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The Attention Abilities and Grey Matter Development of School Aged Children born Very Preterm

by

Rachel E. Lean

A dissertation presented to the
Graduate School of Arts & Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

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List of Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
BPD	Bronchoplumonary dysplasia
BW	Birth weight
EPT	Extremely preterm
FT	Full term
FWE	Family-wise error rate
fMRI	Functional magnetic resonance imaging
GA	Gestational age
IQ	Intellectual quotient
IUGR	Intrauterine growth restriction
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
OR	Odds ratio
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
SPM	Statistical parametric map
VBM	Voxel based morphometry
VLBW	Very low birth weight
VPT	Very preterm
WMI	White matter injury

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Rachel E. Lean

Washington University in St. Louis

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Dedicated to the children and families involved in the
Canterbury Very Preterm Birth Study.
Thank you for sharing your lives.

ABSTRACT OF THE DISSERTATION

The Attention Abilities and Grey Matter Development of

School Aged Children born Very Preterm

by

Rachel E. Lean

Doctor of Philosophy in Psychology

Washington University in St. Louis, 2015

Associate Professor Lori Markson, Chair

Professor Lianne Woodward, Co-Chair

Although children born very preterm (VPT, <33 weeks gestational age) are 2–3 times more likely to receive a diagnosis of ADHD in childhood, the nature and extent of their attention problems is not well understood. Furthermore, little is known about the mechanisms that place VPT children at increased risk of attention impairment. Previous research has shown strong links between white matter abnormalities and adverse motor and cognitive outcomes, but not for attention. This suggests that the mechanism for inattention may be different in this group. Thus, the aims of the current study were 1) to describe the nature and extent of attention problems in VPT children, 2) to document regional structural alterations in grey matter volume between VPT and full term children, and 3) to relate attention outcomes to regional grey matter volumes in VPT children at age 12 years. As part of a prospective longitudinal study, VPT children (n = 110) and full term control children (n = 113) underwent a neurodevelopmental assessment and structural MRI scan at age 12 years. Key attention outcomes included selective, sustained, and

executive attention; assessed with the Test of Everyday Attention for Children and adjusted for social background risk. To examine associations between very preterm birth and grey matter development, structural T1-weighted images were analyzed for all study children using optimized voxel based morphometry (FWE-corrected $p<0.05$), adjusted for age at scan and social background characteristics. Modulated gray matter volume values were then extracted from key brain regions and related to measures of attention within the VPT group. At age 12 years, VPT children were characterized by poorer sustained (ps$\leq$.03) and executive attention (ps$\leq$.01) compared to full term children. Group differences in executive attention remained after adjustment for social background risk (ps$\leq$.02). VPT children evidenced reduced grey matter volume in the bilateral parietal, temporal, left prefrontal, and posterior cingulate cortices; bilateral thalami, and bilateral hippocampus (FWE-corrected $p<0.05$). Increased grey matter volume was also found in the medial occipital and anterior cingulate cortices (FWE-corrected $p<0.05$). Within the VPT group, thalamic volume was correlated with selective attention (r = -.34) and executive shifting attention (r = .32); medial occipital volume correlated with sustained response inhibition (r = .24); and volumes in the thalami (r = -.36) and left temporal (r = -.35), posterior cingulate (r = -.36) and occipital cortices (r = -.30) correlated with executive divided attention. Reduced grey matter volume in the occipital (p = .05) and posterior cingulate (p = .006) regions at age 12 years independently predicted attention after taking into account the infant clinical, neuropathological and social factors also related to attention outcomes. Findings indicate that VPT children experience lapses in attention, difficulty shifting attentional focus, and problems with multitasking. The structural abnormalities identified in regional grey volume at age 12 years suggests that grey matter growth and development is vulnerable to the consequences of very preterm birth. Importantly, regional grey matter volume was differentially

and independently associated with attention abilities in VPT children, highlighting grey matter growth and development as an important neural mechanism for attention in VPT children. The findings of the current study raise concerns for the longer term neurological development of children born very preterm, while also emphasizing the need for tailored educational support services that addresses the attention problems of this group as they transition into higher level education during their early teenage years.

The Attention Abilities and Grey Matter Development of School-Aged Children Born Very Preterm

Chapter 1. General Introduction

1.1. Prevalence of very preterm birth. Very preterm infants are those born less than 33 completed weeks of gestation, with 22 weeks deemed the edge of viability from which a preterm infant might survive (Beck, Wojdyla, Say, *et al.*, 2010; Nuffield Council on Bio-Ethics, 2006; MoH, 2010). The World Health Organization estimates that premature birth (< 37 weeks) accounts for 9.6% of all live births worldwide (Beck *et al.*, 2010). A population based study of all births (n = 3,953,593) in the United States during 2011 reported that 11.7% of all live births were preterm (<37 weeks) and that one third of these births (3.4%) were very preterm (Hamilton, Hoyert, Strobino, & Guyer, 2013). Spontaneous delivery accounts for around half of all preterm births (45%), followed by rupturing of uterine membranes (25%) and medically induced delivery due to fetal or maternal health complications (25-30%) (Goldenberg, Culhane, Iams & Romero, 2008; Moutquin, 2003).

1.2. Public health relevance. Due to advancements in both antenatal observation and perinatal care, the survival rates of very preterm and low birth-weight infants have significantly improved over time (Darlow, Cust & Donoghue, 2003; Effer, Moutquin, Farine, Saigal, Nimrod *et al.*, 2002; Hobar, Badger, Carpenter *et al.*, 2002; Saigal & Doyle, 2008). This is particularly true of infants born on the edge of viability at 22 - 25 weeks gestational age, most of whom now survive to hospital discharge (Effer *et al*, 2002; Nuffield Council on Bio-Ethics, 2006). There remains however, an inverse relationship between gestational age and extent of neonatal morbidity (Jarjour, 2015; Sagal & Doyle, 2008). Very preterm birth is therefore a serious public

health concern given the financial cost of intensive neonatal care, coupled with the financial and social costs associated with the longer term recurrent health and neurodevelopmental problems of very preterm children (Rushing & Ment, 2004; Sagal & Doyle, 2008).

1.3 Neurodevelopmental outcomes. Despite survival gains in very preterm infants, a high rate of neurodevelopmental disability and impairment continues to exist across multiple domains of development. Impairments span neurosensory disorders, motor dysfunction, intellectual impairment, poor executive function skills, educational underachievement, and behavioral problems in both preschool and school-aged children (Allen, Cristofalo & Kim, 2010; Markestad, Kaaresen, Ronnestad, *et al.,* 2005; Wood, Costelo, Gibson, *et al.,* 2004; Woodward, Moor, Hood *et al.,* 2009). Approximately one quarter of very preterm and very low birth weight children have a mild or moderate developmental problem, with an additional quarter having severe or multiple developmental problems (Wolke, 1998). In terms of neuromotor development, between 15 – 19% of very preterm children are diagnosed with cerebral palsy in early childhood in comparison to a diagnosis rate of 0.1 – 0.2% in the general population (Leppert & Allen, 2009; Wood, Costelo, Gibson, *et al.,* 2004; Woodward, Moor, Hood *et al.,* 2009). Furthermore, one quarter (21%) of very preterm children who have a mild to moderate motor impairment at age 2 ½ years are also likely to have a comorbid cognitive impairment on the Mental Development Index of the Bayley Scales of Infant Development (Wood, Costelo, Gibson, *et al.*, 2004). Furthermore, a growing body of research suggests that cognitive impairment persists beyond early childhood and into school age for very preterm children.

Children born very preterm perform less well on standardized measures of general intellectual ability compared to their full term peers, with those born at younger gestational ages at additional risk of poor outcome (Aarnoudse-Moens, Weisglas-Kuperis, van Groudoever *et al.*, 2009;

Anderson & Doyle, 2008; Bhutta, Cleves, Casey *et al.*, 2002; Marlow, Wolke, Bracewell & Samara, 2005). For example, Foulder-Hughes and Cooke (2003) reported that very preterm children (*n* = 198) obtained full scale intellectual quotient scores on the WISC-III nearly 1 SD lower than scores obtained by full term comparison children (n= 268) at age 7 years. In addition, a comprehensive meta-analysis of 15 studies describing the cognitive outcomes of preterm children and matched full-term children aged 5 to 14 years old, suggested that poor test performance of very preterm children did not improve with age (Bhutta, Cleves, Casey *et al.*, 2002). An inverse relationship between gestational age and the risk of cognitive impairment also exists, as extremely preterm children born less than 27 weeks gestational age perform more poorly on measures of intellectual ability compared to very preterm children (Anderson & Doyle, 2008; Woodward, Moor, Hood *et al.*, 2009).

Given the high rate of motor and cognitive impairments observed among very preterm children at school age, children born very preterm are overrepresented in the proportion of children requiring specialist and educational support services (Aarnoudse-Moens Weisglas-Kuperis, van Groudoever *et al*,. 2009; Anderson & Doyle, 2003; Wolke, 1998). One domain of functioning that has been linked to school outcomes for very preterm children is Attention Deficit Hyperactivity Disorder (ADHD) (Jaekel, Wolke & Bartmann, 2013). A large body of research consistently suggests that ADHD is a common and persistent neurobehavioral problem among this group, with risks specific to the ADHD-inattentive subtype in comparison to the Hyperactive/Impulsive or Combined subtypes (Botting, Powls & Cooke, 1997; Elgen, Sommerfelt, Markestad, 2002; Jaekel, Wolke & Bartmann, 2013; Johnson, Hollis, Kcochhar *et al.*, 2011). Furthermore, multivariate analysis has shown that very preterm birth is the strongest predictor of chronic and persistent attention problems; a finding that remains after covariate

adjustment for gender, ethnicity, socio-economic adversity and child intellectual ability (Galera, Cote, Bouvard *et al.*, 2011; Groen-Blokhuis, Middledorp, van Beijstervelt *et al*. 2011; Low Lee, Luna & Feldman, 2011; Nadeau, Tessier, Boivin *et al.* 2003). The attention problems of very preterm children, therefore, is a major developmental concern.

1.4 Attention Deficit Hyperactivity Disorder in very preterm children. Both parent-report screening and clinical measures show that school aged children born very preterm are at increased risk of ADHD and attention problems in childhood (Foulder-Hughes & Cooke, 2003; Hack, Taylor, Schulchter *et al.*, 2009; de Kieviet, van Elburg, Lafeber *et al.*, 2012; Morsing, Asard, Ley *et al.*, 2011). A large meta-analysis by Aarnoudse-Moens, Weisglas-Kuperis, van Groudoever *et al.* (2009) found that parent and teacher ratings on screening measures of attention problems were 0.43 – 0.59 SD higher for very preterm children relative to full term children. Furthermore, between 16 – 20% of very preterm children receive a clinical diagnosis of ADHD-Inattentive subtype by age 7-8 years, which is approximately twice the rate found in full term children (Bhutta, Cleves, Casey *et al*., 2002; Treyvaud, Ure, Doyle, *et al*., 2013; Jaekel, Wolke & Bartmann, 2013). Other estimates suggest that risks of ADHD may be higher with a three to four-fold increase in the proportion of very preterm children meeting diagnostic criteria (Foulder-Hughes & Cooke, 2003; Hack, Taylor, Schulchter *et al.*, 2009). Worryingly, the rate of diagnosis appears to be greater still among extremely preterm children as one recent study reported a 7-fold increase of ADHD-Inattentive subtype disorder in extremely preterm children compared to full term children at age 11 years (Johnson, Hollis, Kcochhar *et al.*, 2010).

