention/hyperactivity [ $t(193.4) = 3.8, p < .001$ ], and peer relationship problems [ $t(174.5) = 3.4, p = .001$ ] subscales. No significant between-group differences were evident in parent reported levels of child conduct problems [ $t(205) = 1.4, p = .17$ ] or prosocial behaviour [ $t(186.1) = 1.5, p = .14$ ]. Teachers reported a generally similar pattern of results, with children born very preterm obtaining higher emotional symptoms scores [ $t(183.9) = 2.1, p = .04$ ], but similar conduct problems [ $t(200) = 0.1, p = .92$ ], peer relationships [ $t(200) = 0.6, p = .55$ ], and prosocial scores [ $t(200) = 0.01, p = .99$ ] compared to children born full-term. However, in contrast to parents, despite a tendency for teachers to rate children born very preterm as showing higher levels of inattention/hyperactivity than children born full-term, this between-group difference did not reach statistical significance [ $t(200) = 1.6, p = .11$ ].

Further examination of the proportions of children whose scores placed them within the clinical range also showed that based on parent report, children born very preterm were significantly more likely than children born full-term to be at risk of later emotional problems [ $\chi^2(1, n = 207) = 8.1, p = .004$ ], inattention/hyperactivity [ $\chi^2(1, n = 207) = 15.6, p < .001$ ], peer relationship problems [ $\chi^2(1, n = 207) = 7.3, p = .007$ ], and overall behavioural difficulties [ $\chi^2(1, n = 207) = 9.3, p = .002$ ]. In contrast, on the basis of teacher report, with the exception of overall behavioural difficulties [ $\chi^2(1, n = 202) = 4.0, p = .046$ ], there were no significant differences between children born very preterm and full-term in terms of their risks of emotional problems [ $\chi^2(1, n = 202) = 2.1, p = .15$ ], inattention/hyperactivity [ $\chi^2(1, n = 202) = 0.1, p = .81$ ], and peer relationship problems [ $\chi^2(1, n = 202) = 0.4, p = .52$ ]. These findings indicate that parents of children born very preterm are much more likely than their child's classroom teachers to perceive their child as experiencing behavioural adjustment problems.

To assess the extent to which behavioural adjustment outcomes reported across the two study groups might vary by child sex, tests of gender by group interactions were conducted for each outcome. No significant interactions were found. Therefore, for all subsequent analyses, male and female data were combined. In addition, given the over-representation of lower socioeconomic status families in the very preterm group, it was further examined whether associations between very preterm birth and later behavioural outcomes might reflect either in full or in part the effects of family socioeconomic status. As shown in Table 4.1, results from this analysis showed that all reported associations remained significant after adjustment for the effects of family socioeconomic status.

**Table 4.1:** Behavioural Adjustment of Children Born Very Preterm and Full-Term

SDQ Subscale	Very Preterm ( <i>N</i> = 104)		Full-Term ( <i>N</i> = 108)		Adjusted <sup>a</sup> OR (95% CI)
	Score, <i>M</i> ± <i>SD</i>	Proportion in clinical range, %	Score, <i>M</i> ± <i>SD</i>	Proportion in clinical range, %	
<b>Emotional symptoms</b>					
Parent report	2.3 ± 2.2**	24.0**	1.4 ± 1.5**	9.3**	3.1 (1.4 – 6.8)
Teacher report	1.8 ± 2.0*	17.5	1.3 ± 1.6*	10.5	1.8 (0.8 – 4.1)
<b>Conduct problems</b>					
Parent report	1.8 ± 1.8	16.0	1.5 ± 1.4	9.3	1.8 (0.8 – 4.3)
Teacher report	0.9 ± 1.6	17.5	0.9 ± 1.8	10.5	1.6 (0.7 – 3.8)

*Note.* Table 4.1 continued on following page. SDQ = Strengths and Difficulties Questionnaire; OR = Odds Ratio; CI = Confidence Interval.

<sup>a</sup>Adjusted for family socioeconomic status.

\**p* < .05. \*\**p* < .01. \*\*\**p* < .001.

**Table 4.1:** Behavioural Adjustment of Children Born Very Preterm and Full-Term

SDQ Subscale	Very Preterm ( <i>N</i> = 104)		Full-Term ( <i>N</i> = 108)		OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)
	Score, <i>M</i> ± <i>SD</i>	Proportion in clinical range, %	Score, <i>M</i> ± <i>SD</i>	Proportion in clinical range, %		
<b>Inattention/hyperactivity</b>						
Parent report	4.2 ± 3.0***	38.0***	2.7 ± 2.5***	14.0***	3.8 (1.9 – 7.4)	3.4 (1.7 – 6.7)
Teacher report	3.6 ± 2.7	15.5	2.9 ± 3.1	14.3	1.1 (0.5 – 2.4)	1.1 (0.5 – 2.4)
<b>Peer relationship problems</b>						
Parent report	1.7 ± 2.0**	27.0**	0.9 ± 1.4**	12.1**	2.7 (1.3 – 5.5)	2.5 (1.2 – 5.3)
Teacher report	1.5 ± 1.9	13.4	1.4 ± 1.8	10.5	1.3 (0.6 – 3.1)	1.3 (0.5 – 3.2)

*Note.* Table 4.1 continued on following page. SDQ = Strengths and Difficulties Questionnaire; OR = Odds Ratio; CI = Confidence Interval.

<sup>a</sup>Adjusted for family socioeconomic status.

\**p* < .05. \*\**p* < .01. \*\*\**p* < .001.



**Table 4.1:** Behavioural Adjustment of Children Born Very Preterm and Full-Term

SDQ Subscale	Very Preterm ( <i>N</i> = 104)		Full-Term ( <i>N</i> = 108)		OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)
	Score, <i>M</i> ± <i>SD</i>	Proportion in clinical range, %	Score, <i>M</i> ± <i>SD</i>	Proportion in clinical range, %		
<b>Prosocial behaviour</b>						
Parent report	8.4 ± 2.0	15.0	8.8 ± 1.5	10.3	1.5 (0.7 – 3.5)	1.3 (0.6 – 3.2)
Teacher report	7.2 ± 2.3	11.3	7.2 ± 2.3	11.4	1.0 (0.4 – 2.4)	0.9 (0.4 – 2.2)
<b>Overall behavioural difficulties</b>						
Parent report	10.1 ± 7.0***	28.0**	6.6 ± 4.6***	11.2**	3.1 (1.5 – 6.5)	2.7 (1.3 – 5.8)
Teacher report	7.9 ± 5.5	20.6*	6.5 ± 5.7	10.5*	2.2 (1.0 – 4.9)	1.7 (0.8 – 4.0)

*Note.* SDQ = Strengths and Difficulties Questionnaire; OR = Odds Ratio; CI = Confidence Interval.

<sup>a</sup>Adjusted for family socioeconomic status.

\**p* < .05. \*\**p* < .01. \*\*\**p* < .001.

#### 4.2.2 Extent of Agreement between Parent- and Teacher-Reported Child Behavioural Adjustment Outcomes

Table 4.2 (page 68) describes the extent of agreement between parent and teacher reports of child behavioural adjustment within each study group. As shown, inter-rater agreement was higher for children born full-term (mean  $AC_1 = .80$ ; range =  $.78 - .85$ ) than for children born very preterm (mean  $AC_1 = .63$ ; range =  $.48 - .77$ ). Inter-rater agreement for children born very preterm was lowest for the inattention/hyperactivity ( $AC_1 = .48$ ) and emotional symptoms ( $AC_1 = .56$ ) subscales.

**Table 4.2:** Extent of Agreement between Parent- and Teacher-Reported Outcomes

SDQ Subscale	Very Preterm	Full-Term
	( <i>n</i> = 93)	( <i>n</i> = 104)
	Parent-Teacher Agreement, $AC_1$	
Emotional symptoms	.56	.78
Conduct problems	.67	.79
Inattention/hyperactivity	.48	.78
Peer relationship problems	.65	.85
Prosocial behaviour	.77	.80
Overall behavioural difficulties	.58	.80

*Note.* SDQ = Strengths and Difficulties Questionnaire;  $AC_1$  = Alternative Chance-correlated Coefficient.

#### 4.2.3 Extent of Situational and Pervasive Behavioural Adjustment Problems

Table 4.3 (page 70) shows the proportions of children born very preterm and full-term identified as showing situational and pervasive behavioural adjustment problems. Although around 40% of very preterm and 20% of full-term children obtained overall behavioural difficulties scores within the clinical range based on parent or teacher report, most of these difficulties were relatively mild and of a situational nature. Rates of pervasive and more severe behavioural adjustment difficulties were low, affecting only 12% of children born very preterm and 3% of children born full-term.

As shown, relative to their full-term peers, the most frequently reported situational problem of children born very preterm was inattention/hyperactivity ( $p = .005$ ), followed closely by emotional problems ( $p = .01$ ). The next most common situational problem was peer relations ( $p = .02$ ). However, no significant between-group differences were evident for situational conduct problems or the extent of prosocial behaviour. These findings largely remained unchanged after adjustment for the effects of family socioeconomic status, with the exception of peer relationship problems ( $p = .06$ ).

Examination of the nature of the pervasive behavioural adjustment problems showed that the most common difficulties in both study groups were inattention/hyperactivity and peer relationship problems. Emotional symptoms, conduct problems, and prosocial issues were relatively rare at age 6 years, especially emotional problems in typically developing children born full-term. As shown, children born very preterm were two times more likely to show pervasive difficulties with inattention/hyperactivity and six times more likely to be experiencing pervasive emotional problems. The odds ratios for each of these difficulties were 2.8 and 8.1, respectively. However, it should be noted that there was some imprecision in this estimate for emotional problems given the very low base rate within the full-term group. These findings were robust to adjustment for the effects of family socioeconomic status.

**Table 4.3:** Prevalence of Situational and Pervasive Behavioural Adjustment Problems

<b>SDQ subscale</b>	<b>Very Preterm (N = 104)</b>	<b>Full-Term (N = 108)</b>	<b>OR (95% CI)</b>	<b>p</b>
<b>Emotional symptoms</b>				
Situational, %	31.7	17.6	2.4 (1.2 – 4.5)	.01
Pervasive, %	5.8	0.9	8.1 (0.96 – 69.1)	.055
<b>Conduct problems</b>				
Situational, %	24.0	16.7	1.7 (0.8 – 3.3)	.15
Pervasive, %	4.8	1.9	3.0 (0.6 – 15.8)	.20
<b>Inattention/hyperactivity</b>				
Situational, %	31.7	16.7	2.6 (1.3 – 5.1)	.005
Pervasive, %	11.5	5.6	2.8 (1.0 – 8.0)	.048
<b>Peer relationship problems</b>				
Situational, %	22.1	11.1	2.4 (1.1 – 5.1)	.02
Pervasive, %	8.7	5.6	1.9 (0.6 – 5.5)	.25
<b>Prosocial behaviour</b>				
Situational, %	18.3	15.7	1.2 (0.6 – 2.5)	.60
Pervasive, %	3.8	2.8	1.4 (0.3 – 6.7)	.63
<b>Overall behavioural difficulties</b>				
Situational, %	26.9	15.7	2.3 (1.1 – 4.5)	.02
Pervasive, %	11.5	2.8	5.5 (1.5 – 20.3)	.01

*Note.* SDQ = Strengths and Difficulties Questionnaire; OR = Odds Ratio; CI= Confidence Interval; Degrees of Freedom = 1.

### **4.3 Discussion**

Drawing on prospective longitudinal data, this study examined the behavioural adjustment outcomes of a contemporary cohort of children born very preterm at age 6 years. Of particular interest was the extent of agreement between parent and teacher evaluations of child behavioural adjustment as well as the prevalence of child situational and pervasive behavioural problems. Methodological strengths of the study included the unselected nature of the very preterm sample, the inclusion of a demographically representative full-term comparison group, the high sample retention over time, and the use of multiple informants to assess child behavioural adjustment. Study findings and their implications are discussed below.

Consistent with previous research (Delobel-Ayoub et al., 2009; Johnson et al., 2010b; Woodward et al., 2009), results from this study demonstrate that by early school age, children born very preterm are at an increased risk of emotional problems and inattention/hyperactivity, but not conduct, peer relationship, or prosocial behaviour problems relative to their full-term peers. However, an important finding from this study is that the rates of child behavioural adjustment difficulties vary considerably depending on the source of information/context assessed, with parents being much more likely than teachers to perceive their very preterm child as having later adjustment difficulties.

These inter-informant discrepancies were further confirmed by the poorer and more variable agreement indices found between parents and teachers in the very preterm group. In line with these results, findings from several earlier studies have also found that rates of later adjustment problems tend to be higher when assessed on the basis of parent report than when based on teacher report (Conrad et al., 2010; Gardner et al., 2004; Indredavik, Vik, Heyerdahl, Kulseng, & Brubakk, 2005). Taken together, these findings tend to suggest that parents of children born very preterm are more likely to perceive their child as showing behavioural adjustment difficulties than teachers. Several possible explanations may account for this finding. First, because almost all teachers in this study were unaware of children's birth status they may have been better placed to provide an unbiased evaluation of child behaviour. Second, teachers also have the advantage of being able to observe a child's behaviour in relation to their larger peer group. Finally, parents and teachers

may differ in their sensitivity to different child problems. For example, teachers may be better placed to identify externalising behaviour problems such as inattention/hyperactivity, whereas parents may be more aware of internalising problems such as anxiety and social withdrawal (de Nijs et al., 2004; Goodman, Ford, Simmons et al., 2000; Hinshaw, Han, Erhardt, & Huber, 1992). Nonetheless, irrespective of the reasons for the poor agreement between parents and teachers, these findings clearly highlight the difficulties of relying solely on information from a single report source and emphasise the need to seek information from multiple, independent informants/contexts to improve the accuracy and clinical validity of reported behavioural adjustment outcomes in children born very preterm.

Examination of the extent of child situational and pervasive emotional symptoms, inattention/hyperactivity, and peer relationship difficulties revealed that situational problems were relatively common affecting between 22% and 32% of children born very preterm and between 11% and 18% of children born full-term. Pervasive problems were much less common, with only 1% of children born full-term showing pervasive emotional problems and 6% showing pervasive inattention/hyperactivity. Rates of emotional problems and inattention/hyperactivity were much higher in the very preterm group with 6% and 12% of children having these more severe difficulties. No between-group differences were evident in the rates of pervasive conduct problems, peer relationship difficulties, or prosocial behaviour. Comparison of the current study findings with those reported by the EPICure study (Samara et al., 2008) of children born extremely preterm revealed a number of similarities and differences. First, not surprisingly given the lower risk nature of our sample, rates of pervasive overall behavioural difficulties were lower, with only 12% of children born very preterm compared to 19% of children born extremely preterm. However, despite these differences in the extent of problems, there was some agreement on the nature of pervasive problems experienced by children born very preterm, with behavioural inattention/hyperactivity being the most frequently reported difficulty, followed by peer relationship difficulties, and emotional problems. While the use of multi-informant SDQ data has been shown (Goodman, Ford, Simmons et al., 2000) to have moderate sensitivity (63.3%) and good specificity (94.6%) in identifying children with clinically diagnosed psychiatric disorders in general, further research examining this issue within the preterm population will be important.