Although studies based on psychiatric measures of inattention provide useful information about risks of ADHD in children born very preterm, the approach offers a behavioral description of attention problems somewhat independently from other equally important features of ADHD.

ADHD-Inattentive subtype is increasingly understood as a neurobehavioral disorder characterized by subtle but central deficits in cognitive and executive functions (Jaekel, Wolke, Bartmann, 2013; Halperin & Schulz, 2006). The assessment of very preterm children's attentional abilities on neuropsychological measures that differentially test key components of attention is crucial to fully characterize the specific nature and extent of attention problems in this high-risk group.

1.5 Thesis outline. Against this general background, the first primary focus of this dissertation concerns the nature and extent of very preterm children's attention problems at school age. The second major focus of this dissertation is to describe concurrent relations between attention problems and volumetric MRI measures of grey matter growth and development in children born very preterm at age 12 years to identify a possible neural mechanism associated with inattention. The current study is organized into eight chapters. Following this chapter are seven chapters which are outlined briefly below.

Chapter 2 provides the conceptual framework for this dissertation. It is divided into five sections: 1) an overview of attention and the key components of attention, 2) a systematic review of recently published studies concerning very preterm children's performance on neuropsychological measures of attention, 2) an overview of the neural bases of attention, 3) a systematic review of recently published studies of volumetric MRI in very preterm children, and 4) the specific aims and hypotheses formulated for the current study.

Chapter 3 provides a description of the research methods of this dissertation. This chapter describes the characteristics of the research design, study sample, procedures and measures used, and a detailed description of the data analysis undertaken to test each research aim.

Chapter 4 presents the first section of study results. It describes the attention outcomes of very preterm children as measured by the Test of Everyday Attention for Children at age 12 years, corrected for extent of prematurity at birth. Of particular interest was the nature of very preterm children's attention problems before and after covariate adjustment, and the relationship between attention problems and younger gestational age.

Chapter 5 describes the findings of the second major focus of the current study; the grey matter growth and development of very preterm children compared to full-term children at age 12 years.

Chapter 6 describes the third and final section of study findings which describes bivariate and multivariate associations between the attention outcomes and regional grey matter growth and development for very preterm children at age 12 years.

Chapter 7 summarizes, integrates and discusses the findings of the current study presented in chapters 4, 5, and 6 in light of previous research. Implications of the current findings are also discussed.

Chapter 8 concludes the dissertation by addressing the limitations and strengths of the current study and considering directions for future research.

Chapter 2. Very Preterm Birth and Attention

2.1 Attention. As part of the information processing system, attention is a crucial component of cognitive functioning that is involved in the moment-to-moment processing of sensory information for efficient goal-directed behavior (Posner & Petersen, 1990; Treisman, 1998). It achieves this by allocating cognitive resources to the domains of the attention system that are responsible for collecting and processing information; allowing individuals to select relevant from irrelevant stimuli, sustain a high level of mental arousal and task engagement, and shift attentional focus. Traditionally, attention was conceptualized as a unitary process of focused attention (James, 1980). Modern theories, however, suggest that attention is not a single process, but is comprised of related but functionally separate cognitive modalities that operate as a unified system (Posner & Petersen, 1990; Treisman, 1998).

2.1.1 Models of attention. Models of attention derived from cognitive neuroscience describe the neural and cognitive processes that underlie and produce attention. A well accepted model proposed by Posner and Peterson (1990) suggests that attention is comprised of three fundamental processes including alerting (a change in state that prepares the brain for incoming information), orienting (moving of shifting attention towards a target), and vigilance (maintenance of the alert state). These three factors represent independent processes that allow an individual to select or focus on relevant targets of stimuli, move flexibly between stimuli or concepts, and sustain attention, respectively (Anderson, Jacobs & Harvey, 2005). The independent but interrelated neural bases of the components of attention are described in chapter 2 section 4.

Neuropsychological models of attention describe the components of attention that can be observed and which support goal-directed behavior. A well accepted neuropsychological model

of attention was proposed by Mirsky, Anthony, Duncan, Ahearn and Kellam (1991). This model compared the performance of a community sample of adults (n = 203, mean age: 28 years ± 9 years) and children (n = 435, mean age: 8 years ± 5.4 years) on eight comparable age-appropriate measures of attention to examine whether the latent structure of attention was similar between the two groups. Principal component analysis of the adult sample identified four attention factors consisting of focused attention, sustained attention, shifting of attentional focus, and encoding information. Importantly, test performance of the child sample loaded similarly onto the adult four factor model, suggesting that a differentiated four factor model of attention appropriately described the structure of attention in children.

An alternative model proposed by Robertson, Ward, Ridgeway and Nimmo-Smith (1996) yielded a slightly different four factor model in adults comprised of sustained attention, selective attention, attentional shifting, and auditory-verbal working memory. This model introduced an online-component of auditory working memory, but generally supported the model developed by Mirsky *et al*. (1991). Both models postulated a higher order component of attention that involved the executive control of attention through shifting attention focus. Together, these models provided the theoretical foundation for a well-recognized neuropsychological model of attention in children (Manly, Anderson, Nimmo-Smith *et al*., 2001)

To develop an age-standardized test battery of attention, Manly, Anderson, Nimmo-Smith *et al*. (2001) examined the Robertson model in a large sample of children aged 6 to 16 years old (n = 293). After adapting the adult subtests used by Robertson, Ward, Ridgeway and Nimmo-Smith (1996) to suit the age of the younger sample, each subtest was ascribed to a latent attentional variable based on their theoretical origins: selective attention, sustained attention, or attentional control. The fit index values of the structural equation modelling supported the 3 factor model

over and above a single latent variable model of attention, suggesting that children's patterns of test performance matched the differentiated model of sustained attention, selective attention, and attentional control in adults. Like Posner and Peterson (1990) and Robertson, Ward, Ridgeway and Nimmo-Smith (1996), the findings of Manly, Anderson, Nimmo-Smith *et al*. (2001) support the conceptualization of selective attention and sustained attention as independent domains of attention, and the inclusion of a third control or executive attention component in children. This three factor model of sustained, selective and executive attention provides an appropriate framework to examine the attention profile of children born very preterm.

2.2 Attention outcomes of very preterm children: A systematic review. Although many existing studies of attention in very preterm children have included screening and clinical measures of ADHD, fewer have examined very preterm children's performance on neuropsychological measures of attention. Thus, the nature and extent of attention problems in very preterm children are less well understood. This issue forms the central focus of the first literature review of this dissertation.

2.2.1 Inclusion criteria. To identify existing published studies describing the nature and extent of attention problems in very preterm children, a comprehensive literature review was conducted. The databases PsycINFO, PubMED, ScienceDirect, and Google Scholar were systematically searched for relevant publications between March 2012 and May 2015. Key search terms included variations and combinations of: selective, sustained, executive attention; attention problems/impairment; inattention; very preterm birth; childhood and school age. Publication inclusion criteria for the literature review were as follows:

General inclusion criteria: Peer reviewed and published between 2000 and 2015, with English as the first language.

Specific inclusion criteria: Studies that 1) included very preterm children (≤ 33 weeks GA and ≤ 2,500g birth weight) as the primary group of interest, 2) included an appropriate full-term comparison group, 3) assessed attention problems at school age (12 ± 4 years), and 4) were of longitudinal or cross-sectional research design, were included. To account for changes in neonatal care, studies with cohorts born prior to 1990 were typically excluded to minimize cohort effects. If the study did not report a birth year, secondary criteria was used and the article was selected if it was published within the last 5 – 6 years to maximize the number of reviewed publications.

Key outcomes of interest: Studies comparing the test scores and rates of impairment between very preterm children and full term children on measures of selective, sustained and executive attention were selected for review. Using these inclusion criteria, 5 studies were selected for detailed review and are summarized in Table 1. One study (Murray, Scratch, Thompson *et al*., 2014) met the selection criteria, but was found to be a duplicate of a previously selected study reporting attention outcomes in detail for the same sample.

Table 1

Summary of the Attention Outcomes of Very Preterm Children at School Age

SAMPLE							METHODS			RESULTS			
Author (date)	**VPT**			**FT**		**Age**	**Measure**	**Statistical analysis**	**Component of attention**	**VPT**	**FT**	**OR (95% C.I.) / *d***	**Study + / -**
	Year born	**GA**	**BW**	***n***	***n***					**Subtest m ± SD**	**Subtest m ± SD**		
Anderson *et al.* (2011)	1997	26.5 ± 2.0	833 ± 164	189	173	8	TEA-Ch WISC-IV	Two way ANOVA to assess birth group and sex interactions on attention measures T-tests for GA and BW groups	Selective	17.0 ± 3.2	18.2 ± 2.1**	2.4 (1.5 – 4.0)	+ Prospective longitudinal + Large sample + Matched FT sample + Blind to group status + Low attrition rate (13%)
									Sustained	7.6 ± 2.3	8.3 ± 2.0**	2.4 (1.4 - 4.1)	
									Shifting	4.2 ± 2.2	5.3 ± 2.7***	3.6 (2.0 – 6.8)	
									Divided	71.9 ± 19.9	80.3 ± 16.5***	3.1 (1.8 – 5.3)	
									Inhibitory control	44.2 ± 29.9	44.0 ± 40.7	0.4 (0.1 – 1.3)	
									Encoding	8.8 ± 2.4	9.6 ± 2.6	1.5 (0.9 – 2.3)	
Bayless & Stevenson (2007)	NR	28.4 ± 2.4	1200 ± 368	40	41	6 – 12	TEA-Ch	MANOVA with group as between-subjects factor, followed by univariate	Selective	7.8 ± 3.1	8.7 ± 2.4	-	+ Both groups similar SES, sex - Small samples - Birth year NR - Limited
									Sustained	7.8 ± 3.3	9.31 ± 3.4	-	
									Shifting	9.0 ± 4.1	12.1 ± 2.5*	0.91	
									Inhibition	7.4 ± 2.7	8.8 ± 2.8*	0.51	

Table 1

Summary of the Attention Outcomes of Very Preterm Children at School Age

SAMPLE							METHODS			RESULTS			
Author (date)	**VPT**				**FT**	**Age**	**Measure**	**Statistical analysis**	**Component of attention**	**VPT**	**FT**	**OR (95% C.I.) / *d***	**Study + / -**
	Year born	**GA**	**BW**	***n***	***n***					**Subtest m ± SD**	**Subtest m ± SD**		
								analysis					clinical data - Low response rate in VPT group (30%)
de Kieviet *et al.* (2012)	2001 – 2003	29.3 ± 1.6	1241 ± 355	66	66	7 – 8	ANT	MANOVA with group as between-subjects factor	Lapses in attention (time in milliseconds)	198 ± 124	133 ± 75**	0.55	+ Prospective longitudinal +Large samples + High sample retention (92%) + Matched FT group - Low risk only sample
Mulder, Pitchford & Marlow (2011)	1997 - 1999	27.6 ± 1.8	NR	56	22	9 – 10	TEA-Ch	Regression with group entered as a dummy variable (FT = 0, VPT = 1)	Selective	10.0 ± 3.0	10.3 ± 2.8	-	+ Moderate VPT sample size + Matched FT group - Small FT sample - Low participant response rate
									Sustained	7.5 ± 3.6	7.9 ± 3.4	-	
									Shifting	7.3 ± 3.4	9.4 ± 3.1**	0.65	
									Inhibitory control	5.9 ± 3.2	9.0 ± 3.7**	0.90	

Table 1

Summary of the Attention Outcomes of Very Preterm Children at School Age

SAMPLE							METHODS			RESULTS			
Author (date)	**VPT**				**FT**	**Age**	**Measure**	**Statistical analysis**	**Component of attention**	**VPT**	**FT**	**OR (95% C.I.) / *d***	**Study + / -**
	Year born	**GA**	**BW**	***n***	***n***					**Subtest m ± SD**	**Subtest m ± SD**		
													(44%) - Limited clinical data
Shum *et al*,. (2008)	NR	26.4 ± 1.9	838.2 ± 151.7	45	49	7 – 9	NEPSY (total)	Independent samples t-test with alpha level .01 to control Type 1 Error	Visual attention	14.5 ± 4.6	16.8 ± 4.6**	0.49	+ Moderate sample size + Adequate response rate (75%) - Birth year NR - Some ELBW-only cases recruited - Limited clinical data
							TMT-B (seconds)		Focused attention	84.7 ± 43.7	63.31 ± 42.1**	0.50	
							Stroop		Selective attention	0.5 ± 0.1	0.5 ± 0.1	0.08	

Note: NR: Not reported, ± Standard Deviation

TEA-Ch: Test of Everyday Attention – Children, WISC-IV: Wechsler Intelligence Scale for Children-IV, ANT: Attention Network Task, NEPSY: A Developmental Neuropsychological Assessment, TMT-B: Trail Making Task – Part B
* $p \leq .05$, ** $p \leq .01$, ***$p \leq .001$

2.2.2 Selective attention. Selective attention is the capacity to orient to, focus on, and select relevant stimuli or sources of information while filtering out or ignoring irrelevant information (Anderson, Jacobs & Harvey, 2005). Children born very preterm in general, tend to perform less well on standardized measures of selective attention than full term children but this difference is small and often fails to reach statistical significance (Bayless & Stevenson, 2007; Mulder, Pitchford & Marlow, 2011; Shum, Neulinger, O'Callaghn *et al*., 2008). For example, Bayless and Stevenson (2007) found that very preterm children born at 28 weeks gestational age obtained lower mean selective attention subtest scores (m = 7.8, SD = 3.1) on the Everyday Attention for Children (TEA-CH) compared to full term children (m = 8.7, SD = 2.4) at ages 6 – 12, but this difference did not reach statistical significance. Similar findings were reported by Mulder, Pitchford and Marlow (2011) who used the same measure of selective attention in a comparable sample of very preterm children also born at a 28 weeks gestational age. This study reported that on average, there was a less than a 1 point difference in selective attention subtest scores between the very preterm and full term children at ages 9 – 10 years. However, it is important to note that Bayless and Stevenson (2007) and Mulder, Pitchford and Marlow (2011) were characterized by small and selective samples, highlighting that group differences may be more prominent in larger and representative groups of very preterm children.

While school aged very preterm and full term children appear to have similar levels of selective attention ability, deficits in selective attention may be more prominent among children born extremely preterm. A large longitudinal study by Anderson Luca, Hutchinson *et al*. (2011) found that Australian children born extremely preterm (m = 26.5 weeks GA) performed significantly less well on the selective attention measure of the TEA-Ch relative to their full term peers at age 8 years, with a two-fold increase in the rate of selective attention impairment among the

extremely preterm group (34% vs. 15%, OR = 2.4). In contrast, Shum, Neulinger, O'Callaghn *et al*. (2008) found that their sample of very preterm/extremely low birth-weight children (m = 26.4 weeks GA) performed as well as full term children on the Stroop task of selective responding, as both groups obtaining a mean score of 0.5 (SD = 0.1). The discrepancy between Anderson Luca, Hutchinson *et al*. (2011) and Shum, Neulinger, O'Callaghn *et al*.'s (2008) findings might be attributable to sample differences. Specifically, Shum, Neulinger, O'Callaghn *et al.*'s (2008) low risk sample attended mainstream school, did not have any serious neurological problems and had a GQ greater than 85 on the McCarthy Scales of Children's Abilities. Anderson Luca, Hutchinson *et al*. (2011) included a comparatively more diverse sample of varying levels of medical and social risk.

2.2.3 Sustained attention. Sustained attention is the ability to consistently maintain an alert or vigilant state in the preparation of incoming or changing task-related information (Anderson, Jacobs & Harvey, 2005, Mahone & Schneider, 2012; Wang, Liu, Fan, 2011). Sustained attention is measured by continuous performance tasks that hold little intrinsic value (*e.g*. auditory recall, digit span, inhibitory control of routine motor responses) or the rate of extremely slow responding indicating substantial lapses in attention and absentmindedness. Although findings across reviewed studies appeared to be mixed, very preterm children tended to make more errors on sustained attention tasks and take longer to complete timed tasks than full term children. For example, Anderson, Luca, Hutchinson *et al*. (2001) found that extremely preterm children were less accurate in the recall of sound items heard during the sustained auditory attention subtest of the TEA-Ch. For every full term child that had an impairment in sustained attention, two extremely preterm children were identified as having a similar level of impairment (15% v. 30%, OR = 2.4). Bayless and Stevenson (2007) found a similar trend in

which very preterm children obtained fewer correct items on the sustained auditory attention subtest than full term children, but this finding did not reach statistical significance. Mulder, Pitchford and Marlow (2011) did not find a significant effect of birth group on sustained attention, although this study was characterized by a low participant response rate (44%) and socioeconomic differences between participants and non-participants which may have biased study findings.

In terms of time taken to complete sustained attention tasks, both de Kieviet, van Elburg, Lafeber *et al*. (2012) and Shum, Neulinger, O'Callaghn *et al*. (2008) found that very preterm children perform less well than full term children. Specifically, de Kieviet, van Elburg, Lafeber *et al*. (2012) reported that very preterm children had a significantly higher proportion of extremely slow responses on the Attention Network Task which was not explained by group differences in lower-level processing speed. Very preterm children also took approximately 20 seconds longer than full term children to complete the Trail Making Task-B measure of focused attention (Shum, Neulinger, O'Callaghn *et al*., 2008). Together, these findings suggest that very preterm children are less able to maintain a vigilant and alert state during tasks and are more prone to short lapses of attention than full term children. Similar findings have also been reported on behavioral measures of sustained inhibition of motor responses (Bayless & Stevenson, 2007; Mulder, Pitchford & Marlow, 2011), suggesting that very preterm children are less able to effectively maintain an awareness and prevent lapsing into absent minded responding.

Very preterm children perform less well on measures of sustained attention compared to their full term peers. However, the magnitude of difficulty in sustained attention for very preterm children shows considerable variation. For example, small to moderate effect sizes (Cohen's d = 0.32) have been reported for TEA-Ch sustained auditory attention and WISC-IV digit span

subtests (Anderson, Luca, Hutchinson *et al*., 2001) while larger effect sizes (Cohen's $d = 0.5 – 0.9$) have been found for measures of sustained attention to inhibition of responding and inhibitory control (Bayless & Stevenson 2007; Mulder, Pitchford & Marlow, 2011). In addition to task differences, variation in effects may also be attributable to differences in sample characteristics and sample size (*cf.* Anderson, Luca, Hutchinson *et al*., 2011 and Shum, Neulinger, O'Callaghn *et al.* 2008). Therefore, additional research is needed to examine aspects of sustained attention in a large and representative group of children born very preterm to lend support to existing findings.

2.2.4 Executive attention. Executive attention is a higher-order component of attention that uses executive-like functions to control attention. It involves the flexible switching or shifting of attention from one stimulus, concept or response mode to another, and dividing cognitive resources across stimuli or tasks that compete for attentional resources (Posner, 2011). Findings of the current review consistently suggested that very preterm children show deficits in the executive attention, both in shifting attention and divided attention (Anderson, Luca, Hutchinson *et al.*, 2001; Bayless & Stevenson 2007; Mulder, Pitchford & Marlow, 2011). For example, very preterm children obtained scaled scores approximately two points lower on average than full term children on the TEA-Ch Creature Counting measure of attention shifting (Mulder, Pitchford & Marlow, 2011). Among extremely preterm children, there was an approximate a three-fold increase in the proportion of scores falling into the impairment range compared to full term children (Anderson, Luca, Hutchinson *et al.*, 2001).

Although relatively strong associations have been reported between very preterm birth and deficits in executive switching attention, fewer studies have examined executive divided attention. In the single study that examined divided attention, Anderson, Luca, Hutchinson *et al.*

(2001) found that very preterm children obtained Sky Search Dual Task decrement scores half a standard deviation higher than the control group (OR 3.1, $p < .001$). This suggests that for very preterm children. Selective attention was adversely impacted when completing the sustained attention task simultaneously. In the same study, impairment in executive divided attention appeared to be more common among the extremely preterm group than the full term group, with over half (62% v. 26%) of extremely preterm children identified as impaired in this domain.

2.2.5 Predictors of attention in very preterm children. Of the studies that described attention outcomes in very preterm children, very few extended their analyses to examine how gestational age or infant clinical factors associated with very preterm birth impacted attention outcomes. Within the preterm group, Anderson, Luca and Hutchinson *et al*. (2011) included two sets of sub-group analyses for children 1) born less than 26 weeks, and 2) born weighing less than 750 grams. Surprisingly, children in the youngest and lightest birth groups did not show poorer attention outcomes compared to their older and heavier preterm counterparts. However, this analysis did not include children born very preterm between 33 and 28 weeks gestational age, which when coupled with children born extremely preterm, may yield clearer linear effects of gestational age on attention (Bayless & Stevenson, 2007).

In addition to the above, only one study examined the extent to which infant clinical factors predicted attention outcomes in very preterm children at school age. Anderson, Luca and Hutchinson *et al*. (2011) identified necrotizing enterocolitis (NEC) and cystic-periventricular leukomalacia (PVL) as key predictors of selective attention, accounting for 26% of the variance in Sky Search scores for extremely preterm children. While it was noted that other neonatal risk factors explained 4 – 11% of variance in the remaining attention outcomes, these factors were not specified. In terms of other clinical factors in the wider literature, there is mixed evidence

suggesting that intraventricular hemorrhaging (IVH) and bronchopulmonary dysplasia (BPD) may be associated with poor attention outcomes at infancy and in adulthood (van de Weijer-Bergsma, Wijnroks & Jongmans, 2008; Wilson-Ching, Molloy, Anderson *et al.*, 2013). However, the extent to which neonatal clinical factors impact attention at school age remains understudied and further research is needed in this area.