In conclusion, study findings reveal that children born very preterm are at increased risk for pervasive inattention/hyperactivity and emotional problems during early school years. Further follow-up of these children will be important to track these early emerging adjustment problems and to monitor children's peer functioning and possible conduct difficulties. Findings also emphasise the importance of including mental health screening as part of routine clinical developmental follow-up assessment for children born very preterm. Finally and importantly, this study highlights the need for caution when drawing conclusions about the prevalence of behavioural adjustment problems amongst very preterm survivors when relying solely on parent report. Combining reports from multiple and independent informants may help improve the identification of clinically relevant behavioural adjustment problems in children born very preterm.

## Chapter 5

### **Predictive Validity of Inattention/Hyperactivity Ratings for ADHD Clinical Diagnosis in Children Born Very Preterm**

It is now well recognised that ADHD is among the most prevalent neurobehavioural morbidities affecting children born very preterm (Bhutta et al., 2002; Johnson & Marlow, 2011). Elevated risks of ADHD symptomatology have been shown as early as the preschool school years in children born very preterm (Delobel-Ayoub et al., 2009; Delobel-Ayoub et al., 2006; Woodward et al., 2009). These behavioural difficulties often persist throughout childhood. Specifically, school-aged children born very preterm are two to four times more likely than their full-term peers to meet the *DSM-IV* criteria for an ADHD clinical diagnosis (Bhutta et al., 2002; Johnson et al., 2010b).

To date, most studies concerned with the very preterm population have been based on child behaviour screening questionnaires completed by parents and/or teachers. However, as there are no definite diagnostic test/s for ADHD, structured or semi-structured clinical interview based on *DSM-IV/IV-TR* criteria, is currently considered as the “gold standard” for diagnosing ADHD (Shemmassian & Lee, 2012). Behavioural screening questionnaires or rating scales, although convenient to administer, provide limited diagnostic information about the age of onset, persistence of symptoms, and/or functional impacts as required for the clinical diagnosis of ADHD (Shemmassian & Lee, 2012). Although the psychometric properties, including the predictive validity of these screening measures have been established in the general population, the extent to which they are predictive of a subsequent clinical diagnosis in the very preterm population remains unclear.

Of the 15 studies previously reviewed (see Table 2.1, pages 21 – 22) concerning the risk of ADHD in children born very preterm, only 1 study (Johnson et al., 2010b) diagnosed ADHD based on structured psychiatric interview. Furthermore, four other studies examined the risk of ADHD in these children using ADHD-specific behaviour



screening questionnaires rated by parents or teachers (P. J. Anderson et al., 2011; Foulder-Hughes & Cooke, 2003; Hoff et al., 2004; Shum, Neulinger, O'Callaghan, & Mohay, 2008). Similarly, as shown in a recent review (Johnson & Marlow, 2011), only five follow-up studies included in this review used diagnostic psychiatric interviews to assess the risk of ADHD in this high-risk population, with reported prevalence varying from 7% to 23%. However, four of the five studies reported their findings based on follow-up of cohorts of children born prior to the 1990s, that is, before the extensive changes in neonatal resuscitation practices, including the use of antenatal corticosteroids, surfactant therapy, and sophisticated neuroprotection approaches (Bissinger & Annibale, 2010; Modanlou et al., 1996). This is of concern as these changes in neonatal resuscitation techniques have been associated with reductions in mortality and long-term morbidity risks (Fanaroff, Hack, & Walsh, 2003; Modanlou et al., 1996). Hence, findings from these earlier cohorts may have limited generalisability to contemporary cohorts of children born very preterm.

A related issue that has also been neglected by existing longitudinal follow-up studies concerns the long-term prognostic utility of early inattention/hyperactivity difficulties shown by children born very preterm. Elevated risks of behavioural inattention/hyperactivity in these children have been consistently reported as early as during preschool and early school years. Nonetheless, to date, the predictive validity of these early emerging behavioural problems for a subsequent ADHD diagnosis has not been evaluated in children born very preterm.

Another measurement issue in most of the existing studies concerns the extent to which children born very preterm are subject to ADHD symptomatology or behavioural inattention/hyperactivity difficulties across multiple contexts, including home and school. This is important as the *DSM-IV/IV-TR* criteria for an ADHD diagnosis requires that at least a few behavioural symptoms are observed across both home and school. However, to date, with the exception of the EPICure study of 6-year-old children born extremely preterm (< 26 weeks of gestation) in the United Kingdom and Ireland, very little is known about the pervasive nature of behavioural inattention/hyperactivity problems in representative samples of children born very preterm (Samara et al., 2008). However, as neurodevelopmental morbidity risks occur in a dose-dependent manner with decreasing gestational age at birth, findings

from this high-risk cohort may not generalise to all children born very preterm. Accordingly, the specific aims of this study are as follows:

- (1) To examine the prevalence of situational and pervasive behavioural inattention/hyperactivity symptoms at ages 4, 6, and 9 years in children born very preterm, compared to children born full-term.
- (2) To describe rates of *DSM-IV* ADHD clinical diagnosis at age 9 years in children born very preterm and full-term.
- (3) To evaluate the predictive validity of situational and pervasive behavioural inattention/hyperactivity symptoms at ages 4 and 6, as well as symptoms at more than one assessment time-point across the ages of 4 to 9 (i.e., persistent symptoms), for a clinical diagnosis of ADHD at age 9 years.

## **5.1 Methods**

### **5.1.1 Sample**

The study sample consisted of a regionally representative cohort of 110 infants born very preterm and 113 infants born full-term, who were being followed-up as part of a prospective longitudinal study. Neonatal clinical characteristics and family backgrounds of the two study groups have been described previously in section 3.1 (pages 55 – 57). Excluding deaths ( $n = 3$ ), sample retention of the very preterm group to ages 4, 6, and 9 years was 99.1% ( $n = 106$ ), 97.2% ( $n = 104$ ), and 96.3% ( $n = 103$ ), respectively. Retention of infants born full-term to ages 4 and 6 was 96% ( $n = 108$ ) and at age 9 years was 97.5% ( $n = 110$ ). There were no significant differences between children lost to follow-up at ages 4, 6, and 9 years and the remainder of the sample, in terms of neonatal clinical and social background characteristics ( $p > .05$ ).

### **5.1.2 Procedure**

At each follow-up, within 2 weeks of their child's birthday, study families attended a comprehensive neurodevelopmental assessment. As part of these follow-up evaluations, children were screened for behavioural inattention/hyperactivity problems based on parent and teacher reports of child behaviour at home and school. At age 9 years, a structured psychiatric interview was also completed with each study child's primary caregiver for a *DSM-IV* psychiatric diagnosis of ADHD assigned by a blinded child psychiatrist.

### 5.1.3 Measures

#### *Behavioural Inattention/Hyperactivity Screening (Ages 4, 6, 9 Years)*

At ages 4 and 6 (corrected) and at age 9 years (uncorrected), all study children were screened for behavioural inattention/hyperactivity symptoms using the parent and teacher rated Inattention/Hyperactivity subscale of the SDQ (Goodman, 1997). As shown in Appendix C (pages 140 – 141), this subscale consists of 5-items rated on a 3-point Likert scale based on the child's behaviour over the last six months, with higher scores indicating poorer outcome. As described previously, this behavioural screening measure has been widely used in epidemiological research and clinical practice, and has been shown to have good concurrent and predictive validity (Goodman & Scott, 1999; Hawes & Dadds, 2004; Mathai et al., 2004). Specifically, the parent and teacher rated SDQ Inattention/Hyperactivity subscale has been shown to have moderate sensitivity (68% – 74%) and good specificity (92% – 93%) for the *DSM-IV* ADHD diagnosis of children aged 5 to 15 years (Goodman, 2001).

Similar to the criterion described in the last chapter, in this study, at each assessment time-point, children with an inattention/hyperactivity subscale score greater than the 90th percentile (defined on the basis of the full-term group) were classified as showing clinically relevant inattentive/hyperactive symptoms. Children exceeding the cut-point based on either the parent or teacher report were classified as showing situational symptoms. Whereas children exceeding the cut-point on both parent and teacher measures were classified as showing pervasive symptoms. Finally, children exhibiting situational and/or pervasive symptoms across more than one assessment time-points were classified as showing persistent symptoms.

#### *ADHD Clinical Diagnosis (Age 9 Years)*

At age 9 years, all study children were assessed for a *DSM-IV* clinical diagnosis of ADHD, based on the DAWBA structured psychiatric diagnostic interview (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). As part of the DAWBA protocol, child diagnostic information was initially collected via parent interview by a trained senior research nurse. This information was then recorded and later on screened for *DSM-IV* ADHD symptoms by a computerised algorithm. Information regarding child behaviour at school was also collected from the child's classroom teacher. Finally, all the information from parent, teacher, and computer screening were collated and

reviewed by a blinded child psychiatrist and an independent diagnosis of ADHD determined. The DAWBA has been used in multiple clinical research settings and has excellent concurrent and predictive validity (Foreman, Morton, & Ford, 2009; Goodman, Ford, Richards et al., 2000). For example, there is significant agreement (Kendall's tau-b = .70) between ADHD diagnosis based on DAWBA interview and clinical case notes, with an estimated sensitivity of 80% and a specificity index of 84% in psychiatric clinic samples (Goodman, Ford, Richards et al., 2000). Similarly, positive and negative predictive values greater than 80% with negligible bias have been reported for DAWBA ADHD diagnosis compared to a clinic diagnosis (Foreman et al., 2009).

#### 5.1.4 Data Analysis

Data analysis was conducted in three stages. First, between-group differences in the rates of situational and pervasive inattention/hyperactivity symptoms were examined using multinomial logistic regression analysis. Second, within each study group, the predictive validity of situational and pervasive inattention/hyperactivity symptoms, for a subsequent clinical diagnosis of ADHD was determined by calculating the sensitivity and specificity indices. Finally, receiver operating characteristic (ROC) curves were fitted to the data to compare the predictive validity of inattention/hyperactivity symptoms at various assessment time-points by comparing the area under the curves (*AUC*). Significant differences in *AUC*s were analysed using the critical *z* value, computed using the following equations (Hanley & McNeil, 1983).

$$z = \frac{(AUC_1 - AUC_2)}{SE(AUC_1 - AUC_2)} \quad (1)$$

$$= \frac{(AUC_1 - AUC_2)}{\sqrt{SE^2(AUC_1) + SE^2(AUC_2) - 2rSE(AUC_1)SE(AUC_2)}}, \quad (2)$$

where,  $AUC_1$  and  $SE(AUC_1)$  denote area and standard error associated with ROC curve 1, respectively;  $AUC_2$  and  $SE(AUC_2)$  denote area and standard error associated with ROC curve 2, respectively; and  $r$  is computed using the following equation.

$$r = r_{hm} \left[ \left( \frac{r_n + r_a}{2} \right) \& \left( \frac{AUC_1 + AUC_2}{2} \right) \right], \quad (3)$$

where,  $r_n$  refers to the correlation coefficient (Kendall's tau-b,  $t$ ) between behavioural inattention/hyperactivity symptoms at two different assessment time-points, for those without a clinical diagnosis of ADHD at age 9 years;  $r_a$  refers to corresponding  $t$  for those with a clinical diagnosis of ADHD at age 9 years; and  $r_{hm}$  corresponds to Hanley and McNeil (1983) determined correlation coefficient values between two ROC curves as a function of  $\left( \frac{r_n + r_a}{2} \right)$  and  $\left( \frac{AUC_1 + AUC_2}{2} \right)$ .

For significant ( $p < .05$ ) differences between two ROC curves, the critical  $z$  value is 1.96. A  $z$  value greater than 1.96 signifies that the predictive validity of test criterion 1 is superior to test criterion 2, whereas  $z$  value less than - 1.96 signifies that the predictive validity of test criterion 2 is superior to test criterion 1.

## 5.2 Results

### 5.2.1 Prevalence of Situational and Pervasive Inattention/Hyperactivity Symptoms

Table 5.1 (page 80) shows the proportions of children born very preterm and full-term meeting criteria for situational and pervasive inattention/hyperactivity symptoms at ages 4, 6, and 9 years. As shown, across all the assessment time-points, very preterm birth was associated with on average a 2-fold increased risk of behavioural inattention/hyperactivity difficulties. These increased risks largely reflected the elevated rates of situational symptoms, affecting between 22% and 32% of children born very preterm compared to between 11% and 17% of children born full-term. In contrast, rates of more severe, pervasive symptoms were relatively modest across both the study groups, affecting between 7% and 12% of children born very preterm and between 5% and 7% of children born full-term. However, there were no significant between-group differences in terms of children's risk of pervasive symptoms at ages 4 ( $p = .40$ ) and 9 years ( $p = .17$ ). As shown, these findings remained unchanged after adjustment for the effects of child sex and family socioeconomic status.

**Table 5.1:** Prevalence of Situational and Pervasive Inattention/Hyperactivity Symptoms

Inattention/ Hyperactivity Symptoms	Very Preterm ( <i>N</i> = 107)	Full -Term ( <i>N</i> = 110)	OR (95% CI)	<i>p</i>	<i>p</i> <sup>a</sup>
<b>Age 4 years<sup>b</sup></b>					
Situational, %	22.3	14.0	1.8 (0.9 – 3.8)	.10	.12
Pervasive, %	6.8	4.7	1.7 (0.5 – 5.5)	.40	.42
<b>Age 6 years<sup>c</sup></b>					
Situational, %	31.7	16.7	2.6 (1.3 – 5.1)	.005	.007
Pervasive, %	11.5	5.6	2.8 (1.0 – 8.0)	.048	.05
<b>Age 9 years<sup>d</sup></b>					
Situational, %	28.2	10.9	3.5 (1.6–7.3)	.001	.005
Pervasive, %	10.7	7.3	2.0 (0.7–5.2)	.17	.19

*Note.* OR = Odds Ratio; CI= Confidence Interval; Degrees of Freedom = 1.

<sup>a</sup>Adjusted for child sex and family socioeconomic status.

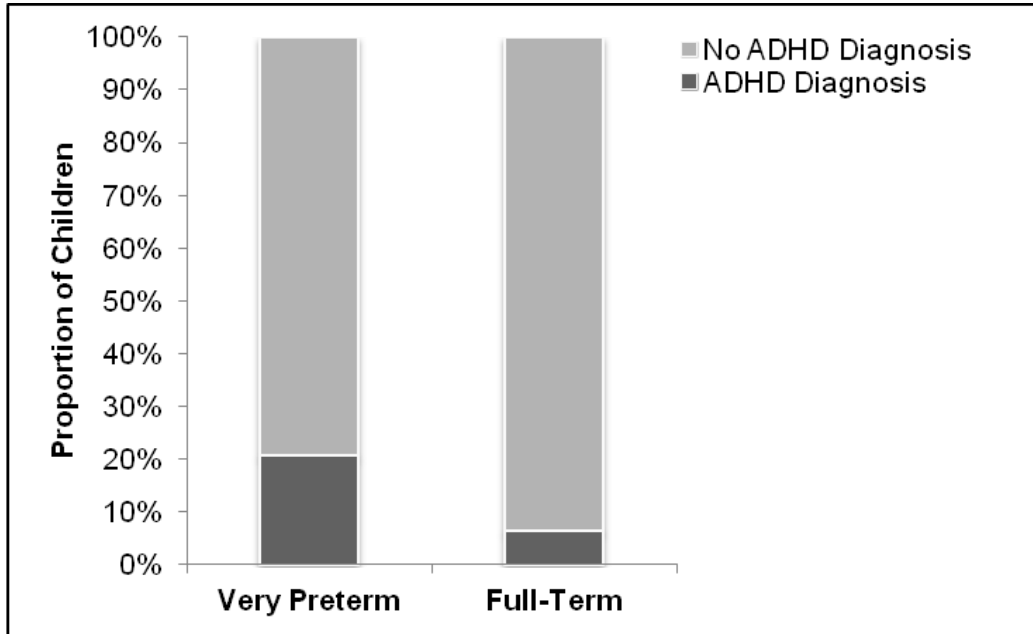
<sup>b</sup>Excludes 4 very preterm and 3 full-term children.

<sup>c</sup>Excludes 3 very preterm and 2 full-term children.

<sup>d</sup>Excludes 4 very preterm children.

### 5.2.2 Prevalence of *DSM-IV* Clinical Diagnosis of ADHD

As shown in Figure 5.1 (page 81), very preterm birth was associated with an elevated risk of *DSM-IV* clinical diagnosis of ADHD at age 9 years. Specifically, 20.6% (*n* = 21) of children born very preterm compared to 6.4% (*n* = 7) of children born full-term met the clinical diagnostic criteria for ADHD [ $\chi^2(1, n = 211) = 9.2, p = .002$ ; OR: 3.8; 95% CI: 1.5 – 9.3]. These findings were robust after adjustment for the effects of child sex and family socioeconomic status ( $p = .02$ ; OR: 3.1; 95% CI: 1.2 – 7.9).



**Figure 5.1:** Prevalence of *DSM-IV* clinical diagnosis of ADHD at age 9 years.

### 5.2.3 Predictive Validity of Behavioural Inattention/Hyperactivity Symptoms at Ages 4 and 6 Years

Table 5.2 (page 83) shows the predictive validity of situational and pervasive behavioural inattention/hyperactivity symptoms at ages 4 and 6, for a *DSM-IV* ADHD diagnosis at age 9 years. Across both study groups, children exhibiting situational symptoms were much less likely than children exhibiting pervasive symptoms to be at an elevated risk of a later ADHD diagnosis (very preterm: 29% – 48% vs. 67% – 75%; full-term: 13% – 22% vs. 33% – 40%). These differences in predictive validity between situational and pervasive symptoms were further confirmed by the lower specificity indices for situational than pervasive symptoms (very preterm: 71% – 84% vs. 95% – 97%; full-term: 85% – 87% vs. 95% – 97%). Unlike specificity, sensitivity indices were relatively lower across all symptoms categories for both study groups. However, it is important to note that there were considerable gains in sensitivity indices of behavioural inattention/hyperactivity symptoms (situational and pervasive) at age 6 compared to age 4 years. Within the very preterm group, although sensitivity of situational symptoms for a subsequent ADHD diagnosis increased from 69% at age 4 to 75% at age 6 years, there was significant decline in specificity from age 4 to 6 years (84% vs. 71%). Nonetheless, within the same study group, in terms of pervasive symptoms, considerable increase in sensitivity from age 4 to 6 years was evident (44% vs. 75%) without any corresponding decline in specificity (97% vs. 95%).

Although these differences in predictive validity between situational and pervasive inattention/hyperactivity symptoms for an ADHD clinical diagnosis were generally consistent across both study groups, they were more prominent for children born very preterm than full-term. Furthermore, much higher proportions of children born very preterm than full-term exhibiting inattention/hyperactivity symptoms at ages 4 and 6 met the criteria for a subsequent clinical diagnosis of ADHD at age 9 years. Specifically, compared to 48% and 67% of children born very preterm, 13% and 40% of children born full-term showing situational and pervasive symptoms, respectively at age 4 years, received a later diagnosis of ADHD. Similarly, relative to 29% and 75% of children born very preterm, 22% and 33% of children born full-term exhibiting situational and pervasive symptoms, respectively at age 6 years had a subsequent diagnosis of ADHD.



**Table 5.2:** Predictive Validity of Behavioural Inattention/Hyperactivity Symptoms at Ages 4 and 6 for a Clinical Diagnosis of ADHD at Age 9 Years

Inattention/ Hyperactivity Symptoms	ADHD Clinical Diagnosis, Age 9 years				Sensitivity, % (95% CI)		Specificity, % (95% CI)	
	Very Preterm (N = 21)	Full-Term (N = 7)	Very Preterm	Full-Term	Very Preterm	Full-Term	Very Preterm	Full-Term
<b>Age 4 years<sup>a</sup></b>								
None, % (n)	7.1 (5)	2.3 (2)						
Situational, % (n)	47.8 (11)	13.3 (2)	68.8 (41.5 – 87.9)	50.0 (9.2 – 90.8)	84.4 (74.0 – 91.3)	86.6 (77.8 – 92.4)		
Pervasive, % (n)	66.7 (4)	40.0 (2)	44.4 (15.3 – 77.3)	50.0 (9.2 – 90.8)	97.0 (88.7 – 99.5)	96.6 (89.5 – 99.1)		
<b>Age 6 Years</b>								
None, % (n)	5.2 (3)	1.2 (1)						
Situational, % (n)	29.0 (9)	22.2 (4)	75.0 (42.8 – 93.3)	80.0 (29.9 – 98.9)	71.4 (59.8 – 80.9)	85.4 (76.4– 91.5)		
Pervasive, % (n)	75.0 (9)	33.3 (2)	75.0 (42.8 – 93.3)	66.7 (12.5 – 98.2)	94.8 (84.7 – 98.7)	95.3 (87.9 – 98.5)		

Note. CI = Confidence Interval.

<sup>a</sup>Excludes 1 very preterm and 1 full-term child.

#### **5.2.4 Predictive Validity of Persistent Behavioural Inattention/Hyperactivity Symptoms Across Ages 4 to 9 Years**

Table 5.3 (page 85) describes the predictive validity of persistent behavioural inattention/hyperactivity symptoms across the ages of 4 to 9, for a clinical diagnosis of ADHD at age 9 years. As shown, within both study groups, children showing persistent inattention/hyperactivity symptoms were much more likely to have an ADHD clinical diagnosis than those exhibiting nonpersistent symptoms. In addition, children born very preterm exhibiting persistent situational symptoms had a relatively lower risk of receiving a subsequent ADHD diagnosis compared to those exhibiting persistent pervasive symptoms (52% – 67% vs. 78% – 100%). However, these differences in predictive validity between persistent situational and pervasive symptoms were not very prominent among the full-term group (27% – 33% vs. 0% – 33%). Sensitivity and specificity indices further supported these findings.

In terms of between-group differences, specificity indices for the different persistent symptoms criteria were comparable across the very preterm and full-term groups. However, sensitivity indices for persistent symptoms were generally higher for the very preterm than full-term group. Specifically, persistent situational symptoms at two or three time-points had an estimated sensitivity of 92% for the very preterm compared to 75% for the full-term group, for an ADHD clinical diagnosis. Similarly, sensitivity for persistent pervasive symptoms at two or three time-points was estimated at 88% and 67% for children born very preterm and full-term, respectively, for an ADHD diagnosis.

Finally, ROC curves as shown in Figure 5.2 (page 86) were fitted to the data to take into account the trade-off between sensitivity and specificity indices. Significant differences between the areas under the curves were evaluated using the  $z$  values (see Table 5.4, page 87). As shown in Table 5.4, within the very preterm group, persistent symptoms at two or three time-points ( $AUC = 0.909$ ) have better predictive validity compared to symptoms shown at ages 4 years ( $AUC = 0.794$ ;  $z = -2.0$ ), 6 years ( $AUC = 0.813$ ;  $z = -2.0$ ), or persistently at ages 4, 6, and 9 years ( $AUC = 0.659$ ;  $z = 3.29$ ). In contrast, within the full-term group, persistent symptoms at two or three time-points ( $AUC = 0.859$ ) have similar predictive validity as symptoms shown at ages 4 years ( $AUC = 0.769$ ;  $z = -0.69$ ) or 6 years ( $AUC = 0.824$ ;  $z = -0.53$ ).

**Table 5.3:** Predictive Validity of Persistent Behavioural Inattention/Hyperactivity Symptoms for a Clinical Diagnosis of ADHD at Age 9 Years

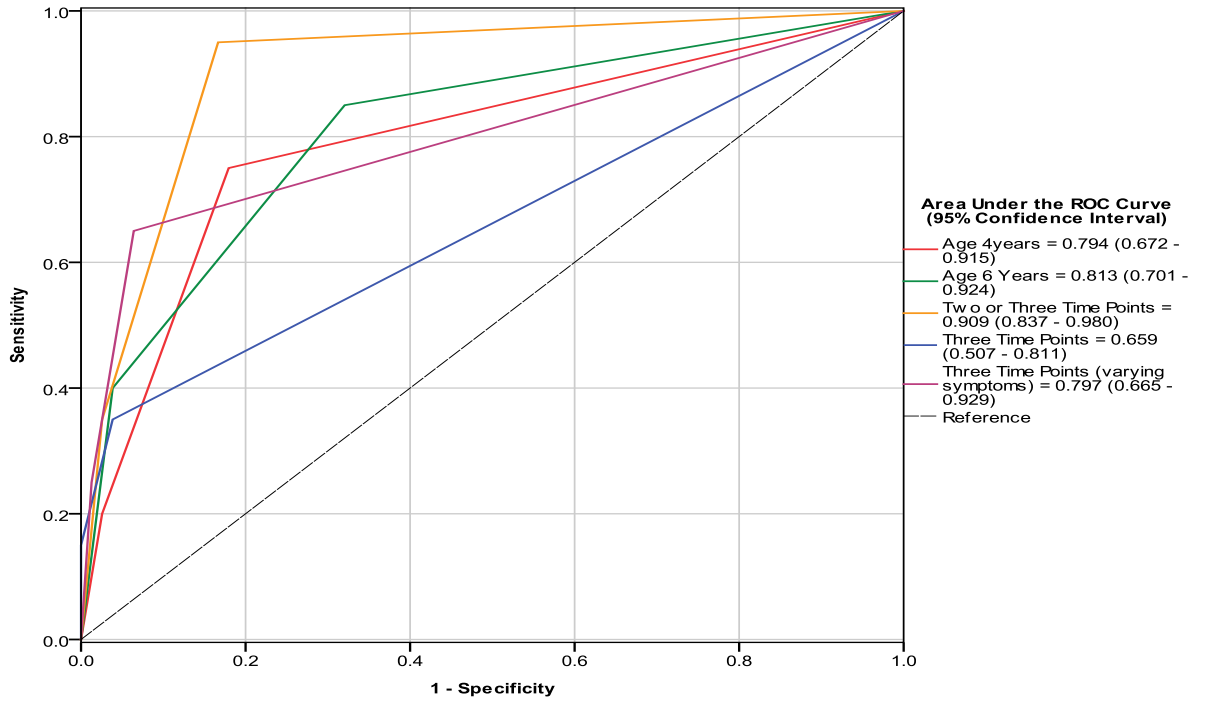
Inattention/ Hyperactivity Symptoms, Ages 4, 6, 9 Years	ADHD Clinical Diagnosis, Age 9 years		Sensitivity, % (95% CI)		Specificity, % (95% CI)	
	Very Preterm (N = 20)	Full-Term (N = 6)	Very Preterm	Full-Term	Very Preterm	Full-Term
<b>Two or three time-points</b>						
Nonpersistent, % (n)	1.5 (1)	1.1 (1)				
*Situational, % (n)	52.2 (12)	27.3 (3)	92.3 (62.1 – 99.6)	75.0 (21.9 – 98.7)	85.5 (75.2 – 92.2)	91.6 (83.6 – 96.0)
*Pervasive, % (n)	77.8 (7)	33.3 (2)	87.5 (46.7 – 99.3)	66.7 (12.5 – 98.2)	97.0 (88.7 – 99.5)	95.6 (88.5 – 98.6)
<b>Three time-points</b>						
Nonpersistent, % (n)	14.8 (13)	5.0 (5)				
*Situational, % (n)	57.1 (4)	0	23.5 (7.8 – 50.2)	0 (0 – 53.7)	96.2 (88.4 – 99.0)	98.0 (92.1 – 99.6)
*Pervasive, % (n)	100.0 (3)	50.0 (1)	18.8 (5.0 – 46.3)	16.7 (0.8 – 63.5)	100.0 (93.9 – 100)	99 (93.6 – 99.9)
<b>Three time-points (varying symptoms)</b>						
Non-persistent, % (n)	8.8 (7)	3.1 (3)				
*Situational <sup>a</sup> , % (n)	66.7 (8)	33.3 (2)	53.3 (27.4 – 77.7)	40.0 (7.2 – 83.0)	94.8 (86.5 – 98.3)	95.9 (89.2 – 98.7)
*Pervasive <sup>b</sup> , % (n)	83.3 (5)	33.3 (1)	41.7 (16.5 – 71.4)	25.0 (1.3 – 78.1)	98.6 (91.7 – 99.9)	97.9 (91.9 – 99.6)

Note. \* = persistent symptoms; CI = Confidence Interval.