2.2.6 Methodological limitations in the very preterm birth and attention literature.

Findings from the systematic literature review consistently suggested that very preterm children perform less well on measures of sustained and executive attention and that this group is at increased risk for attentional impairment compared to their full term peers. There was also mixed evidence for poorer selective attention outcomes. However, many of the reviewed studies are limited by a range of methodological issues which pose challenges for understanding the specific nature of inattention in very preterm children. These limitations include low participant response and retention rates, small and selective samples, and the inadequate reporting of infant clinical characteristics.

First, low participant response rates lend studies towards smaller and more selective or biased samples (Siegel, 1994). Families of higher social background risk or who have children with less severe health complications or developmental problems are less likely to partake in and/or continue with study participation (Castro, Yolton, Haberman *et al.*, 2004; Siegel 1994). Within the preterm literature, Bayless and Stevenson (2007), Mulder, Pitchford and Marlow (2011) and Shum, Neulinger, O'Callaghn *et al.* (2008) all reported low to adequate participant response or retention rates, ranging from 44% to 75%. Furthermore, Mulder, Pitchford and Marlow (2011) acknowledged that their participants were less likely to come from income deprived families compared to non-participants, suggesting that their findings might be representative of very

preterm children from more advantaged families. Thus, the findings of studies characterized smaller and lower risk samples may underestimate the true extent of attention problems in very preterm children.

Secondly, the selective recruitment of preterm infants and children also affects the methodological robustness of a study. Lukeman and Melvin (1993) note that it is important to recruit preterm neonates according to gestational age rather than by birth-weight alone in an effort to exclude infants who may be born term equivalent age but small-for-gestational-age (Craig, Jackson & Hay, 2007). This is important to consider as developmental outcomes can vary as a function of being born small-for-gestational-age or with a birth weight appropriate-for-gestational-age (Aylward, 2002; Morsing, Asard, Ley *et al.*, 2011). Shum, Neulinger, O'Callaghn *et al.* (2008), for example, included 15 small-for-gestational-age only children in their sample of 45 preterm children which might account for the inconsistency of findings in relation to other preterm studies (*cf.* Anderson, Luca and Hutchinson *et al*., 2011).

Thirdly, the inadequate reporting of infant clinical and social background information reduces the ability to ascertain whether study findings are attributable to very preterm children of low and high medical or social risk. For example, Bayless and Stevenson (2007) only report gestational age, birth weight, days on supplementary oxygen, and length of hospital stay. The inclusion of information such as antenatal corticosteroid use, NEC, retinopathy of prematurity (ROP), BPD, grades of IVH and cystic PVL (*e.g.* Anderson, Luca and Hutchinson *et al.*, 2001), enables 1) the interpretation of results relative to perinatal risk and 2) to determine whether findings are comparable across groups of very preterm infants and children. Given these existing methodological issues, there is a strong need for longitudinal studies characterized by large and representative samples of children, detailed reporting of infant clinical information, and high

rates of sample retention to fully describe the attention impairments of children born very preterm.

2.3 The neuroanatomical correlates of attention. In addition to the neuropsychological assessment of children born very preterm, there has been a steady growth in the number of follow-up studies including magnetic resonance imaging (MRI) to examine developmental changes in brain structure and function in association with neurodevelopmental outcomes in children born very preterm (Toga, Thompson & Sowell, 2006; Lenrrot & Giedd, 2006; Petersen & Posner, 2012). Early neuropathology and brain development on term-equivalent MRI and ultrasound appears to be particularly important in explaining adverse cognitive, motor and behavioral outcomes in children born very preterm (Ancel, Livinec, Larroque *et al*., 2006; Edgin, Inder, Anderson *et al*. 2008; Woodward, Edgin, Thompson & Inder, 2005), while less is known about the impacts of longer term brain growth and development. As such, the inclusion of concurrent structural MRI and neuropsychological measures of attention is necessary to examine the longer term impacts of very preterm birth on brain development in regions involved in the circuitry of attention. The following chapter provides an overview of magnetic resonance imaging (MRI) and the neuroanatomical correlates of attention.

2.3.1 Overview of MRI in developmental follow-up. Magnetic Resonance Imaging (MRI) is an imaging modality that uses radio waves and magnetic fields to create in vivo images of the anatomical structure of the brain (Giedd, 2008). As a measure of cerebral anatomy, structural MRI characterizes the macro-structural properties of brain tissue in terms of grey matter volume and morphometry. Three-dimensional units called voxels are assigned tissue-probability values based on the tissue characteristics present in the corresponding voxel, and then classified into tissue type depending on MRI signal intensity. Voxels consisting of mostly

myelinated axons are assigned white matter tissue-probability values, whereas voxels of brain tissue with fewer myelinated axons are classified as grey matter (Giedd, 2008). To reduce likelihood of white and grey matter tissue misclassification, tissue probability maps based on pediatric brain atlases can be used as an initial segmentation of grey and white matter boundaries (Lenrrot & Giedd, 2006).

Within the past 20-years, rapid advancement of neuroimaging techniques has allowed for the increasingly detailed study of brain tissue structures and neural activity than was previously available to large longitudinal studies (Posner &Petersen, 2012). Examining regional differences in cortical volume between high-risk pediatric and control samples has brought to light the neuroanatomical pathologies linked with adverse neurodevelopmental outcomes, particularly for ADHD (Toga, Thompson & Sowell, 2006). While poor performance on neuropsychological measures of attention might suggest the presence of structural and functional abnormalities in the brain regions implicated in the neural circuitry of attention (Petersen & Posner, 2012), this issue is not well understood in children born very preterm.

2.3.2. The neuroanatomical correlates of attention. As previously outlined, the attention system is comprised of differentiated components of attention. Each component is subserved by its own neural network separate from the information processing system (Posner & Peterson, 1990). These networks consist of brain structures that, while independent, interact and rely on each other for efficient functioning (Elliot, 2003). The brain regions associated with each network of attention are shown in Figure 1 below. These neural networks are differentially activated during tasks that differentially test the components of attention (Konrad, Neufang, Thiel *et al.*, 2005). Although the regions of interest associated with attention are generally agreed upon in adult samples, the attention networks of children may also involve additional regions

compensate for neural immaturity relative to adults (Bunge, Dudukovic, Thomason *et al.*, 2002; Konrad, Neufang, Thiel *et al.*, 2005).

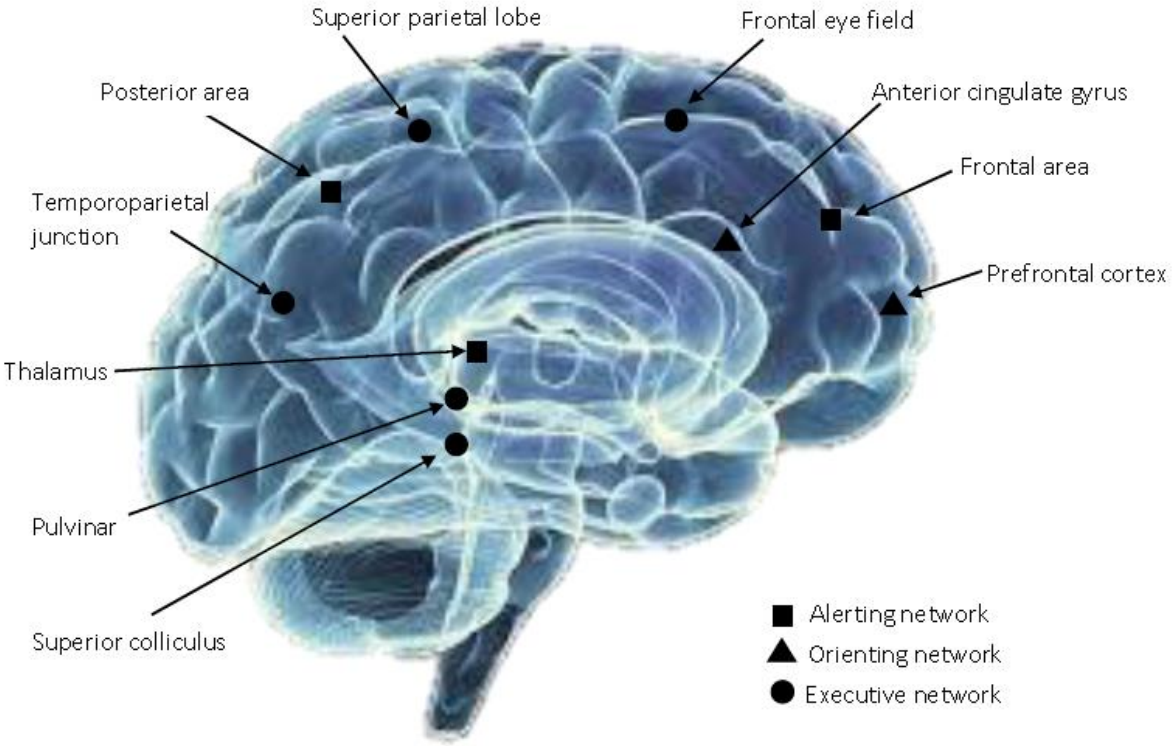


Figure 1. Neuroanatomical regions associated with the alerting, orienting and executive networks of attention. Adapted from Posner and Rothbart (2007).

2.3.3 The alerting network. The alerting network underlies focused and sustained attention, wherein a series of regions are activated as the brain prepares neural pathways for the detection of incoming task-relevant information (Cohen, 2014; Konrad, Neufang, Thiel *et al.*, 2005). Posner and Peterson (1990) suggest that the right cerebral cortex is implicated in alerting and sustained attention tasks. Specific areas within the right cortex include the frontal lobe, right ventral prefrontal cortex, and parietal lobe (Fan, McCandliass, Sommer, *et al*, 2002; Konrad, Neufang, Thiel *et al*., 2005). The left superior parietal gyrus has also been implicated in alerting tasks; creating a fronto-parietal network (Konrad, Neufang, Thiel *et al*., 2005). Experimental

fMRI in children has shown that the brain regions activated during the altering condition of the Attention Network Task were localized to the right middle occipital cortex and the right superior temporal gyrus (Konrad, Neufang, Thiel *et al*., 2005). This finding suggests that the alerting network is still immature in children aged 8 – 12 years and that other brain circuitry maybe involved for sustaining attention.