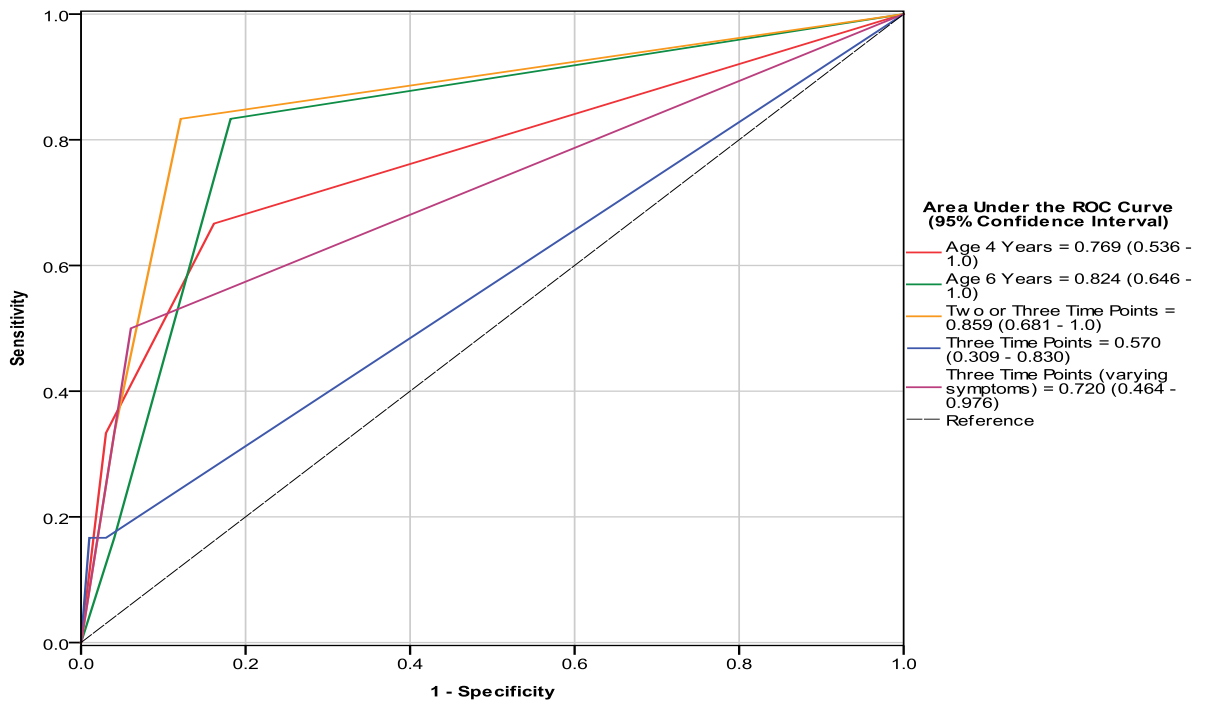
<sup>a</sup>Situational only or situational at two time-points and pervasive at third.

<sup>b</sup>Pervasive only or pervasive at two time-points and situational at third.

**(A) Children Born Very Preterm**



**(B) Children Born Full-Term**



**Figure 5.2:** Receiver operating characteristic curves for comparing the predictive validity of behavioural inattention/hyperactivity symptomatology patterns.

**Table 5.4:** Comparison of Area Under Receiver Operating Characteristic Curves

<b>Inattention/Hyperactivity Symptoms, Ages 4, 6, 9 Years</b>	<b>z values</b>	
	<b>Very Preterm (n = 98)</b>	<b>Full-Term (n = 105)</b>
Age 4 vs. 6 years	- 0.25	- 0.44
Age 4 years vs. Two or three time-points	- 2.0	- 0.69
Age 4 years vs. Three time-points	1.82	1.47
Age 4 years vs. Three time-points (varying symptoms)	- 0.05	0.46
Age 6 years vs. Two or three time-points	- 2.0	- 0.53
Age 6 years vs. Three time-points	1.81	2.21
Age 6 years vs. Three time-points (varying symptoms)	0.25	0.95
Two or three vs. Three time-points	3.29	2.37
Two or three vs. Three time-points (varying symptoms)	1.87	1.04
Three vs. Three time-points (varying symptoms)	- 2.16	- 0.68

*Note.*  $z < - 1.96$  = criterion 2 superior to criterion 1;  $z > 1.96$  = criterion 1 superior to criterion 2.

### 5.3 Discussion

As shown in the previous chapter, considerable discrepancy exists between parent and teacher reports of child behaviour, and is more pronounced for children born very preterm than full-term. In order to improve the clinical validity and prognostic utility of parent and teacher reports, classification of child behaviour difficulties as situational and pervasive symptoms (based on the extent of agreement between parent and teacher reports) has been recommended. Accordingly, this study examined the prevalence of situational and pervasive inattention/hyperactivity symptoms at ages 4 and 6 (corrected) and at age 9 years (uncorrected) in a regional cohort of children born very preterm. Of particular interest was to cross-validate the classification of children with situational and pervasive inattention/hyperactivity symptoms based on parent and teacher ratings of child behaviour across the ages of 4 to 9, for *DSM-IV* diagnosis of ADHD at age 9 years. Methodological strengths of the

current study include: (1) use of both situational and pervasive symptoms classification to determine the nature and extent of child behavioural difficulties; (2) longitudinal evaluation of behavioural symptoms, including the use of persistent symptoms criteria; and (3) the use of a structured psychiatric interview to identify children meeting clinical criteria for an ADHD diagnosis.

Consistent with previous longitudinal follow-up research (Delobel-Ayoub et al., 2009; Delobel-Ayoub et al., 2006; Larroque et al., 2011), results from this study showed that inattention/hyperactivity difficulties in children born very preterm emerge early, and can be easily recognised using standardised behavioural screening tools. Specifically, children born very preterm had a 2-fold increased risk than their full-term peers of being screened as positive for inattention/hyperactivity difficulties across all the ages assessed, with situational symptoms being more prevalent. Rates of more severe, pervasive symptoms were lower and comparable to the full-term group. Furthermore, comparisons of the prevalence of pervasive inattention/hyperactivity in this study with those reported by the EPICure study at age 6 years (Samara et al., 2008) showed that rates of pervasive symptoms were much lower in the current study across all the assessment time-points (7% – 12% vs. 31%). This difference may be due to the fact that the EPICure sample was a high-risk group limited to a much narrower gestation (< 26 weeks).

In line with previous research (Johnson et al., 2010b; Johnson & Marlow, 2011), results from this study also showed that children born very preterm are at an elevated risk of *DSM-IV* ADHD diagnosis at age 9 years, compared to children born full-term. Although the prevalence of ADHD diagnosis within the very preterm group in the current study is higher than those reported by previous studies using similar diagnostic measures (Johnson & Marlow, 2011), the odds ratios across these studies were comparable. The difference in rates of ADHD diagnosis may be due to the fact children in this study were assessed at a younger age than all the previous studies.

Examination of the predictive validity of behavioural inattention/hyperactivity symptoms at ages 4 and 6, for a clinical diagnosis of ADHD at age 9 years showed that children manifesting pervasive symptoms were much more likely than those with situational symptoms to receive a subsequent psychiatric diagnosis of ADHD.

While these findings were consistent across both study groups, it was more prominent for children born very preterm than full-term, suggesting potentially greater stability of symptoms over time for these children. These results are similar to findings from mainstream child psychiatric research studies (Ablow et al., 1999; Goodman, Ford, Simmons et al., 2000; Mannuzza, Klein, & Moulton, 2002), which show that children exhibiting pervasive behavioural problems are subject to more severe and persistent impairments of greater long-term clinical significance than children with situational difficulties. Furthermore, specificity (i.e., the ability to correctly identify those without the disorder) and sensitivity indices (i.e., the ability to correctly identify those with the disorder) of inattention/hyperactivity symptoms at ages 4 and 6 years for an ADHD diagnosis, were generally comparable across study groups. However, an important finding of the current study is that persistent inattention/hyperactivity symptoms shown by children born very preterm have better predictive validity than children born full-term. Specifically, sensitivity indices for persistent symptoms were found to be relatively higher for children born very preterm than full-term. Comparisons of the predictive validity of various classifications of behavioural inattention/hyperactivity symptoms in the current study highlighted different trends for children born very preterm and full-term. Inattention/hyperactivity symptoms shown by children born full-term at age 6 years can be as reliable marker as persistent symptoms shown at two or three time-points, for an ADHD diagnosis at age 9 years. In contrast, within the very preterm group, persistent inattention/hyperactivity symptoms shown at two or three time-points have been demonstrated to be the most accurate marker of a subsequent ADHD diagnosis.

Taken together, from a clinical perspective, the current study findings may have implications for neurobehavioural follow-up programmes of children born very preterm, which are as follows: (1) inattention/hyperactivity screening based on multiple independent informants of child behaviour provides optimal diagnostic and prognostic utility; (2) if child behaviour information is available at single time-point only, the use of pervasive symptoms criterion will provide better predictive validity than situational symptoms, for a subsequent clinical diagnosis of ADHD; (3) if child behaviour information is available at more than one time-point, the use of either pervasive or situational symptoms criteria will generally provide similar predictive

validity, for later ADHD diagnosis; (4) although repeated behaviour screening over time is highly recommended, it is equally important to decide an optimal threshold for further clinical referral. For example, in the current study symptoms at three time-points (though seems logical to be a better indicator) had very poor sensitivity for subsequent ADHD diagnosis indicating that it may be too stringent criterion. In contrast, symptoms at two or three time-points had considerable gains in sensitivity without compromises in specificity.

Given the exploratory nature of the current study, there are a number of limitations that need to be considered in the interpretation of these findings, as well as issues that could be addressed by future research. First, the sample size of children born full-term diagnosed with ADHD at age 9 years was very small ( $N = 7$ ). Thus, findings from this study may have limited generalisability due to low base rate; although sensitivity and specificity indices used to examine the predictive validity are considered to be base rate invariant. Second, given the research design of this study, it was not feasible to categorise persistent symptoms in an appropriate and nonoverlapping manner. Therefore, it will be necessary to compare the predictive validity of behavioural inattention/hyperactivity symptoms exhibited at two time-points only versus symptoms shown at three time-points only.

In conclusion, study findings show that children born very preterm are at an elevated risk of behavioural inattention/hyperactivity difficulties across the ages of 4 to 9 years. However, the risks are relatively modest for more severe, pervasive than situational problems. Findings also emphasise that early emerging behavioural inattention/hyperactivity problems shown by these children, and identified using standardised child behaviour screening measures, may have longer-term clinical and prognostic significance. However, it is important to consider these behavioural difficulties across more than one assessment time-point and based on multi-informant reports of child behaviour for better clinical validity.



## Chapter 6

### **Neonatal Cerebral Tissue Volumes Associated with Persistent ADHD Symptoms in Children Born Very Preterm**

As described in previous chapters, ADHD and its associated symptoms are the most common neurobehavioural problem affecting children born very preterm (Bhutta et al., 2002; Johnson et al., 2010b; Johnson & Marlow, 2011). Existing follow-up studies provide limited information about the extent to which these children exhibiting inattention/hyperactivity difficulties represent a stable group. Identifying children born very preterm subject to persistent ADHD symptoms is important as they are likely to be the most significantly impaired group in academic achievement, cognitive, and social functioning (Biederman et al., 2009; Biederman, Petty, Evans, Small, & Faraone, 2010).

To date, the neonatal neuropathological mechanisms that may place children born very preterm at an elevated risk of ADHD remain poorly understood. However, existing studies suggest perinatal cerebral injuries and atypical cerebral structural development as two potential mechanisms for pathogenesis of ADHD symptoms in children born very preterm (Abernethy et al., 2002; Indredavik et al., 2010; Nosarti et al., 2005; Whitaker et al., 2011).

Perinatal cerebral injuries, particularly germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH) with ventriculomegaly or periventricular haemorrhagic infarction have been shown to be associated with ADHD symptoms during early school age and adolescence (Indredavik et al., 2010; Whitaker et al., 2011; Whitaker et al., 1997). However, with advances in neuroprotection approaches, incidence of these severe cerebral injuries is declining (Volpe, 2003). Recently, noncystic periventricular leukomalacia or diffuse white matter injury, readily detected using neonatal MRI, has been recognised as the emerging characteristic pattern of perinatal cerebral injury in children born very preterm (Volpe, 2003, 2009). Moreover, perinatal diffuse white matter injury has been

shown to be a potential early predictor of long-term cognitive and behavioural deficits in these children (Clark & Woodward, 2010; Edgin et al., 2008; Woodward et al., 2011). Nonetheless, research to date has not examined the relationships between perinatal diffuse cerebral white matter injury and subsequent risks of ADHD in children born very preterm.

Atypical cerebral development in children born very preterm is characterised by delayed maturation or impaired brain growth, as a result of perinatal cerebral injuries and/or clinical complications associated with premature birth (Inder et al., 1999; Inder et al., 2005; Thompson et al., 2007). Importantly, global and regional neuroanatomical alterations evident at term age in these children have been shown to be associated with later neurodevelopmental outcomes, particularly oculomotor function, working memory, mental and psychomotor development (Peterson et al., 2003; Shah et al., 2006; Thompson et al., 2008; Woodward et al., 2005). Associations between ADHD symptoms and poor cerebral structural growth and maturation, particularly the hippocampus, corpus callosum, and caudate nucleus have also been found in adolescents who were born very preterm (Abernethy et al., 2002; Indredavik, Vik et al., 2005; Nosarti et al., 2005). However, the relationship between neonatal cerebral development and subsequent risk of ADHD in children born very preterm remains unclear. Accordingly, the specific aims of this study are as follows:

- (1) To evaluate the risk of persistent ADHD symptoms between the ages of 4 and 9 years in children born very preterm and full-term.
- (2) To examine associations between qualitatively defined cerebral white matter abnormalities on MRI at term equivalent age and subsequent risk of persistent ADHD symptoms in children born very preterm.
- (3) To examine the relationships between neonatal cerebral structural development based on volumetric measures of global and regional cerebral tissues, identified using quantitative evaluation of MRI at term equivalent age, and children's subsequent risk of persistent ADHD symptoms.

## **6.1 Methods**

### **6.1.1 Sample**

The study sample consisted of a regionally representative cohort of 110 infants born

very preterm and 113 infants born full-term, who were followed-up as part of a prospective longitudinal study. Neonatal clinical characteristics and family backgrounds of the two study groups have been described previously in section 3.1 (pages 55 – 57). Excluding deaths ( $n = 3$ ), 92.5% ( $n = 99$ ) of infants born very preterm and 93.8% ( $n = 106$ ) of infants born full-term were assessed at all three follow-up ages of interest in this study (i.e., 4, 6, and 9 years).

### **6.1.2 Procedure**

At term equivalent, all infants born very preterm and 10 infants born full-term underwent an MRI that was analysed using qualitative and quantitative measures of cerebral injury/abnormality and structural development. At ages 4 and 6 (corrected for the extent of prematurity) and at age 9 years (uncorrected), all study children attended a comprehensive neurodevelopmental assessment that included a screening for behavioural inattention/hyperactivity symptoms, and a structured psychiatric evaluation for an ADHD clinical diagnosis at age 9 years.

### **6.1.3 Measures**

#### *MRI Procedure (Term Age)*

At term equivalent, all infants born very preterm underwent a cerebral structural MRI scan without sedation. In addition, a subsample of 10 infants born full-term was also scanned on the week of their due date. Prior to imaging, infants were fed, wrapped, swaddled, and placed in a vacuum-fixation bean bag (Vac Fix; S & S X-ray Products, Brooklyn, NY) to minimize motion artefacts. Images were acquired using a 1.5 Tesla General Electric Signa System (GE-Medical Systems, Milwaukee, WI, USA). Two different imaging protocols were applied: (1) a three-dimensional T1 spoiled gradient recalled sequence (1.5 mm coronal slices, flip angle 45°, repetition time 35 ms, echo time 5 ms, field of view 18 cm, matrix 256 × 256), and (2) a T2 double-echo (interleaved acquisition) spin echo sequence (3 mm axial slices, repetition time 3000 ms, echo times 36 ms and 162 ms, field of view 18 cm, matrix 256 × 256). Images were analysed for neonatal cerebral injuries and/or abnormalities utilising qualitative structural and quantitative volumetric techniques.

#### *Qualitative Image Analysis*

MRI images were qualitatively analysed for cerebral white matter abnormality using

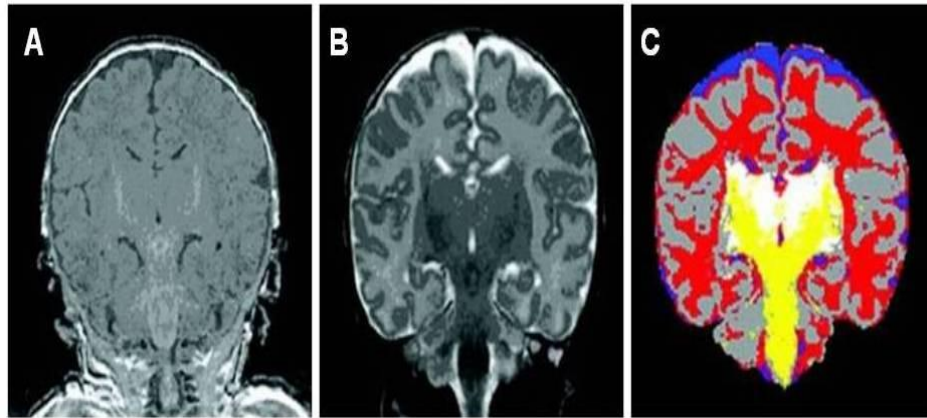
a standardised scoring scale (Inder et al., 2003; Woodward et al., 2006). Scans were rated by two independent raters, including a paediatric neuroradiologist and a neonatal neurologist. Inter-rater agreement was 95%, with a consensus rating given to discrepant cases. White matter abnormality was assessed on a 3-point scale of 1 (not present/normal), 2 (mild/focal), 3 (moderate/severe/extensive) across the following five domains: nature and extent of white matter signal abnormality, periventricular white matter volume loss, cystic abnormalities, ventricular dilatation, and thinning of the corpus callosum. An overall white matter abnormality score was also created by summing scores across all the five domains. Based on the overall white matter composite score, children were further classified as having none (scores of 5 – 6), mild (scores of 7 – 9), or moderate to severe white matter abnormality (scores of 10 – 15).

#### Quantitative Volumetric Analysis

Postacquisition image processing for quantitative volumetric analysis was undertaken on a computer workstation. A sequence of image processing algorithms was used to reduce imaging system noise and align T1 and T2 images for tissue segmentation (Huppi et al., 1998). The segmentation was done using a spatially varying model through alignment with an anatomical template of a 40-week-old infant (Warfield, Kaus, Jolesz, & Kikinis, 2000). As shown in Figure 6.1 (page 95), each MRI slice was segmented into five different cerebral tissue subtypes: cortical grey matter, subcortical grey matter, myelinated white matter, unmyelinated white matter, and cerebrospinal fluid. The total cerebral tissue volume was computed as the sum total of all the grey and white matter. The intracranial cavity volume was computed as the sum total of all the grey matter, white matter, and cerebrospinal fluid within the skull.

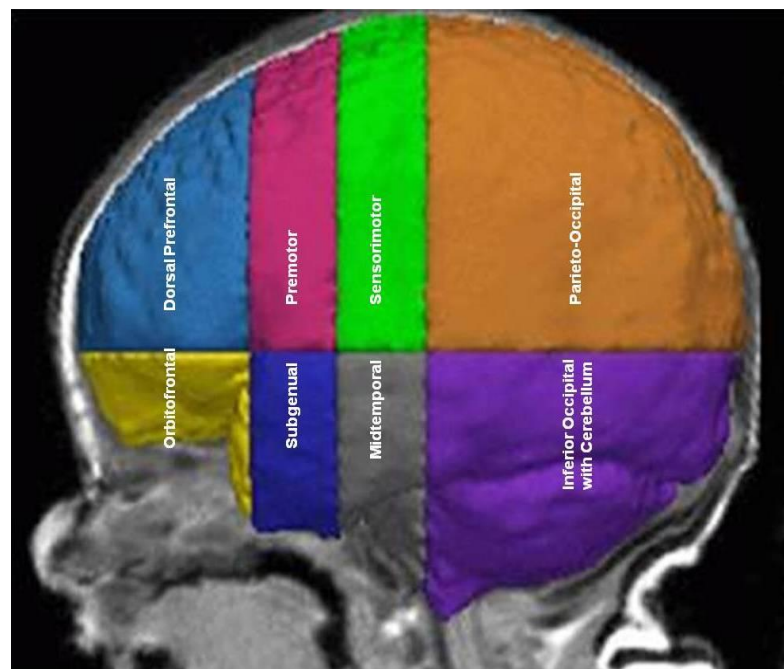
For regional analysis of cerebral tissue volumes, each brain image was segmented (see Figure 6.2, page 95) using the Talairach parcellation scheme (Peterson et al., 2003; Peterson et al., 2000) into eight anatomical subregions: dorsal prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, midtemporal, parieto-occipital, and inferior occipital with cerebellum, using a combination of one axial and three coronal planes. The axial plane was passed through the anterior commissure and posterior commissure line. The first coronal plane was positioned at the most

anterior part of the genu of the corpus callosum, the second coronal plane at the anterior border of the anterior commissure, and the third coronal plane through the posterior commissure.



**Figure 6.1:** Postacquisition cerebral tissue segmentation atlas.

(A) Coronal T1-weighted SPGR image, (B) coronal T2-weighted image; co-registered to create (C) cerebral tissue segmentation atlas, representing cortical grey matter (grey), subcortical grey matter (white), myelinated white matter (yellow), unmyelinated white matter (red), and cerebrospinal fluid (blue).



**Figure 6.2:** Parcellated image of cerebral subregions (left hemisphere).

Quantitative volumetric postacquisition image processing was feasible for 82% ( $n = 90$ ) of children born very preterm, with the remaining scans being affected by motion artefacts and MRI signal intensity errors that limited registration and tissue segmentation. There were no significant differences in neonatal clinical and social background characteristics between children included and excluded from this analysis due to image processing problems ( $p > .05$ ). For the full-term group, postacquisition image processing was feasible for 8 out of 10 children.

#### *Persistent ADHD Symptoms (Ages 4, 6, 9 Years)*

As described earlier in subsection 5.1.3 (pages 77 – 78), inattention/hyperactivity symptoms at ages 4, 6, and 9 years were assessed based on parent and teacher ratings of child behaviour using the Inattention/Hyperactivity subscale of the SDQ. An ADHD clinical diagnosis at age 9 years was also determined based on the DAWBA structured psychiatric interview. For this study, children were classified as showing persistent ADHD symptoms if they met the clinical cut-point for behavioural inattention/hyperactivity symptoms (either situational or pervasive) on the SDQ across all the three assessment time-points between the ages of 4 and 9, along with an ADHD psychiatric diagnosis at age 9 years.

#### **6.1.4 Data Analysis**

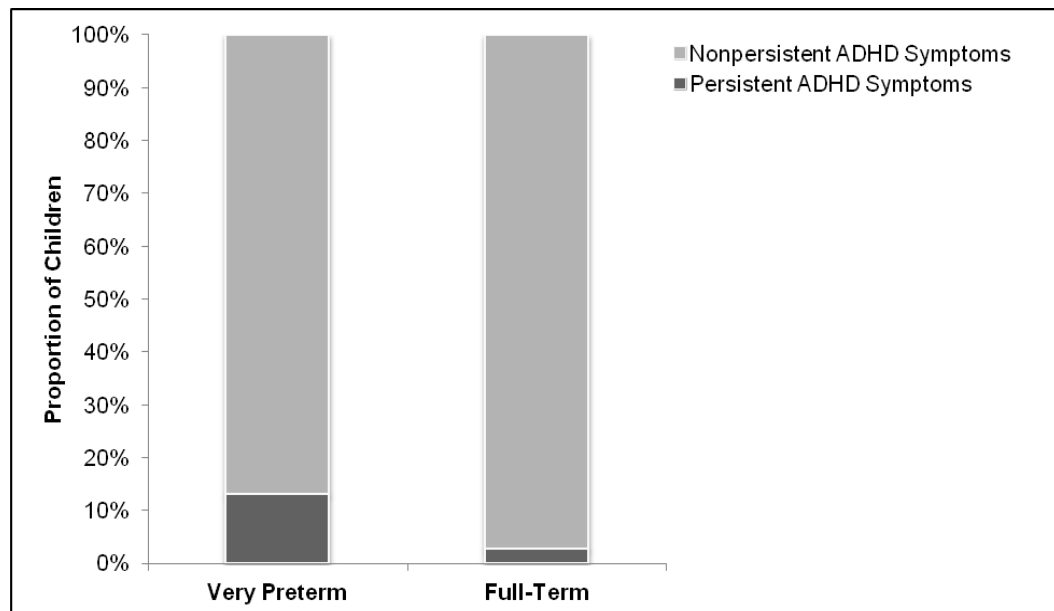
Data analysis was conducted in three stages. First, between-group differences in the proportions of children with persistent ADHD symptoms were examined using the chi-square test for independence; with odds ratio (OR) and 95% confidence interval (CI) calculated to evaluate the strength of associations. Second, within the very preterm group, associations between neonatal cerebral white matter abnormality based on qualitative MRI measures at term equivalent and later risk of persistent ADHD symptoms were examined using the chi-square test for independence or Fisher's exact test as appropriate, with tests for linear trend. Third, associations between neonatal cerebral tissue volumes and persistent ADHD symptoms were examined using one-way analysis of variance, with tests for linear trend. Results for this analysis have been reported in terms of both absolute volumes of each tissue subtype and relative proportions within the intracranial cavity. As the proportions of cerebral tissues differ greatly in absolute volumes; results have been further presented as relative differences in order to estimate the magnitude of volumetric

reductions for different tissue subtypes. Relative differences were calculated by dividing the absolute mean difference of each tissue by the absolute mean volume of the control groups, after adjusting for the intracranial cavity volume. Subsequently, logistic regression model was fitted to the data to examine associations between total global cerebral tissue volumes and subsequent risk of persistent ADHD symptoms in children born very preterm, after adjustment for a range of neonatal clinical, neurological, and social factors.

## 6.2 Results

### 6.2.1 Prevalence of Persistent ADHD Symptoms

As shown in Figure 6.3 (page 97), very preterm birth was associated with an increased risk of persistent ADHD symptoms across the ages of 4 to 9 years. Specifically, 13.1% ( $n = 13$ ) of children born very preterm compared to 2.8% ( $n = 3$ ) of children born full-term showed persistent ADHD symptoms [ $\chi^2(1, n = 205) = 7.5$ ,  $p = .006$ ; OR: 5.2; 95% CI: 1.4 – 18.8]. These findings remain unchanged after adjustment for the effects of child sex and family socioeconomic status ( $p = .02$ ; OR: 5.0; 95% CI: 1.3 – 18.7).



**Figure 6.3:** Prevalence of persistent and nonpersistent ADHD symptoms between the ages of 4 and 9 years.

### **6.2.2 Associations between Neonatal Cerebral White Matter Abnormality and Risk of Persistent ADHD Symptoms**

Table 6.1 (page 99) describes the associations between neonatal cerebral white matter abnormalities as evident on MRI at term equivalent age and risk of persistent ADHD symptoms during early childhood. This analysis was confined to very preterm group only. As shown, across all the white matter abnormality measures, there were no evidence of any significant linear associations between severity of neonatal white matter abnormality and later risk of persistent ADHD symptoms ( $p > .05$ ). Although not statistically significant, there was a tendency for children classified as having moderate to severe white matter abnormality being at a relatively higher risk of persistent ADHD symptoms, compared to children with mild or no white matter abnormality (22% vs. 10.0% – 12%). Specifically, children classified as having extensive diffuse white matter signal changes in the periventricular white matter and marked reductions in white matter volumes were relatively more likely than children without those severe neonatal neurological abnormalities to be at risk of persistent ADHD symptoms. Furthermore, although 33% of children with extensive cystic abnormalities compared to 11% with focal cystic abnormalities were at risk of persistent ADHD symptoms, these results should be interpreted with caution given the small number of children classified as having these injuries.