2.3.4 The orienting network. The orienting network prioritizes sensory information to support selective attention, and is comprised of both frontal and posterior regions that make up the dorsal and ventral networks (Fan, McCandliass, Sommer *et al*., 2002; Petersen & Posner, 2012). The dorsal orienting network includes the intraparietal sulcus and superior parietal lobe; regions that are associated with the disengagement and reorientation of attention (Posner & Petersen, 2012; Posner, Waker, Friedrich *et al.,* 1984). Petersen and Posner (2012) also recognize the thalamus as playing an important role in coordinating the reorientation of attention to selected stimuli. First, the parietal lobe is responsible for disengaging attention from its present focus. Second, the midbrain area orientates attention to the area of the new target, and third, the pulvinar of the thalamus relays the information from the newly indexed location. The ventral pathway includes the temporal-parietal junction in connection with the thalamus, and is important for covert visual reorienting of attention and pattern recognition in selective attention tasks (Fan, McCandliass, Sommer, *et al*, 2002; Posner & Petersen, 1990). Konrad, Neufang, Thiel *et al*. (2005) also found increased neural activity in the temporal-parietal junction among adults during the orienting component of the Attention Network Task task-based fMRI, in addition to activity in the right inferior frontal gyrus and bilateral superior parietal cortex. In children, the same orienting task activated neural firing in the superior frontal gyrus and the bilateral occipital cortex (Konrad, Neufang, Thiel *et al*., 2005).

2.3.5 The executive network. The executive attention network provides top-down support for higher-level attentional functions, particularly during tasks that present incongruent information that competes for attention or when attentional resources must be divided across tasks (Murray, Scratch, Thompson *et al.*, 2014). A number of executive attention circuits have been postulated but the executive network generally draws upon prefrontal and anterior cingulate regions (Fan, McCandliass, Sommer, *et al*, 2002; Konrad, Neufang, Thiel *et al*., 2005; Petersen, Skudlarski, Gatenby *et al.*, 1999; Pisapia & Braver, 2006, Pirot, Godbout, Mantz, *et al*., 1992). In neuropsychological evaluation of children, bilateral prefrontal lesions appear to be particularly associated with global deficits in executive attention skills, including poor shifting of attention (Anderson, Jacobs & Harvey, 2005). While the prefrontal region is the higher-order executive control center of attention that initiates and coordinates cognitive control, the cingulate cortex modulates and coordinates the limbic system's state arousal with the frontal system's execution of responding during tasks that compete for attention (Cohen, 20014). The anterior cingulate cortex also plays a role in the detection of cognitive interference effects that compete for attention (Pisapia & Braver, 2006). For example, Pardo, Pardo, Janer and Raichle (1990) found that the largest regional cerebral blood flow effect in adults during the Stroop interference condition of the Color/Word task was in the anterior cingulate cortex. The anterior cingulate cortex may, therefore, play an important role in the detection of stimulus conflict and the recruitment of processing centers of attention for the execution of task-relevant behavior.

Posner and Petersen (1990) further describe the executive network as having two identifiable circuits involved in the subcomponents of executive attention. The front-parietal circuit includes the dorsolateral prefrontal cortex, intraparietal sulcus, inferior parietal lobe; which modulate task response selection and the initiation of responding during conflict trials. In contrast, the cingulo-

opercular system comprised of the medal frontal cortex, dorsal anterior cingulate cortex, and thalamus; and is responsible for maintaining consistent responding across trials and monitors task performance as a whole. Although the left-sided middle frontal gyrus has been implicated as part of the executive network for children aged 8 – 12 years similar to adults, other areas of activation in children include the right superior temporal gyrus and the bilateral occipital cortex (Konrad, Neufang, Thiel *et al*., 2005).

2.3.6 The neural bases of attention in children born very preterm. Structural and functional MRI imaging in adults has identified the presence of three anatomically separate neural networks that underlie the key components of attention. These networks and their associated brain areas highlight key regions of interest to examine when investigating attention processes in children born very preterm. However, the extent to which very preterm birth impacts the growth and development of the brain regions implicated in attention is not well understood. On term-equivalent MRI, regional reductions in cerebral tissue volume have been found in the dorsal prefrontal, orbitofrontal, and parieto-occipital regions in very preterm infants (Bora, Pritchard, Chen *et al.*, 2014); regions that are theoretically consistent with current models of attention (Fan, McCandliass, Sommer, *et al*, 2002; Konrad, Neufang, Thiel *et al.*, 2005; Posner & Petersen, 2012). However, studies including concurrent measures of grey matter growth and development and attention at school age are virtually non-existent despite the high rate of neural injury and abnormality in this population.

2.4 Neuropathological outcomes of infants born very preterm. Very preterm birth is associated with a myriad of early neuronal injuries and abnormalities. Both ultrasound and MRI at term-equivalent age indicate that there is a higher incidence of IVH, ventricular dilation (DIL), white matter (WM) cysts, and hypoxic-ischemic related tissue atrophy among very preterm

infants relative to the general obstetric population (Hart, Whitby, Griffiths & Smith, 2008; Inder, Anderson, Spencer *et al*., 2003; Inder, Huppi, Warfield *et al.*, 1996; Taylor, Minich, Bangert *et al*., 2004; Thompson, Warfield, Carlin *et al*., 2007). Importantly, these early markers of diffuse white matter injury (WMI) resulting from the negative sequelae of ischemic, inflammatory and excitotoxic events of preterm birth (Volpe, 2009) are strong predictors of outcomes in children born very preterm (Ancel, Livinec, Larroque *et al*., 2006; Edgin, Inder, Anderson *et al*. 2008; Woodward, Edgin, Thompson & Inder, 2005; Woodward, Clark, Bora, Inder, 2012). A number of studies report significant associations between diffuse WMI and poor motor and cognitive development among children born very preterm (Edgin, Inder, Anderson *et al*. 2008; Woodward, Anderson, Austin, Howard, Inder, 2006; Woodward, Clark, Bora, Inder, 2012). In contrast, weaker associations have been found with respects to WMI and ADHD and attention outcomes, which instead show stronger associations with neonatal grey matter abnormalities (Bora, Pritchard, Chen *et al.*, 2014; Murray, Scratch, Thompson, *et al*., 2014). Thus, grey matter may be an important mechanism for inattention in children born very preterm.

Volumetric MRI at term-equivalent age has shown that infants born very preterm have reduced cortical and subcortical gray matter volume compared to full term born infants (Inder, Warfield, Wang *et al.*, 2005). Current perspectives suggest that structural abnormalities in grey matter growth and development are an important secondary marker of the diffuse neuronal abnormalities sustained around the time of very preterm birth (Inder, Huppi, Warfield *et al*, 1999; Volpe, 2009). The primary form neural injury associated with very preterm birth is injury to pre-oligodendrocytes that produce myelin; a process that either impacts or is further impacted by poor axonal differentiation and/or sub-optimal myelination of axon fibers (Leviton & Gressens, 2007; Volpe, 2009, *see Appendix A*). Structural differences in grey matter volume

among very preterm children reflect the longer tissue growth failure associated with suboptimal or delayed myelination poor axonal differentiation, and compromised synaptogenesis and pruning over time (Inder, Huppi, Warfield *et al.*, 1999; Volpe, 2009). There is now a growing body of research suggesting that structural alterations in grey matter persist beyond infancy into childhood and adolescence. This forms the central focus of the second literature review for the dissertation.

2.5 Grey matter development in children born very preterm: A systematic review

2.5.1 Inclusion Criteria. To identify published studies examining the growth and development of grey matter in very preterm children at school age, a second systematic literature review was undertaken. The databases PsycINFO, PubMED, ScienceDirect, and Google Scholar were systematically explored for relevant publications from March 2012 to March 2015. Key search terms included different variations and combinations of: total grey matter/ volume(s); regional grey matter/ volume(s), structural MRI, voxel based morphometry, regions of interest, very/preterm birth, school age, and childhood. Publication selection criteria for the literature review were as follows:

General publication selection criteria: Peer reviewed and published between 2000 and 2015, with English as the first language.

Specific publication selection criteria: Studies that 1) included non-medically selected preterm children (≤ 33 weeks GA and ≤ 2,500g birth weight) sample as the primary group of interest, 2) included an appropriate full-term comparison group, 3) examined either total or regional grey matter volumes at school age (12 ± 4 years), 4) of longitudinal or cross-sectional research design were included. To account for changes in neonatal care impacting early brain development, thus minimizing cohort effects, an additional selection criteria stipulated that studies with cohorts

born prior to 1980 were excluded (*for rationale, see* Darlow, Cust & Donoghue, 2003; Effer *et al*., 2002; Moore, Hennessy, Myles *et al.*, 2012). Three articles that otherwise met study selection criteria were excluded on this basis (Allin, Matsumoto, Santhouse *et al*., 2001; Nosarti, Al-Asady, Frangou *et al.*, 2002; Nosarti, Allim, Frangou, 2005).

Key outcomes of interest: Structural MRI studies comparing the total and regional grey matter volume between children born very preterm and full term children at school age. Using these criteria, 9 studies were reviewed and are summarized in Table 2 below.

2.5.2 Global grey matter volume of children born very preterm. A global reduction in grey matter volume in very preterm children at school age was a consistent finding across a number of studies selected for detailed review. As an overall indication of grey matter growth and development, total cerebral grey matter of very preterm children and adolescents was approximately 3.8 – 8.8% smaller than full term children and adolescents aged 9 to 15 years old (Kesler, Ment, Vohr *et al.*, 2004*;* Nagy, Ashburner, Andersson *et al.*, 2009*;* Parker, Mitchell, Kalpakidou *et al.*, 2008; Soria-Pastor, Padilla, Zubiaurre-Elorza *et al.*, 2009). This difference remained after covariate adjustment for total brain volume, sex and age (Nagy, Ashburner, Andersson *et al.*, 2009). In addition to cortical grey matter, subcortical grey matter volume was also significantly smaller in vey preterm children compared to full term children (Kesler, Ment, Vohr *et al.*, 2004).

In terms of tissue growth, Ment, Kesler and Vohr *et al.* (2009) examined the comparative change in total brain volume and hemispheric grey matter volume in very preterm and full term children between ages 8 and 12 years old. Both groups of children evidenced an overall increase in total brain volume of around 2 – 3% suggesting that total brain size increases at late school age for

Table 2
Summary of Volumetric MRI Findings in Children Born Very Preterm at School Age

Author (date)	Sample						Methods		Results						
	VPT				FT										
	Year born	GA	BW	*n*	*n*	Age	MRI methods	Research objective	Whole brain	VPT > FT GM volume	VPT < FT GM volume	Other key findings	Rationale of findings	Study +/-
Ment, Kesler, Vohr *et al.*, (2009)	1989 – 1992	28.4	972	55	20	8 - 12	Volumetric: BrainImage and FSL Serial MRI scans at 8 and 12 years	Volumetric change in whole brain and regional tissues between ages 8 - 12 years	TBV change for both groups 2 – 3% L cerebral GM change: VPT: -2%, FT: -10% R cerebral GM change: VPT -3%, FT: -9%	Bilateral parietal cortices at 12 years Trend for bilateral frontal cortex at 12 years (n.s)	Bilateral temporal cortex, and L deep cortical GM at 12 years	Largest change in parietal GM for both groups Rate of reduction in GM volume less in VPT than FT VPT females smaller L. cerebral GM volume than VPT males	Temporal delay in nonlinear maturational changes in GM	+ Prosp. long. + 78.2% rate of usable T1s + Detailed infant clinical data - Data artefact from 2 different MRI scanners used

Table 2
Summary of Volumetric MRI Findings in Children Born Very Preterm at School Age

Sample							Methods		Results					
Author (date)	**VPT**			**FT**		**Age**	**MRI methods**	**Research objective**	**Whole brain**	**VPT > FT GM volume**	**VPT < FT GM volume**	**Other key findings**	**Rationale of findings**	**Study +/-**
	Year born	**GA**	**BW**	***n***	***n***									
Kesler, Reiss, Vohr *et al.*, (2007)	1989 – 1992	28.5	972.5	29	22	12	VBM: SPM2	Between groups differences in regional GM volumes Analysis restricted to male subjects; no differences found in female subjects	VPT reduced cerebral GM (p = .04), did not remain after controlling for TBV	N.I	VPT reduced prefrontal, and temporal volume, reduced temporal volume remained after controlling for TBV Bilateral posterior superior temporal gyri Basal ganglia	Bilateral superior temporal gyri represented region of peak GM volume difference, pronounced in L hemisphere No correlations between GM volumes and GA, BW, or cognitive outcomes	Male vulnerability related to redundancy in certain X-chromosome genes that regulate neurobiology and brain plasticity	+ Prosp. long. + Matched FT sample + Optimized VBM - Low risk sample no IVH or PVL - Small sample

Table 2
Summary of Volumetric MRI Findings in Children Born Very Preterm at School Age

Author (date)	Sample						Methods		Results					
	VPT				FT									
	Year born	GA	BW	*n*	*n*	Age	MRI methods	Research objective	Whole brain	VPT > FT GM volume	VPT < FT GM volume	Other key findings	Rationale of findings	Study +/-
Kesler, Ment, Vohr *et al.*, (2004)	1989 – 1992	28.3	966	73	33	7 - 11	Volumetric: BrainImage	Between groups differences whole brain, cortical and subcortical deep GM volume Regional enlargements and reductions investigated	VPT cerebral GM 3.8% smaller than FT VPT subcortical GM 6.9% smaller than FT	VPT frontal lobe volume 2.2% larger than FT VPT parietal lobe volume 4.5% larger than FT	VPT parietal lobe volume 4.5% smaller than FT	BW negatively correlated with parietal and frontal GM volume IVH any grade 6 hours after birth negatively correlated with temporal GM volume	Disrupted maturation from 1) delayed synaptic pruning → increased anterior volumes, 2) tissue atrophy from hypoxic-ischemic events → decreased temporal volume	+ Prosp. long. + Matched FT sample - Small FT sample - 134/200 (67%) of eligible VPT subjects scanned - 61/134 (46%) of acquired MRI scans for VPT excluded artefacts
Peterson, Vohr, Staib *et al.* (2000)	1989 – 1992	28.7	997	25	39	8.6	Volumetric: ANALYZE 7.5 Manual parcellation of each hemisphere into 8 ROIs	Between groups differences in cortical and subcortical GM ROIs: Amygdala Hippoca	VPT regional (GM and WM) reductions in bilateral premotor (-12%), sensorimotor (-14%), midtemp	N.S	VPT bilateral reductions: Amygdala L: -20.2%, R: -30.0% Hippocampus L: -16.0% R: -12.0%	VPT reductions in GM persist excluding IVH cases R amygdala positively correlated with GA Bilateral	VPT birth → disruptions in blood flow or nutrient delivery → Regional structural abnormalities; not likely the result of	+ Prosp. long. + Matched FT sample + Detailed infant clinical data - Small sample - Cortical measures did not

Table 2
Summary of Volumetric MRI Findings in Children Born Very Preterm at School Age

Author (date)	Sample						Methods		Results						
	VPT				FT										
	Year born	GA	BW	*n*	*n*	Age	MRI methods	Research objective	Whole brain	VPT > FT GM volume	VPT < FT GM volume	Other key findings	Rationale of findings	Study +/-
								mpus Basal ganglia nuclei (caudate, putamen, globus palidus)	oral (-7-10%), L parieto-occipital (8%), cerebellum (-7%)		Caudate L: -12.3% R: -11.9% Putamen L: -11.4% R: -12.6% Globus Palidus L: -13.8% R: -12.5%	globus palidus positively correlated with 5-Minute Apgar scores L caudate nucleus negatively correlated with IVH	hemorrhagic or hypoxic lesions (weak association with IVH)	segment GM and WM
Nagy, Ashburner, Andersson *et al.* (2009)	1988 – 1993	28.5	1069.5	74	69	14.9 Range: 12 - 17	VBM: SPM5	Between groups differences in total brain volume; Voxel-wise comparison of GM volumes	VPT total GM volume 8.8% smaller than FT GM volume associated with GA < 30 weeks and BW < 1000g	No differences found	Unadjusted: VPT reduced volume in bilateral temporal, central, prefrontal, orbitofrontal, and parietal lobes, caudate nuclei, hippocampi, thalami Adjusted	GM volume/WM volume ratio *n.s.* Findings did not change excluding cases SGA or with abnormal radiologic readings GM differences milder than	VPT birth → Stress response → Increased endogenous corticosteroid levels → Inhibition of tissue growth	+ Large sample + Matched FT group + Prosp. long. - 74/182 (41%) VPT retention

Table 2
Summary of Volumetric MRI Findings in Children Born Very Preterm at School Age

Author (date)	Sample						Methods		Results						
	VPT				FT										
	Year born	GA	BW	*n*	*n*	Age	MRI methods	Research objective	Whole brain	VPT > FT GM volume	VPT < FT GM volume	Other key findings	Rationale of findings	Study +/-
											for gender & age at scan: VPT reduced volume on temporal and parietal lobes	previous reports		
Nosarti, Giourouk ou, Healy *et al.* (2008)	1979 - 1982 and 1983 - 1984	29.1	1276	218	12 8	14 - 15	VBM: SPM2	Nature and extent of GM abnormali ties Associati on between Gm and 1) GA, and 2) PVH and ventricula r dilation	NR	VPT increases in bilateral temporal and frontal lobes, cingulate gyri, fusiform gyri, cerebellu m	VPT reductions in temporal, frontal, occipital cortices and cerebellum , including putamen, insula, cuneus, fusiform gyrus, thalamus, caudate nucleus Peak GM difference in the	Evidence of structural covariance In volume between regions structurally associated Greatest structural alterations found in cases with PVH and ventricular dilation	1) Compromi sed synaptogen esis → increased tissue atrophy → reduced GM volume 2) Less efficient or delayed cell death or synaptic pruning → increased GM volume	+ 2 VPT cohorts + Large sample + 76% VPT sample retention + 82% of VPT group 1 and 61% of VPT group 2 had MRI + 89% rate of usable T1s + FT group matched age and SES - Limited

Table 2
Summary of Volumetric MRI Findings in Children Born Very Preterm at School Age

Author (date)	Sample						Methods		Results						
	VPT			FT		Age	MRI methods	Research objective	Whole brain	VPT > FT GM volume	VPT < FT GM volume	Other key findings	Rationale of findings	Study +/-
	Year born	GA	BW	*n*	*n*									
											middle temporal gyrus			infant clinical data
Parker, Mitchell, Kalpakidou *et al.* (2008)	1982 – 1984	28.6	1235	65	34	15 and 18	Volumetric: SPM2 Serial MRI at 15 years and at 18 years	Total grey matter volume and change in volume between VPT and FT ROI: Cerebellum	Main effect of group and time point on total GM volume VPT 7.7% smaller at age 15 years, 7.4% smaller at 18 years than FT	N/A	N/A	N.s trend for VPT reduced volume in cerebellum to FT Volume of cerebellum decreased between 15 – 18 years for VPT, no change for FT	1) Changes in any region result in cascade of alterations in other regions 2) Delayed maturation or excessive synaptic pruning → structural alterations	+ Large VPT sample + Serial MRI - Limited infant clinical data for VPT group - 58% sample assessed at both time points - 48% sample MRI at both time points
Soria-Pastor, Padilla, Zubiaurre- Elorza *et al.* (2009)	1996 – 1998	32.5	1754	20	22	9.3 (8-10)	VBM: SPM5	Between groups differences in total GM volume, and regional	PT total GM volume 6.1% smaller than FT	N.s.	VPT smaller bilateral middle temporal gyrus and L. post-central	GM volume in both regions positively correlated with 1) GA at birth and 2) IQ scores	1) Delayed or disrupted brain maturation processes 2) WM	+ Matched FT group - Small samples - Low risk sample only - Limited

Table 2
Summary of Volumetric MRI Findings in Children Born Very Preterm at School Age

Author (date)	Sample						Methods		Results					
	VPT			FT										
	Year born	GA	BW	*n*	*n*	Age	MRI methods	Research objective	Whole brain	VPT > FT GM volume	VPT < FT GM volume	Other key findings	Rationale of findings	Study +/-
								structural alterations in GM volume			gyrus of parietal lobe	at age 8-10 years	damage → reductions in GM as a secondary effect	infant clinical data
Abernethy, Palaniappan & Cooke (2002)	1980 – 1981	28.6	1103	87	8	15 – 16	Cross sectional measurement and manual tracing	Between-groups differences in caudate nuclei volumes and hippocampal formations Associations with ADHD diagnosis	N.I.	N.s	VPT reduced volume in bilateral caudate nuclei than FT Differences in bilateral hippocampal volumes n.s., but VPT lower hippocampal ratio to FT indicating structural asymmetry	VPT with ADHD showed further volumetric reduction in R. caudate nuclei	Poor early postnatal growth persists into adolescence	+ Large VPT sample + Prosp. long. - Small FT sample - Limited infant clinical data

N.I Not investigated, N.s. Not statistically significant ($p > .05$), Prosp. long. Prospective longitudinal research design/cohort

both groups. There was however, a significant between-groups difference in the rate of non-linear change in cerebral grey matter volume in each hemisphere from 8 to 12 years. Left cerebral grey matter volume showed a 10% reduction in full term children whereas very preterm children only showed a 2% reduction in volume. A similar pattern was reported for right cerebral grey matter. Importantly, these findings suggest that very preterm children have delayed grey matter growth and development compared to their full term peers. A number of the reviewed studies suggested that structural alterations on grey matter volume between very preterm and full term children are regionally specific.

2.5.3 Regional reductions of grey matter volume in children born very preterm. A number of grey matter cortical and subcortical structures were identified as having reduced grey matter volume in very preterm children compared to full term children at school age. Commonly identified cortical regions included the bilateral temporal, parietal and prefrontal cortices (Kesler, Ment, Vohr *et al.,* 2004; Kesler, Reiss & Vohr *et al.,* 2007; Ment, Kesler & Vohr *et al.,* 2009; Nagy, Ashburner, Andersson *et al*., 2009; Nosarti, Giouroukou & Healy *et al.,* 2008). Regional reductions in the temporal and parietal cortices remained in very preterm children after covariate adjustment for total brain volume, sex and age at scan (Ment, Kesler & Vohr *et al.,* 2009; Nosarti, Giouroukou & Healy *et al.,* 2008). Linear associations between decreasing gestational age and reduced grey matter volume was also found in a small (n = 20) of very preterm children at age 9 years (Soria-Pastor, Padilla, Zubiaurre-Elorza *et al.,* 2009).