**Table 6.1:** Associations between Neonatal Cerebral White Matter Abnormality and Risk of Persistent ADHD Symptoms in Children Born Very Preterm

	ADHD Symptoms		$\chi^2$	<i>p</i>
	Ages 4 to 9 Years			
	Nonpersistent ( <i>N</i> = 85)	Persistent ( <i>N</i> = 13)		
<b>White matter abnormality</b>				
None, % ( <i>n</i> )	90.0 (18)	10.0 (2)		
Mild, % ( <i>n</i> )	88.3 (53)	11.7 (7)		
Moderate to severe, % ( <i>n</i> )	77.8 (14)	22.2 (4)	1.2	.34
<b>White matter signal abnormality</b>				
Normal, % ( <i>n</i> )	90.7 (39)	9.3 (4)		
Focal ( $\leq 2$ regions), % ( <i>n</i> )	85.0 (34)	15.0 (6)		
Extensive ( $\geq 2$ regions), % ( <i>n</i> )	80.0 (12)	20.0 (3)	1.3	.30
<b>Periventricular white matter volume loss</b>				
Normal, % ( <i>n</i> )	90.0 (45)	10.0 (5)		
Mild to moderate, % ( <i>n</i> )	85.4 (35)	14.6 (6)		
Diffuse, % ( <i>n</i> )	71.4 (5)	28.6 (2)	1.6	.24
<b>Cystic abnormalities</b>				
None, % ( <i>n</i> )	87.2 (75)	12.8 (11)		
Focal (single, < 2 mm), % ( <i>n</i> )	88.9 (8)	11.1 (1)		
Extensive (multiple), % ( <i>n</i> )	66.7 (2)	33.3 (1)	0.5	.50
<b>Ventricular dilatation</b>				
Normal, % ( <i>n</i> )	89.2 (33)	10.8 (4)		
Mild to moderate, % ( <i>n</i> )	84.8 (39)	15.2 (7)		
Marked dilatation, % ( <i>n</i> )	86.7 (13)	13.3 (2)	0.2	.83
<b>Thinning of the corpus callosum</b>				
Normal, % ( <i>n</i> )	92.0 (23)	8.0 (2)		
Focal, % ( <i>n</i> )	83.3 (50)	16.7 (10)		
Global, % ( <i>n</i> )	92.3 (12)	7.7 (1)	0.1	.81

Note. Degrees of Freedom = 1.

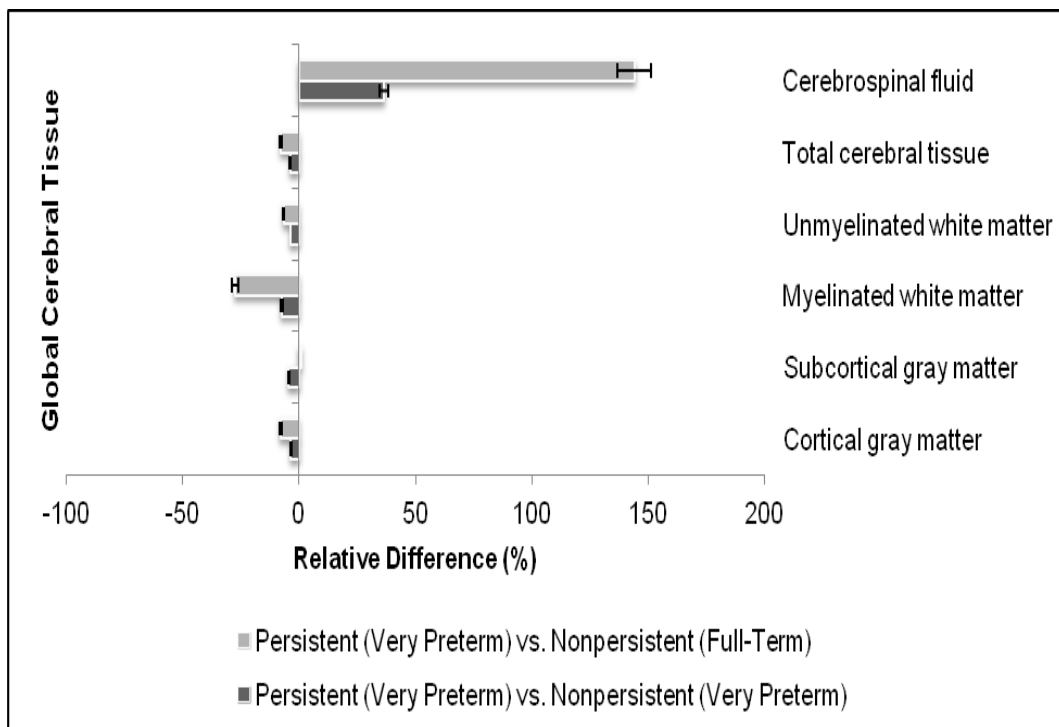
### 6.2.3 Associations between Neonatal Global Cerebral Tissue Volumes and Risk of Persistent ADHD Symptoms

Figure 6.4 (page 101) and Table 6.2 (pages 102 – 103) describe the associations between neonatal MRI measures of global cerebral tissue volumes at term equivalent age and children's later risk of persistent ADHD symptoms. This analysis was confined to children born very preterm and a subsample of children born full-term with nonpersistent ADHD symptoms who also underwent a neonatal cerebral structural MRI scan. As shown in Table 6.2, although linear association between absolute volumes of total cerebral tissues and risk of persistent ADHD symptoms failed to reach statistical significance [ $F(1, 83) = 2.5, p = .12$ ]; clear reductions in total cerebral tissue volumes were evident in terms of relative proportion of total cerebral tissues within the intracranial cavity for children born very preterm showing persistent ADHD symptoms [ $F(1, 83) = 11.7, p = .001$ ]. Specifically, 4% to 8% less total cerebral tissues at term age were found in children born very preterm at risk of persistent ADHD symptoms during early childhood, as compared to the control groups (see Figure 6.4).

Consistent with the loss of total cerebral tissue volumes, concomitant volumetric increase of cerebrospinal fluid (absolute volumes and relative proportions within intracranial cavity) at term equivalent age was linearly associated with an increase in risk of persistent ADHD symptoms in children born very preterm ( $p \leq .002$ ). Specifically, as shown in Figure 6.4, children born very preterm exhibiting persistent ADHD symptoms had 15.1 ml (36%) and 33.3 ml (144%) more cerebrospinal fluid at term equivalent age, compared to children born very preterm and full-term showing nonpersistent ADHD symptoms, respectively, after adjusting for the intracranial cavity volume.

Volumetric reductions of total cerebral tissues and corresponding increase of cerebrospinal fluid in children born very preterm with persistent ADHD symptoms appeared to be primarily due to the loss of myelinated white matter. Although not statistically significant, linear trends were evident suggesting possible associations between myelinated white matter volumes at term equivalent age and subsequent risk of persistent ADHD symptoms ( $p \leq .11$ ). As shown in Figure 6.4, children born very preterm at risk of persistent ADHD symptoms had 1.1 ml (7%) and 4.7 ml

(27%) less myelinated white matter than children born very preterm and full-term exhibiting nonpersistent ADHD symptoms, respectively, after adjustment for the intracranial cavity volume. Furthermore, as shown in Table 6.2, no significant linear associations were evident between neonatal global cerebral volumes (absolute and relative proportions within intracranial cavity) of cortical grey matter ( $p \geq .33$ ), subcortical grey matter ( $p \geq .94$ ), unmyelinated white matter ( $p \geq .32$ ), and children's later risk of persistent ADHD symptoms.



**Figure 6.4:** Relative difference in global cerebral tissue volumes.

**Table 6.2:** Associations between Neonatal Global Cerebral Tissue Volumes and Risk of Persistent ADHD Symptoms

Global Cerebral Tissue Volume	ADHD Symptoms, Ages 4 to 9 Years			F	p
	Nonpersistent		Persistent		
	Full-Term (N = 6)	Very Preterm (N = 67)	Very Preterm (N = 13)		
<b>Cortical grey matter</b>					
Absolute volume, ml	193.4 ± 27.1	177.9 ± 38.3	176.5 ± 33.2	0.8	.36
Relative percentage within intracranial cavity	41.5 ± 5.9	39.3 ± 6.6	38.4 ± 6.4	0.9	.33
<b>Subcortical grey matter</b>					
Absolute volume, ml	12.3 ± 3.0	12.6 ± 4.2	12.3 ± 3.5	< 0.001	1.0
Relative percentage within intracranial cavity	2.6 ± 0.6	2.8 ± 0.9	2.7 ± 0.7	0.006	.94
<b>Myelinated white matter</b>					
Absolute volume, ml	17.8 ± 8.2	13.4 ± 5.7	12.9 ± 5.4	2.9	.09
Relative percentage within intracranial cavity	3.8 ± 1.6	3.0 ± 1.2	2.8 ± 1.2	2.7	.11

Note. Table 6.2 continued on following page. ± = Mean ± Standard Deviation; Degrees of Freedom = 1.

**Table 6.2:** Associations between Neonatal Global Cerebral Tissue Volumes and Risk of Persistent ADHD Symptoms

Global Cerebral Tissue Volume	ADHD Symptoms, Ages 4 to 9 Years			F	p
	Nonpersistent		Persistent		
	Full-Term (N = 6)	Very Preterm (N = 67)	Very Preterm (N = 13)		
<b>Unmyelinated white matter</b>					
Absolute volume, ml	218.0 ± 26.2	206.2 ± 31.8	202.5 ± 31.5	1.0	.32
Relative percentage within intracranial cavity	46.7 ± 5.1	45.9 ± 6.0	43.9 ± 5.6	0.9	.34
<b>Total cerebral tissue</b>					
Absolute volume, ml	441.4 ± 25.2	410.1 ± 49.9	404.2 ± 39.6	2.5	.12
Relative percentage within intracranial cavity	94.6 ± 2.6	91.0 ± 4.0	87.8 ± 4.9	11.7	.001
<b>Cerebrospinal fluid</b>					
Absolute volume, ml	25.0 ± 12.7	41.0 ± 19.4	57.7 ± 26.5	10.7	.002
Relative percentage within intracranial cavity	5.4 ± 2.6	9.0 ± 4.0	12.2 ± 4.9	11.7	.001

Note. ± = Mean ± Standard Deviation; Degrees of Freedom = 1.

#### 6.2.4 Neonatal Predictors of Persistent ADHD Symptoms

Table 6.3 (page 106) shows the associations between neonatal clinical and social risk factors and children's later risk of persistent ADHD symptoms during early childhood. This analysis was confined to very preterm group only. As shown, there were no significant differences in terms of gestational age and birth weight between children born very preterm showing persistent and nonpersistent ADHD symptoms ( $p \geq .40$ ). Although not statistically significant, relative to children born very preterm exhibiting nonpersistent ADHD symptoms, those children at risk of persistent ADHD symptoms were more likely to be male (48% vs. 69%); required supplementary oxygen at 36 weeks of life (33% vs. 54%); administered postnatal dexamethasone (5% vs. 15%); suffered from patent ductus arteriosus (42% vs. 62%); and had ultrasound evidence of cystic periventricular leukomalacia (5% vs. 15%). The only significant perinatal clinical complication associated with an increased risk of persistent ADHD symptoms was grade III or IV intraventricular haemorrhage identified using neonatal cranial ultrasound [ $\chi^2(1, n = 97) = 8.4, p = .02$ ].

In terms of social risk factors, younger maternal age was significantly more likely to be associated with children's later risk of persistent ADHD symptoms [ $t(97) = 2.1, p = .04$ ]. In addition, although not statistically significant, being born in minority ethnic communities also had a tendency for elevated risks of persistent ADHD symptoms in children born very preterm [ $\chi^2(1, n = 99) = 3.4, p = .09$ ].

Finally, the extent to which neonatal clinical, social, and neurological factors, including MRI measures of overall cerebral white matter abnormality and loss of global total cerebral tissue volumes in children born very preterm, made unique and independent contribution in placing children at subsequent risk of persistent ADHD symptoms during early childhood was assessed. For retaining variables in the final regression model,  $p < .10$  criterion was used due to the potential loss of statistical power resulting from decline in sample sizes. Results showed that after taking into account all the variables listed in Table 6.3, the proportion of total cerebral tissues within the intracranial cavity at term equivalent age was an independent predictor of persistent ADHD symptoms ( $\beta = -0.15, p = .049$ ), although this was marginally significant. In addition, ultrasound evidence of grade III or IV intraventricular haemorrhage was also a significant independent predictor of persistent ADHD

symptoms ( $\beta = 2.96$ ,  $p = .02$ ). There were no interactive relationships evident between these risk factors. Jointly these two neonatal variables explained between 13.2% (Cox & Snell  $R^2$ ) and 22.9% (Nagelkerke  $R^2$ ) of the variance in very preterm children's later risk of persistent ADHD symptoms, and correctly classified 87% of the cases.

**Table 6.3:** Associations between Neonatal Clinical and Social Characteristics and Risk of Persistent ADHD Symptoms in Children Born Very Preterm

Measure	ADHD Symptoms		<i>t</i> / $\chi^2$	<i>p</i>
	Ages 4 to 9 Years			
	Nonpersistent ( <i>N</i> = 86)	Persistent ( <i>N</i> = 13)		
<b>Infant clinical characteristics</b>				
Gestational age at birth, <i>M</i> ± <i>SD</i> , weeks	27.9 ± 2.3	27.3 ± 2.8	0.9	.40
Birth weight, <i>M</i> ± <i>SD</i> , grams	1,061.5 ± 322.2	1,062.3 ± 286.5	0.01	.99
Male sex, %	47.7	69.2	2.1	.15
Twin birth, %	34.9	15.4	2.0	.21
Intrauterine growth restriction <sup>a</sup> , %	10.5	15.4	0.3	.64
Oxygen therapy at 36 weeks, %	32.6	53.6	2.2	.21
Antenatal corticosteroid use, %	86.0	76.9	0.7	.41
Postnatal dexamethasone use, %	4.7	15.4	2.3	.18
Necrotising enterocolitis, %	8.1	0	1.1	.59
Patent ductus arteriosus, %	41.9	61.5	1.8	.18
Intraventricular haemorrhage grade III or IV <sup>b</sup> , %	3.5	25.0	8.4	.02
Cystic periventricular leukomalacia, %	4.7	15.4	2.2	.18
<b>Social background characteristics</b>				
Maternal age, <i>M</i> ± <i>SD</i> , years	31.3 ± 4.8	28.2 ± 6.2	2.1	.04
Mother not a high school graduate, %	39.5	46.2	0.2	.65
Single parenthood, %	16.3	15.4	0.01	1.0
Minority ethnicity, %	11.6	30.8	3.4	.09
Family socioeconomic status <sup>c</sup> Semiskilled/unskilled/unemployed, %	29.1	38.5	0.5	.53

*Note.* Degrees of Freedom = 97 (*t*); 1 ( $\chi^2$ ).

<sup>a</sup>Birth weight more than 2 standard deviations below the mean for gestational age.