In addition to reduced cortical grey matter in very preterm children, reductions in grey matter volume were also reported for a range of subcortical grey matter structures. Specifically, very preterm children evidenced reduced grey matter volume in the hippocampus, thalami, basal ganglia, amygdala, caudate nuclei, putamen and globus palidus (Abernethy, Palaniappan &

Cooke, 2002; Kesler, Reiss & Vohr *et al.*, 2007; Nagy, Ashburner, Andersson *et al*., 2009; Nosarti, Giouroukou & Healy *et al.*, 2008; Peterson, Vohr, Staib *et al.*, 2000). In terms of associations with infant clinical factors, volumetric reductions in the amygdala, globus palidus, and caudate nuclei at age 8 years were significantly associated with decreased gestational age, poorer 5-minute Apgar scores, and presence of IVH, respectively (Peterson, Vohr, Staib *et al.*, 2000).

2.5.4 Regional increases of grey matter volume in children born very preterm.

Although less commonly reported, structural alterations in grey matter growth and development also included regional increases in grey matter volume in very preterm children compared to full term children at school age. Within very preterm children, regional increases in grey matter volume were found in the parietal and prefrontal cortices, the cerebellum, and middle temporal, prehippocampal and fusiform gyri at ages 8 to 15 years (Ment, Kesler, Vohr *et al.*, 2009; Nosarti, Giouroukou, Healy *et al.*, 2008). In contrast, Nagy, Ashburner & Andersson *et al*. (2009) did not identify any grey matter regions that were characterized by increased grey matter volume in their sample of very preterm children aged 12 to 17 years. The authors note that their findings, consistent with previous analyses of this cohort, are less severe than found in other groups of very preterm subjects and likely due to the low-risk nature of their sample as very few infants (<25%) required mechanical ventilation during the neonatal period.

2.5.5 Methodological limitations in structural MRI literature of children born very preterm.

Findings from the second literature review suggest that structural alterations in grey matter volume persist beyond infancy and into childhood and adolescence for children born very preterm. Structural alterations in grey matter include both regional decreases and increases of volume across a range of cortical and subcortical structures, and serial MRI suggested that

structural alterations might reflect a delay in the timing of grey matter growth for very preterm children (Ment, Kesler and Vohr *et al.,* 2009). However, many of the reviewed studies were limited by two main methodological issues, including small and selective samples and the inadequate reporting of infant clinical characteristics.

First, many studies were characterized by small and selective samples of children born very preterm. For example, the sample sizes of Kesler, Reiss and Vohr *et al*. (2007), Peterson, Vohr and Staib *et al.* (2000) and Soria-Pastor, Padilla and Zubiaurree (2009) ranged from 20 to 29 participants. Reasons for small sample size were attributable to low participant response rates, intentionally restricting the sample to the first 20 enrolled in the larger study, and excluding children with abnormal neonatal ultrasound. Other longitudinal studies experienced substantial data loss due to MRI artefacts and motion on structural T1-weighted images (Kesler, Ment, Vohr *et al*., 2004) and longitudinal sample attrition over time (Nagy, Ashburner, Andersson *et al*., 2009; Nosarti, Giouroukou, Healy *et al.,* 2008). Consequentially, it remains unclear whether previous study findings will replicate in larger and more diverse samples of very preterm children.

Second, a number of studies provided only limited information regarding the infant clinical characteristics and social background information of very preterm samples (Abernethy, Palaniappan & Cooke, 2002; Nosarti, Giouroukou, Healy *et al.,* 2008; Parker, Mitchell, Kalpakidou *et al.,* 2008; Soria-Pastor, Padilla & Zubiaurree, 2009). Thus, the extent to which current findings relating to the grey matter development of children born very preterm might represent children of low, moderate or high medical and social risk backgrounds is not well understood. In addition, while some studies considered more detailed infant clinical information in relation to grey matter outcomes (Kesler, Ment, Vohr *et al.,* 2004; Nagy, Ashburner,

Andersson *et al.*, 2009; Peterson, Vohr, Staib *et al.*, 2000), none considered the possible influence of early exposure to socio-familial adversity.

2.6 Rationale for the current study. Despite higher levels of attention problems and grey matter abnormalities in children born very preterm, no study has examined the concurrent relationships between very preterm children's performance on neuropsychological measures of attention and structural MRI at school age. Previous research has shown strong links between cerebral white matter injury/abnormalities and poorer neuromotor and cognitive outcomes for very preterm children, while no such relationship has been reported for attention outcomes (Bora, Pritchard, Chen, *et al.*, 2014; Woodward, Clark, Bora & Inder, 2012; Woodward, Clark, Pritchard, *et al.*, 2011). This suggests that the mechanism for inattention may be different for very preterm children. As suggested earlier, one mechanism that may have longer term implications for the attention outcomes of very preterm children is cerebral grey matter growth and development, and in particular, regional grey matter volume.

Infants born very preterm have reduced grey matter volume in both cortical and deep nuclear grey matter structures; a secondary marker of neuronal injury, poor axonal differentiation and compromised synaptogenesis and pruning over time (Inder, Huppi, Warfield, *et al*. 1999; Inder, Warfield, Wang, *et al.*, 2005; Volpe, 2009). Longer term structural alterations in gray matter volume has been linked to general cognitive dysfunction in children born very preterm (Allin, Matsumoto, Santhouse *et al.*, 2001; Peterson, Vohr, Staib *et al.*, 2000). In terms of attention, strong relationships between neonatal gray matter volume and clinical measures of attention in childhood have been reported. For example, a recent study by Bora, Pritchard, Chen *et al.* (2014) found that reductions in the relative percentage of total cerebral tissue within the intracranial cavity of the dorsal prefrontal, orbitofrontal, premotor, sensorimotor, and parieto-occipital

regions at term equivalent age was significantly associated with increased risk of persistent ADHD diagnosis in very preterm children to age 9 years. In contrast, this study did not find significant relationships with respect to either myelinated or unmyelinated white matter volume. Associations between reduced deep cortical gray matter abnormality on term-equivalent MRI and poor selective, sustained and executive attention have also been found for very preterm children at age 7 years (Murray, Scratch, Thompson *et al.*, 2014). However, no study has examined concurrent relations between structural measures of grey matter volume and sustained, selective and executive attention at school age, and as such, the longer-term neural mechanisms of inattention remain poorly understood in very preterm children. This issue forms the central rationale for the current study.

2.7 Aims of the current study. Collectively, the reviewed findings suggest that very preterm born children are a vulnerable group at increased risk of adverse neurodevelopmental outcomes compared to their full term peers (Aarnoudse-Moens *et al*., 2009; Bhutta *et al*., 2002). Particular risks include increased rates attention impairment (Mulder, Pitchford & Marlow, 2011; Shum *et al.*, 2008). However, divided attention remains understudied, and the nature of attention impairments among those born at younger gestational ages is not well understood (Anderson *et al*., 2011; Bayless & Stevenson, 2007; van de Weijer-Bergsma, Winjroks & Jongmans, 2008). In addition to risks of attention impairment, very preterm children also show structural alterations in grey matter growth and development in childhood which may be an important mechanism for attention outcomes (Bora, Pritchard, Chen *et al*, 2014; Nagy, Ashburner, Andersson *et al.*, 2009; Peterson, Vohr, Staib *et al.*, 2000). Despite these risks, no study to date has examined the attention outcomes of very preterm children in association with concurrent structural MRI. Furthermore, previous research has reported only weak to modest

associations between early infant clinical and neuropathological factors and attention (Anderson *et al*, 2011; Wilson-Ching, Molloy, Anderson *et al*. 2013) suggesting that other longer term developmental factors, such as grey matter volume in childhood, may be important in explaining risks of inattention in very preterm children. Therefore, the research aims and hypotheses of the current study were:

1. To describe the nature and extent of attention problems of very preterm and full term children on the Test of Everyday Attention for Children at age 12-years, corrected for extent of prematurity. The three key components of attention measured were selective, sustained and executive attention.

Hypothesis 1a: Very preterm children will have significantly poorer mean selective, sustained, and executive attention scores on the TEA-Ch compared to full term children. These differences will remain after covariate adjustment for social risk index, a factor known to modify risk of ADHD in very preterm children (Lindstrom, Lindblad & Hjern, 2011; Wolke, 1998).

Hypothesis 1b: Very preterm children will have significantly higher rates of impairment on the selective, sustained, and executive attention subtests of the TEA-Ch compared to full term children. These differences will remain after covariate adjustment for social risk index.

Hypothesis 1c: Very preterm children will show the greatest performance impairment relative to full term children on the higher-order executive attention measures of switching and divided attention.

Hypothesis 1d: As very preterm children born at younger gestational ages may be at further risk of poor neurodevelopmental outcomes compared to their more mature counterparts (Johnson, 2007; Wolke, 1998), it is hypothesized that children born extremely preterm (< 27 weeks

gestational age) age at birth will obtain poorer selective, sustained, and executive attention scores and increased rates of attention impairment at age 12 years.

2. To document the cerebral structural alterations of very preterm and full term children at age 12 years, using whole brain volumetric MRI measures and voxel based morphometry.

Hypothesis 2a: Very preterm will have significantly lower mean modulated grey matter volume values compared to full term children in the parietal, temporal, frontal and thalamic regions. These differences will remain after covariate adjustment for corrected age at MRI scan and social risk index.

Hypothesis 2b: Very preterm children will have significantly higher mean modulated grey matter volume values compared to full term children in the occipital lobe and anterior cingulate cortex. These differences will remain after covariate adjustment for corrected age at MRI scan and social risk index.

3. To examine associations between very preterm children's selective, sustained and executive attention impairment and mean grey matter volume values within specific regions of interest at age 12 years. Key grey matter regions of interest were selected from both theory-driven and data-driven approaches. Previous research has implicated the parietal, occipital, temporal, frontal, and anterior cingulate cortices and thalami in neurocognitive models of attention. Areas where regional differences in grey matter density were identified between very preterm and full term children were similarly examined, and included the posterior cingulate cortex and hippocampi.

Hypothesis 3a. Within the very preterm group, poorer selective, sustained, and executive attention scores will be significantly correlated with reduced grey matter volume in the key regions identified in the voxel based morphometry analysis.

4. To examine the extent to which regional grey matter volume makes an independent contribution to attention outcomes at age 12-years, after taking into account neonatal and social factors also correlated with attention in the very preterm group.

Hypothesis 4a: After taking into account 1) infant clinical factors including intrauterine growth restriction, retinopathy of prematurity, steroid exposure; 2) infant neuropathological factors including periventricular leukomalacia, white matter injury; and 3) social risk index at term, regional grey matter volumes that differentially correlated with the components of attention will be independent predictors of TEA-Ch test scores.

Chapter 3. Methods

3.1 Research design. The current study forms part of a larger prospective longitudinal study investigating the neurodevelopmental outcomes of children born very preterm, evaluated at age 12 years. This multidisciplinary study examines the neurological, health, motor, and psychological development of children born less than 33 completed weeks of gestation. The study sample was recruited during the neonatal period and has since undergone comprehensive neurodevelopmental evaluations at regular follow-up intervals. These intervals span age 2, 4, 6, 9 and 12 years. This dissertation utilizes concurrent neurodevelopmental and structural MRI data collected at age 12 years.