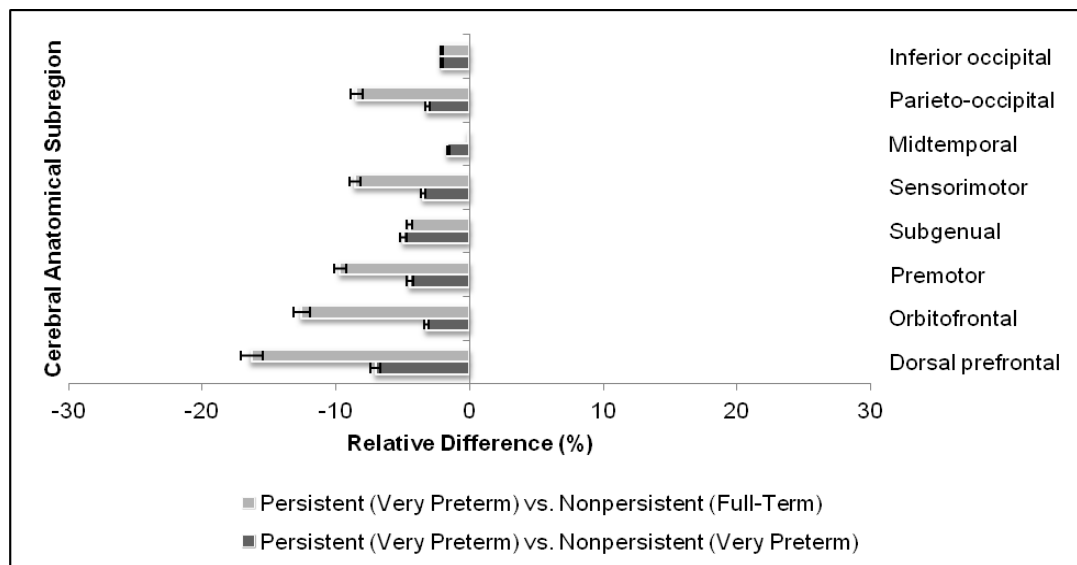
<sup>b</sup>Based on Papile classification.

<sup>c</sup>Assessed using the Elley-Irving Socioeconomic Index (Elley & Irving, 2003).



### 6.2.5 Associations between Neonatal Regional Cerebral Tissue Volumes and Risk of Persistent ADHD Symptoms: An Exploratory Analysis

Table 6.4 (pages 108 – 110) shows the associations between regional total cerebral tissue volumes at term equivalent age and children’s risk of persistent ADHD symptoms between the ages of 4 and 9 years. This exploratory analysis showed no significant linear associations between absolute volumes of neonatal regional total cerebral tissues across all the eight anatomical subregions, and children’s later risks of persistent ADHD symptoms ( $p > .05$ ). However, clear reductions in regional total cerebral tissue volumes were evident in terms of relative proportions of total cerebral tissues within each subregion ( $p \leq .02$ ). Specifically, compared to children born full-term and very preterm showing nonpersistent ADHD symptoms, children born very preterm at risk of persistent ADHD symptoms had the largest volumetric reductions in the proportion of total cerebral tissues within the dorsal prefrontal [ $F(1, 83) = 11.0, p = .001$ ], orbitofrontal [ $F(1, 83) = 5.2, p = .02$ ], premotor [ $F(1, 83) = 10.3, p = .002$ ], sensorimotor [ $F(1, 83) = 12.7, p = .001$ ], and parieto-occipital subregions [ $F(1, 83) = 9.5, p = .003$ ]. As shown in Figure 6.5 (page 107), among all the subregions, total cerebral tissue volume in the dorsal prefrontal region showed the largest reductions. Children born very preterm at risk of persistent ADHD symptoms had 3.2 ml (7%) and 8.2 ml (16%) less total cerebral tissues in the dorsal prefrontal region than very preterm and full-term children showing nonpersistent ADHD symptoms, respectively, after adjusting for intracranial cavity volume.



**Figure 6.5:** Relative difference in total regional cerebral tissue volumes.

**Table 6.4:** Associations between Neonatal Regional Total Cerebral Tissue Volumes and Risk of Persistent ADHD Symptoms

Regional Cerebral Tissue Volume	ADHD Symptoms, Ages 4 to 9 Years			F	p
	Nonpersistent		Persistent		
	Full-Term (N = 6)	Very Preterm (N = 67)	Very Preterm (N = 13)		
<b>Dorsal prefrontal region</b>					
Absolute volume, ml	51.4 ± 15.5	44.7 ± 9.6	44.8 ± 9.1	1.8	.19
Relative percentage within intracranial cavity	92.1 ± 5.5	83.7 ± 8.3	78.8 ± 8.3	11.0	.001
<b>Orbitofrontal region</b>					
Absolute volume, ml	11.5 ± 5.3	9.1 ± 3.8	8.7 ± 3.9	2.0	.16
Relative percentage within intracranial cavity	93.5 ± 3.0	87.5 ± 8.4	83.8 ± 10.8	5.2	.02
<b>Premotor region</b>					
Absolute volume, ml	56.6 ± 9.2	50.6 ± 8.3	50.0 ± 6.3	2.8	.10
Relative percentage within intracranial cavity	93.0 ± 2.6	88.8 ± 5.1	85.0 ± 5.7	10.3	.002

Note. Table 6.4 continued on following page. ± = Mean ± Standard Deviation; Degrees of Freedom = 1.

**Table 6.4:** Associations between Neonatal Regional Total Cerebral Tissue Volumes and Risk of Persistent ADHD Symptoms

Regional Cerebral Tissue Volume	ADHD Symptoms, Ages 4 to 9 Years			F	p
	Nonpersistent		Persistent		
	Full-Term (N = 6)	Very Preterm (N = 67)	Very Preterm (N = 13)		
<b>Subgenual region</b>					
Absolute volume, ml	22.5 ± 6.3	22.6 ± 4.8	21.3 ± 4.3	0.2	.63
Relative percentage within intracranial cavity	84.5 ± 6.6	84.8 ± 5.3	80.7 ± 5.2	2.1	.15
<b>Sensorimotor region</b>					
Absolute volume, ml	69.5 ± 7.2	55.0 ± 12.1	57.7 ± 18.0	3.4	.07
Relative percentage within intracranial cavity	96.9 ± 1.7	92.7 ± 4.1	89.6 ± 5.2	12.7	.001
<b>Midtemporal region</b>					
Absolute volume, ml	32.5 ± 7.3	31.2 ± 5.6	30.4 ± 5.4	0.5	.46
Relative percentage within intracranial cavity	91.5 ± 3.8	92.7 ± 2.9	91.3 ± 3.4	0.01	.93

Note. Table 6.4 continued on following page. ± = Mean ± Standard Deviation; Degrees of Freedom = 1.

**Table 6.4:** Associations between Neonatal Regional Total Cerebral Tissue Volumes and Risk of Persistent ADHD Symptoms

Regional Cerebral Tissue Volume	ADHD Symptoms, Ages 4 to 9 Years			F	p
	Nonpersistent		Persistent		
	Full-Term (N = 6)	Very Preterm (N = 67)	Very Preterm (N = 13)		
<b>Parieto-occipital region</b>					
Absolute volume, ml	126.0 ± 8.9	115.9 ± 16.6	115.5 ± 14.0	1.8	.18
Relative percentage within intracranial cavity	96.7 ± 2.7	91.9 ± 5.0	89.1 ± 5.8	9.5	.003
<b>Inferior occipital region with cerebellum</b>					
Absolute volume, ml	70.6 ± 13.5	80.3 ± 14.6	75.0 ± 11.6	0.4	.53
Relative percentage within intracranial cavity	97.4 ± 1.5	96.5 ± 2.2	95.3 ± 5.7	2.0	.16

Note. ± = Mean ± Standard Deviation; Degrees of Freedom = 1.

### 6.3 Discussion

As described in the previous chapter, children born very preterm are on average two times more likely than their full term peers of being screened as positive for behavioural inattention/hyperactivity symptoms between the ages of 4 and 9 years, based on parent and teacher ratings of child behavioural adjustment. However, findings from that study provide limited information about the extent to which children born very preterm exhibiting behavioural difficulties show those symptoms persistently over time. It is also important to identify potential neonatal neurological predictors of these persistent behavioural difficulties in order to target appropriate follow-up and timely interventions for optimising developmental outcomes.

Against this background, this prospective longitudinal follow-up study examined associations between neonatal cerebral development and injury/abnormality, and subsequent risks of persistent ADHD symptomatology in a regionally representative cohort of children born very preterm. To the best of the author's knowledge, this is the first study documenting the elevated risk of persistent ADHD symptoms in school-aged children born very preterm, and the extent to which such risks are explained by *in vivo* disruptions to typical cerebral development and white matter abnormalities identified on MRI at term equivalent age.

Results from this study show that children born very preterm are at a 5-fold increased risk of exhibiting persistent ADHD symptoms during the early school years, compared to their full-term peers (13.1% vs. 2.8%). In line with these results, findings from the follow-up of a large population-based cohort of low birth weight children (96% born preterm) reported a prevalence of 12.4% for a lifetime ADHD diagnosis (i.e., symptoms present from age 5 years) when assessed at age 16 years using the DISC-IV structured interview completed with parents (Whitaker et al., 2011). Taken together, these findings tend to suggest that almost one-tenth of children born very preterm are at an elevated risk of persistent behavioural inattention/hyperactivity difficulties. Although this rate is still high, it is reassuring that the rate is much lower than prevalence typically reported by cross-sectional studies across various ages. Thus, it can be speculated that a large proportion of children born very preterm showing inattentive/hyperactive behavioural difficulties may represent only transient problems and not life-time impairments.

The study findings also provide useful insights into neonatal neuropathological mechanisms that may account for increased risk of ADHD symptoms in survivors of very preterm birth. First, global total cerebral tissue volume at term equivalent age shown to be an independent predictor for later risk of persistent ADHD symptoms in this study, explains why some children born very preterm without any obvious evidence of perinatal cerebral white matter injury also exhibit ADHD symptoms or inattention/hyperactivity difficulties. This is in line with findings from a diffusion tensor imaging study, reporting significant associations between behavioural inattention/hyperactivity and lower fractional anisotropy values in the corpus callosum and internal capsules, in 11-year-old children who were born very preterm and without any cranial ultrasound evidence of perinatal cystic periventricular leukomalacia or intraventricular haemorrhage (Nagy et al., 2003). Associations between reductions in total cerebral tissue volumes and ADHD have also been consistently shown in the general population (Castellanos et al., 2002; Seidman et al., 2005). Specifically, as described in a recent review, 7 out of 12 studies included in the analysis found that children and adolescents at risk of ADHD on average show 3% to 5% reduction in total cerebral volumes compared to control groups (Seidman et al., 2005).

Second, findings from this study also help to specify the timing of neuroanatomical alterations often associated with risk of ADHD in very preterm populations. While previous research has demonstrated associations between elevated risk of ADHD and poor cerebral maturation; these studies have exclusively focused on adolescents who were born preterm (Abernethy et al., 2002; Nosarti et al., 2005; Skranes et al., 2007). One exception is a recent study highlighting the potential aetiological relationships between neonatal cerebral structural development and later risk of ADHD (Rogers et al., 2012). In that study, hippocampal volumes measured using quantitative MRI measures at term age were found to be predictive of parent reported inattention/hyperactivity problems in 5-year-old children who were born at less than 30 weeks of gestation (Rogers et al., 2012). Thus, findings from that study along with the current study findings tend to suggest that atypical cerebral growth and maturation, evident as early as during term equivalent age, may have longer-term clinical prognostic significance for development of ADHD symptoms in children born very preterm. It can also be speculated that neuroanatomical

alterations evident in adolescents who were born very preterm and are at risk of ADHD, may represent impaired developmental origins of cerebral maturational processes from the neonatal period, and the inability to eventually catch-up with typical development even over a considerable period of time.

Third, study findings also highlight the potential role of regional neuroanatomical development for an elevated risk of ADHD symptoms in children born very preterm. Specifically, children born very preterm with persistent ADHD symptoms were found to have loss of total cerebral tissue volumes within the dorsal prefrontal, orbitofrontal, premotor, sensorimotor, and parieto-occipital subregions among the eight parcellated anatomical subregions. This is in agreement with findings from the general population highlighting the role of frontal and parietal lobes in the development of ADHD symptomatology (Castellanos et al., 2002; Seidman et al., 2005). Reduced frontal lobe volumes in children with ADHD compared to control groups are a robust finding in general population. Specifically, as shown in a recent review, all the studies included in this analysis found smaller frontal lobe volumes in children and adolescents with ADHD, with nine studies reporting significant volumetric reductions in the dorsolateral prefrontal cortex (Seidman et al., 2005). Although the role of parietal cortex is generally underestimated in the pathogenesis of ADHD, a few studies have shown volumetric decrease in parietal lobe in children with ADHD (Castellanos et al., 2002; Seidman et al., 2005). From a theoretical perspective, the role of fronto-parietal network has been highlighted for alerting, orienting, and executive attentional networks, and thus may potentially have direct relevance in the pathophysiology of ADHD symptoms (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fan, Yanhong, Fossella, & Posner, 2001). Although occipital lobe has not generally been associated with ADHD symptoms, this anatomical region may be of interest due to its involvement in visual information processing (Seidman et al., 2005).

Consistent with previous research (O'Callaghan & Harvey, 1997; Whitaker et al., 2011; Whitaker et al., 1997), ultrasound evidence of perinatal grade III or IV intraventricular haemorrhage (comparable with GMH-IVH with ventriculomegaly or periventricular haemorrhagic infarction) was found to be a significant independent predictor for later risks of ADHD in children born very preterm. Specifically, in the

current study, 25% of children with persistent ADHD symptoms had grade III or IV intraventricular haemorrhage. In contrast, qualitatively defined MRI measures of neonatal cerebral white matter injury/abnormality were generally not found to be associated with elevated risk of persistent ADHD symptoms in this study. It can be speculated that the observed discrepancy between ultrasound and MRI measures of white matter abnormality in this study may reflect potential limitations in the qualitative evaluation of white matter abnormality, although any such explanations need to be considered as highly tentative.

Finally, limitations of this study need to be acknowledged while interpreting the findings. The first issue concerns the possibility of misclassification of cerebral tissues in regions where a single voxel contains overlapping tissue subtypes. However, the effects of any such misclassification error was minimised by single operator processing of all the images and may have reduced variability by systematically distributing the effects of this confounding factor throughout the study group. Second, there was limitation with the regional parcellation scheme used in this study. As parcellation was strictly based on anatomical localisation with the commissure, it was not possible to delineate cerebral anatomical regions based on their functional relevance. Third, postacquisition processing of MRI data was feasible for only 82% of the very preterm sample, with the remaining scans being affected by motion artefacts limiting registration and tissue segmentation. However, there was no evidence of any systematic bias as a result of the sample attrition owing to motion artefacts.

In conclusion, study findings suggest that children born very preterm are at an elevated risk of persistent ADHD symptoms during early childhood, compared to their full-term peers. This increased risk can at least in part be attributed to the detrimental effects of perinatal cerebral white matter injury and early disturbances to cerebral structural growth and maturation associated with very preterm birth. Hence, the study findings assist in understanding the neuropathological pathways associated with later risks of ADHD symptomatology in children born very preterm.



## Chapter 7

### General Discussion

As part of a prospective longitudinal follow-up study of a regionally representative, contemporary cohort of children born very preterm, three research studies were undertaken to examine a range of issues concerned with measurement of ADHD symptomatology and/or behavioural inattention/hyperactivity problems, and the potential neonatal neural mechanisms associated with subsequent risk of ADHD in these children. Specifically, the primary aims of these studies were as follows:

- (1) To examine the extent of agreement between parent and teacher reports of child behavioural adjustment using standardised screening measures.
- (2) To describe the prevalence of situational and pervasive behavioural inattention/hyperactivity problems based on agreement between parent and teacher reports of child behaviour, and the extent to which children classified as showing these behavioural difficulties meet the clinical criteria for a subsequent diagnosis of ADHD.
- (3) To assess the risk of persistent ADHD symptoms and the extent to which such risks can be explained by qualitatively defined cerebral white matter abnormalities and quantitative volumetric measures of cerebral structural development as identified on MRI at term equivalent age.

The key findings presented in chapters 4, 5, and 6 will be briefly reviewed below, specifically discussing the strengths and limitations of the current research, along with potential clinical and theoretical implications of the study findings. The thesis concludes by pointing out some directions for future research.

#### 7.1 Strengths and Limitations

While specific strengths and limitations of the research studies in this thesis have already been discussed in the previous chapters, some of the more general strengths and limitations pertaining to all the three studies are described below.

Strengths of the current study include: (1) prospective longitudinal follow-up research design; (2) unselected nature of the very preterm sample; (3) inclusion of a regionally representative full-term comparison group matched to the very preterm group for sex, birth date, and place of birth; (4) high rates of sample recruitment and retention over time; (5) extensive database of information regarding children's perinatal clinical history and social background information; (6) availability of neonatal MRI measures of cerebral white matter injury/abnormality and structural development; (7) child behaviour assessment based on face-to-face interview by a trained research nurse completed with primary caregiver; (8) the use of multiple, independent informants to evaluate child behavioural adjustment; (9) ADHD clinical diagnosis assigned by a child psychiatrist blinded to child's perinatal complications, and based on a structured psychiatric interview; and (10) defining clinical cut-points for behavioural screening measures based on score distribution of the full-term control group to avoid potential problems associated with use of test norms.

Limitations of the current study also need to be acknowledged while interpreting the findings. First, screening of behavioural inattention/hyperactivity problems was based on Inattention/Hyperactivity subscale of the SDQ. Although this subscale has been shown to have good concurrent and predictive validity, it should be noted that the scale included only five items to assess child inattentive/hyperactive behaviour. The limited number of assessment items may lead to an under- or over-estimation of the actual incidence of behavioural difficulties. In addition, although this subscale is shown to assess core symptoms of ADHD, the use of an ADHD-specific behavioural screening measure would have strengthened the findings of this study.

Second, behavioural inattention/hyperactivity difficulties or risk of ADHD clinical diagnosis in the current study were assessed as categorical outcomes. However, it was observed that a few children born very preterm that did not meet the clinical cut-points or diagnostic criteria showed subclinical problems. Thus, the use of a continuous approach and/or subclinical symptoms category to evaluate the risk of behaviour difficulties may have provided a better explanation of the study findings.

Third, due to the nature of the behavioural screening measure used in this study, it was not possible to classify ADHD and its associated symptoms into the inattentive,

hyperactive, or combined ADHD subtypes. Such classification may have provided a more complete interpretation of the study findings and better clinical validity.

Finally, information regarding maternal mental health and maternal smoking during pregnancy was not available in this study, which may have potential implications for development of child behavioural inattention/hyperactivity difficulties. The lack of genetic data may also be considered as a limitation of the current study. However, findings from a recent Swedish national cohort study reported no significant genetic biases in the relationship between gestational age at birth and children's later risk of ADHD (Lindstrom et al., 2011).

## **7.2 Clinical and Theoretical Implications**

While specific implications of the findings of the research studies in this thesis have already been discussed in the previous chapters, some of the more general potential clinical and theoretical implications will be discussed below.

Chapter 4 described the behavioural adjustment outcomes of children born very preterm and full-term at early school age, based on parent and teacher ratings on standardised child behaviour screening measures. Results showed that parents are much more likely than teachers to perceive their very preterm child as having behavioural difficulties. Although discrepancy between informants of child behaviour is an established finding in general populations, this study highlighted that agreement between parent and teacher reports of child behaviour was much lower in the very preterm than the full-term group. Inter-rater agreement for children born very preterm was lowest for the inattention/hyperactivity subscale among the five subscales examining behavioural adjustment. *Thus, reliance on a single informant source to examine behavioural adjustment outcomes of children born very preterm may lead to an over- or under-estimation of the actual prevalence of problems. Combining reports from multiple and independent informants may be necessary to minimise the effects of report source bias for better clinical prognostic validity.* These findings may also have implications for further development of clinical diagnostic and behaviour screening tools, with limited scope for misidentification of child behaviour difficulties. For example, providing objective reference for parents to evaluate their child behaviour may help to reduce

subjective judgements of parents to a large extent while reporting behavioural problems. Similarly, the use of neuropsychological and cognitive assessment for making inferences about child behaviour can also improve accuracy of identification of behavioural adjustment difficulties. At the same time, it is important to acknowledge that the structured nature of the assessment and the clinical set-up may not always provide adequate information regarding adjustment difficulties. Results from such assessment used in conjunction with parent report of child behaviour can be a valid alternative. Nonetheless, such approach, although seems ideal may not be truly feasible due to time-constraints and lack of resources.

As proposed in chapter 4, classification of child behaviour difficulties as situational (parent- or teacher-identified) or pervasive (parent- and teacher-identified) symptoms can be an efficient approach for increasing the clinical validity of results based on behavioural screening questionnaires. Accordingly, chapter 5 described the rates of behavioural inattention/hyperactivity symptoms at ages 4, 6, 9 years in this study cohort. Results showed that although children born very preterm were at a 2-fold elevated risk of inattention/hyperactivity problems than their full-term peers across all the assessment time-points, most of these difficulties were relatively mild and of a situational nature. Rates of pervasive and more severe difficulties were relatively low and comparable to the full-term group. *Thus, along with the need to utilise multi-informant reports of child behaviour, this study highlights the importance of combining reports from different informants to determine the nature and extent of severity of behavioural adjustment difficulties.* Given the heterogeneity of difficulties found in very preterm population, such information will be relevant for clinical follow-up screening as well as behavioural intervention programmes. For example, children exhibiting pervasive behavioural problems will be more likely to need an immediate referral for further follow-up and clinical assessment than those exhibiting situational symptoms. Hence, this approach may help in the appropriate identification of problems and optimal utilisation of clinical resources and expertise.

Furthermore, as described in chapter 5, the extent to which children classified as showing pervasive inattention/hyperactivity problems at ages 4 and 6 were likely to meet the criteria for an ADHD psychiatric diagnosis at age 9 years, compared to children exhibiting situational symptoms were also examined. *Study findings suggest*

*that inattention/hyperactivity symptoms shown by children born very preterm during preschool and early school years may have longer-term clinical significance than symptoms shown by children born full-term. While classification of symptoms as situational and pervasive was shown to be an effective approach to improve clinical validity, findings also showed that multiple screenings of inattention/hyperactivity symptoms over time can be an equally valid approach for identifying children at risk of later clinical diagnosis of ADHD.* Taken together, the high rates of attentional problems evident in the current study cohort as well those reported across other studies emphasise the importance of including inattention/hyperactivity screening as part of routine clinical developmental follow-up assessment for children born very preterm. Although inclusion of psychiatric diagnostic interview as part of routine follow-up of children born very preterm may not be very feasible due to constraints of time and resources; the high predictive validity of behavioural screening questionnaires for a clinical diagnosis as shown in this study may justify the clinical utility of these measures to be part of follow-up assessments. This may also increase the likelihood of early identification of behavioural difficulties which are often considered subtle in this high-risk population.

Chapter 6 described the proportions of children born very preterm who are at risk of exhibiting persistent ADHD symptoms in relation to neonatal neuropathology. Results from this study showed that 13% of children born very preterm relative to 3% of children born full-term are at risk of persistent ADHD symptoms between the ages of 4 and 9 years. Identification of these children with pervasive difficulties is important as they are likely to be the most seriously impaired in terms of academic, cognitive, social and occupational functioning, and may benefit only from specialised intervention programmes. As expected, social background factors showed weak associations with risk of ADHD in children born very preterm. *Findings from this study do suggest the potential role of neonatal neuropathology in placing children born very preterm at an elevated risk of ADHD symptoms.* The two potential neonatal neuropathological substrates (i.e., perinatal cerebral white matter injury and impaired cerebral structural growth and maturation) shown to be independently associated with later risk of ADHD may assist in the early identification of very preterm children at greatest risk of later developmental challenges, thereby allowing appropriate interventions and timely follow-up to optimise the

developmental outcomes. *The loss of cerebral tissue volumes shown to be localised in the anatomical regions known to be associated with the development of ADHD symptomatology in general population, offers additional support for inferring a causal relationship between neonatal cerebral development and risk of ADHD in survivors of very preterm birth.* Finally, neurocognitive profiling of children born very preterm at risk of persistent versus transient ADHD symptoms may help to delineate the neurodevelopmental strengths and weaknesses among these subgroups.

### **7.3 Future Research Directions**

Based on the findings from the current study coupled with similar findings from previous research, it appears that inattention/hyperactivity difficulties in children born very preterm emerge at an early developmental stage. Although results from this study showed potentially greater stability of symptoms over time, and reasonable predictive validity of these early emerging problems identified using standardised screening measures for later clinical diagnosis; further replication of these findings in large epidemiological sample is warranted. Furthermore longer-term follow-up of these children will be important to monitor the persistence of these behaviour problems into adolescence and adulthood. Additionally, it is also important to examine the possible consequences of these persistent difficulties in terms of academic achievement, cognitive, and social functioning in these children.

Although results from this thesis have highlighted the associations between impaired neonatal cerebral structural development and subsequent risk of ADHD, these findings are based on complex volumetric techniques which may not be readily available to the paediatric neuroradiologist. Thus, further research is needed to extend the validity of current findings using simpler, readily available measure of cerebral growth and maturation such as brain metrics (e.g., bifrontal and biparietal diameters). Findings from this study also highlighted the importance of regional cerebral development. However, further research is warranted to replicate these preliminary findings and to extend it further to examine associations between functionally defined anatomical subregions and risk of attentional problems. Given the relative immaturity of cerebral structures like myelinated white matter and prefrontal regions at term equivalent age due to the temporal pattern of cerebral maturation, it would be interesting to see if the current findings may have long-term

significance in indicating an overall delayed and impaired maturational process. Extending current findings using sophisticated techniques such as diffusion tensor imaging will also be helpful in providing useful insights regarding microstructural alterations in cerebral white matter including axonal growth and organisation, and the potential impact on the development of ADHD symptomatology.

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## Appendix A

### Common Medical Problems in Preterm Infants<sup>9</sup>

**Respiratory distress syndrome (RDS):** Lung problem developing shortly after birth due to lack of endogenous surfactant in the lungs. Surface tension increases in the smallest airways and lungs get non-compliant (stiff). Treated with instillation exogenous surfactant in the airway. Common reason for mechanical ventilation.

**Patent ductus arteriosus (PDA):** The duct is a blood vessel between the pulmonary artery and the aorta, essential for foetal blood circulation. The duct should close after birth but can stay open in preterm infants, shunting too much blood to the lungs and leaving too little blood for other organs. Can be closed with drugs or surgery.

**Necrotising enterocolitis (NEC):** Inflammation and necrosis of the bowel, leading to various abdominal symptoms. Treated with bowel rest and antibiotics, but surgical bowel resection is commonly performed in cases of bowel necrosis and/or perforation.

**Bronchopulmonary dysplasia (BPD):** A more chronic lung problem, related to short gestational age, RDS, PDA, and mechanical ventilation. Months of ventilatory support and supplementary oxygen may be needed in severe cases. Some, but not all, children can be prone to asthma-like problems and have reduced lung function.

**Retinopathy of prematurity (ROP):** Overgrowth of blood vessels in the immature retina of the eye, related to factors such as short gestational age and oxygen administration. Low-grade retinopathy usually resolves without specific therapy but laser treatment may be needed in severe forms. Worst-case scenario includes retinal detachment and blindness.

**Infections:** Very common, due to an immature immune system and much exposure to bacteria from the environment (including staff). Bacteria of low virulence and fungi are common pathogens. Can usually be treated successfully with antibiotics, but infection-related mortality is significant.

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<sup>9</sup>From *“Neurodevelopmental Outcomes of Preterm Birth: From Childhood to Adult Life,”* edited by C. Nosarti, R. M. Murray, and M. Hack. 2010. Published by Cambridge University Press, (page 11).

## Appendix B

### Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder<sup>10</sup>

A. Either (1) or (2):

(1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

#### *Inattention*

- (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- (b) often has difficulty sustaining attention in tasks or play activities
- (c) often does not seem to listen when spoken to directly
- (d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
- (e) often has difficulty organising tasks and activities
- (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books or tools)
- (h) is often easily distracted by extraneous stimuli
- (i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

#### *Hyperactivity*

- (a) often fidgets with hands or feet or squirms in seat
- (b) often leaves seat in classroom or in other situations in which remaining seated is expected

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<sup>10</sup>From "American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*," 2000. Washington, DC, American Psychiatric Association.



- (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- (d) often has difficulty playing or engaging in leisure activities quietly
- (e) is often “on the go” or often acts as if “driven by a motor”
- (f) often talks excessively

*Impulsivity*

- (g) often blurts out answers before questions have been completed
- (h) often has difficulty awaiting turn
- (i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The disturbance does not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

**Subtypes:**

**Attention-Deficit/Hyperactivity Disorder, Combined Type:** if both criteria A1 and A2 are met for the past 6 months.

**Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type:** if criterion A1 is met but criterion A2 is not met for the past 6 months.

**Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type:** if criterion A2 is met but criterion A1 is not met for the past 6 months.

# Appendix C

## Strengths and Difficulties Questionnaire (SDQ)

### Strengths and Difficulties Questionnaire

P or T 4-10

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. Please give your answers on the basis of the child's behaviour over the last six months or this school year.

Child's name .....

Male/Female

Date of birth.....

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

Signature .....

Date .....

Parent / Teacher / Other (Please specify):

**Thank you very much for your help**

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### 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.

<u>Emotional Symptoms Scale</u>	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

<u>Conduct Problems Scale</u>	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

<u>Hyperactivity Scale</u>	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

<u>Peer Problems Scale</u>	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

<u>Prosocial Scale</u>	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 or 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).