3.2 Description of the sample. The study sample consisted of two groups of children (*n* = 223) born between 1998 and 2000 at Christchurch Woman's Hospital, New Zealand. Across both groups, exclusion criteria included congenital abnormality, fetal alcohol syndrome, family residing outside of the recruitment region, mother non-English speaking, and mother unable to give informed consent. Infants born from multiple births were included in the study. Figure 2 shows the longitudinal sample retention for both groups of very preterm and full term children from birth to age 12 years.

3.2.1 The very preterm sample. The first group was comprised of infants born less than 33 weeks completed gestation (*n* = 110). These infants were consecutively admitted to Christchurch Woman's Hospital level III Neonatal Intensive Care Unit (NICU) which is the sole provider of tertiary care for infants born prematurely in the Canterbury region. Mothers of infants eligible for study inclusion were approached for participation by the research nurse or

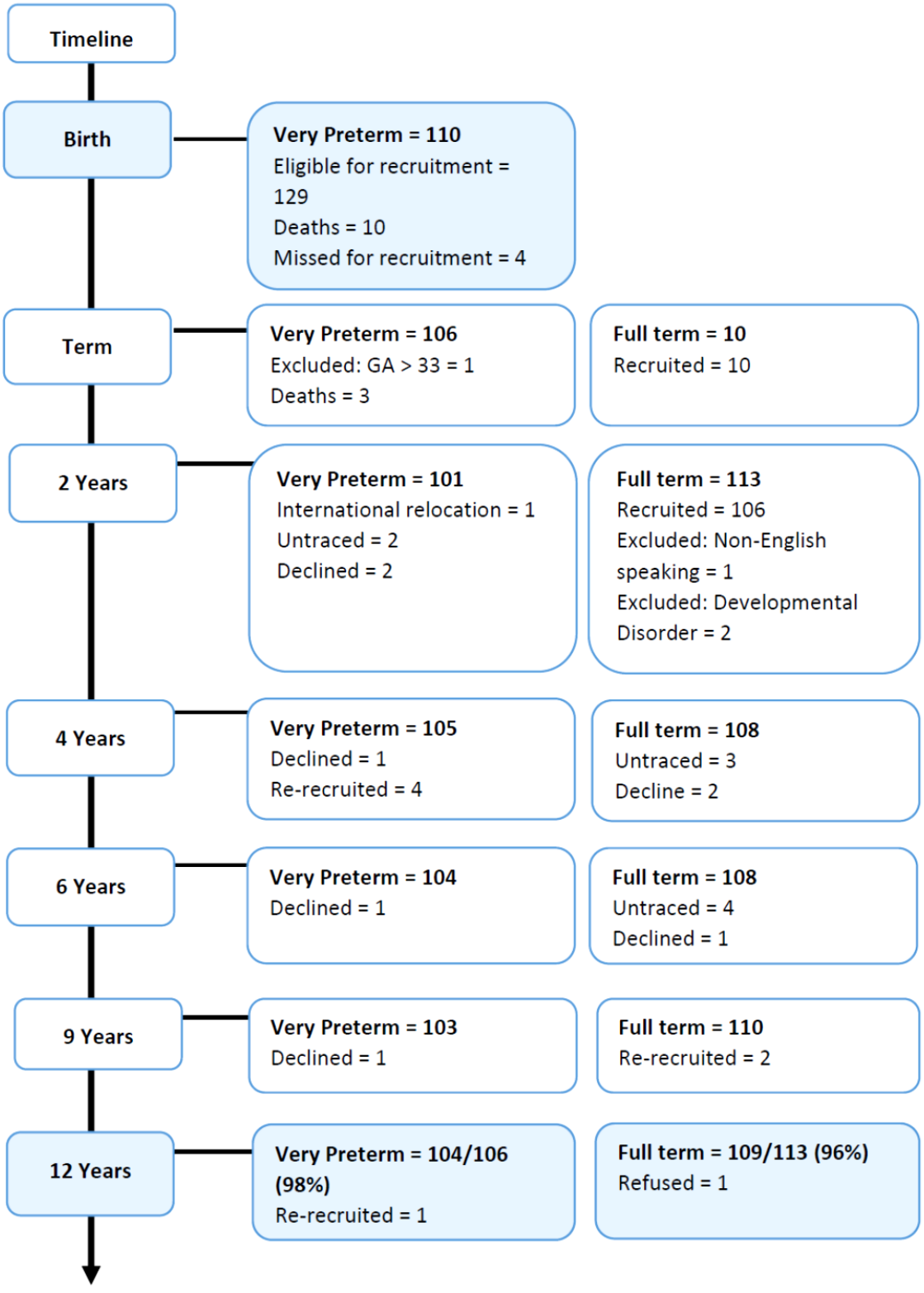


Figure 2. Overview of the longitudinal sample retention for the current study spanning birth to age 12 years.

neonatologist following NICU-III admission. Of those approached, 92% consented to study participation. Excluding deaths (n = 10), reasons for non-recruitment included missed for recruitment (n = 4) and declining participation (n = 5). At term equivalent age (*i.e.* the infant's expected date of delivery), infant clinical characteristics were collected. Parents completed a detailed lifestyles interview containing demographic and social background information. There were no significant infant clinical or social background characteristics between recruited and non-recruited infants and mothers ($p > .05$). Excluding deaths ($n = 3$), 98% (104/106) of very preterm children were evaluated at the 12 year follow-up.

3.2.2 The full term sample. The second group was comprised of 113 infants born full term (38 – 42 weeks gestation) identified from hospital birth records and contacted at age 2 years. Full term infants were identified by selecting for each very preterm infant, the second previous or second next same gender term-born infant in the Christchurch Women's birth register. Of the families approached at 2 years, 62% consented to study participation. A comparison of the socio-demographic characteristics of the full-term group with regional census data (Statistics New Zealand, 2001) indicated that these families were representative of the Canterbury region. At age 12 years, 96% (109/113) of full term children recruited at term were retained to follow-up were evaluated at age 12-years. Reasons for sample loss included study withdrawal (n = 3) and lost to follow-up (n = 1).

3.3 Characteristics of the sample.

3.3.1 Infant clinical characteristics. Table 3 displays the infant clinical characteristics of very preterm and full term children for which attention data was collected at the 12 year evaluation. As expected, very preterm infants were born at a significantly younger gestational age ($p <.001$) and lighter birth weight ($p <.001$) than full term children. For every full term infant

born with intrauterine growth restriction, defined as a birth weight greater than 2 standard deviations below the mean for gestational age and sex, approximately ten very preterm children were born with intrauterine growth restriction ($p = .002$). There were no significant differences in the proportion of males and females between the groups ($p = .68$), and around a third of very preterm births were multiple births compared to only 3% of full term children ($p < .001$).

In terms of the infant clinical characteristics of the very preterm sample, Table 3 shows that the very preterm group was characterized by a range of perinatal complications. For example, nearly a third of very preterm infants had blood culture confirmed sepsis. A moderate proportion of very preterm infants (37%) were identified as having retinopathy of prematurity (ROP); a condition in which optic blood vessels are damaged due to oxygen toxicity and relative hypoxia from extensive oxygen supplementation. A similar proportion of very preterm infants (34%) required supplementary oxygen at 36 weeks due to the presence of bronchopulmonary dysplasia (BPD) in the lungs. In contrast, only 4% of very preterm infants had necrotizing enterocolitis (NEC) suggesting that intestinal disease was less common. In terms of steroid administration, a large proportion (84%) of infants received antenatal corticosteroids but very few infants (6%) received the postnatal steroid dexamethasone.

In terms of early neuropathology, 7% of very preterm infants were identified as having cystic periventricular leukomalacia (PVL), or focal white matter injury near the lateral ventricles. The incidence of grade 3 or 4 intraventricular hemorrhaging was lower at 5% of very preterm infants. In contrast, the prevalence of diffuse white matter injury was more common in the sample. Based on neonatal MRI scored and reviewed by a blinded pediatric neuroradiologist and pediatric neurologist, white matter injury at term equivalent age (39 – 41 weeks gestation) was defined as the extent of: presence and severity of periventricular white matter volume loss, white matter

signal abnormality, presence of cystic abnormalities, ventricular dilation, thinning of corpus callosum, and reduced myelination (Woodward, Anderson, Austin, Howard & Inder, 2006). From this scoring, 61% of the sample was identified as mild white matter injury and 17% as moderate/severe white matter injury.

3.3.2 Social background characteristics at term. Table 3 below also shows the social background characteristics of the very preterm and full term sample. As shown, there was a similar proportion of young mothers (p = .43), single parent mothers (p = .25), and mothers of non-European ethnicity (p = .84) across the very preterm and full term groups. Very preterm infants, however, were significantly more likely than full term infants to be born to mothers who did not have an educational qualification (p = .001) and mothers who reported a low socio-economic household (p < .001). A composite social risk factor index was created to represent cumulative social risk as a continuous variable (min = 0, max = 5). For example, mothers who delivered their infants younger than 21 years, had no educational qualification, did not have a partner, identified as an ethnic minority and reported a low SES household were assigned a maximum social risk score of 5. As shown in Table 3, very preterm infants were significantly more likely to be born to mothers of higher social risk compared to full term infants (p <.001). As shown in Figure 3, mothers of very preterm infants were more likely to report two to three social risk factors.

Table 3
Infant Clinical and Social Background Characteristics of Very Preterm Children and Full Term Children

Measure	**Full-Term (*n* = 106)**	**Very Preterm (*n* = 100)**	**t / X^2**	***p***
Infant Clinical Characteristics				
Gestational age (wks), M ± SD	39.53 ± 1.2	27.92 ± 2.4	44.53	<.001
Birth weight (gm), M ± SD	3601.08 ± 405.2	1063.48 ± 314.2	50.39	<.001
IUGR (< 2SD for gestation and sex), %	0.9	11.0	9.49	.002
Male, %	53.8	50.0	0.29	.68
Twin birth, %	2.8	34.0	33.93	<.001
Confirmed sepsis, %	-	29.3		
ROP, %	-	37.4		
NEC, %	-	4.0		
Antenatal steroid, %	-	84.0		
Dexamethasone, %	-	6.0		
Oxygen at 36 weeks, %	-	34.0		
Cystic PVL, %	-	7.0		
IVH grade 3 or 4, %	-	5.0		
Diffuse white matter abnormality, %				
Mild	-	60.6		
Moderate/Severe	-	17.2		
Social Background Characteristics				
Young mother (< 21 years), %	1.9	4.0	0.81	.43
No educational qualification (< 16 years), %	18.9	40.0	11.13	.001
Single parent at term, %	12.3	19.0	1.78	.25
Non-European, %	12.3	14.0	0.14	.84
Low socio-economic status [a], %	10.4	30.0	12.43	<.001
Social Risk Index, M ± SD	0.56 ± 0.81	1.07 ± 1.03	-3.98	<.001

[a] Established from the Elley-Irving Socioeconomic Index (Elley & Irving, 2003), ROP: Retinopathy of prematurity, NEC: Necrotizing enterocolitis, PVL: Periventricular leukomalacia

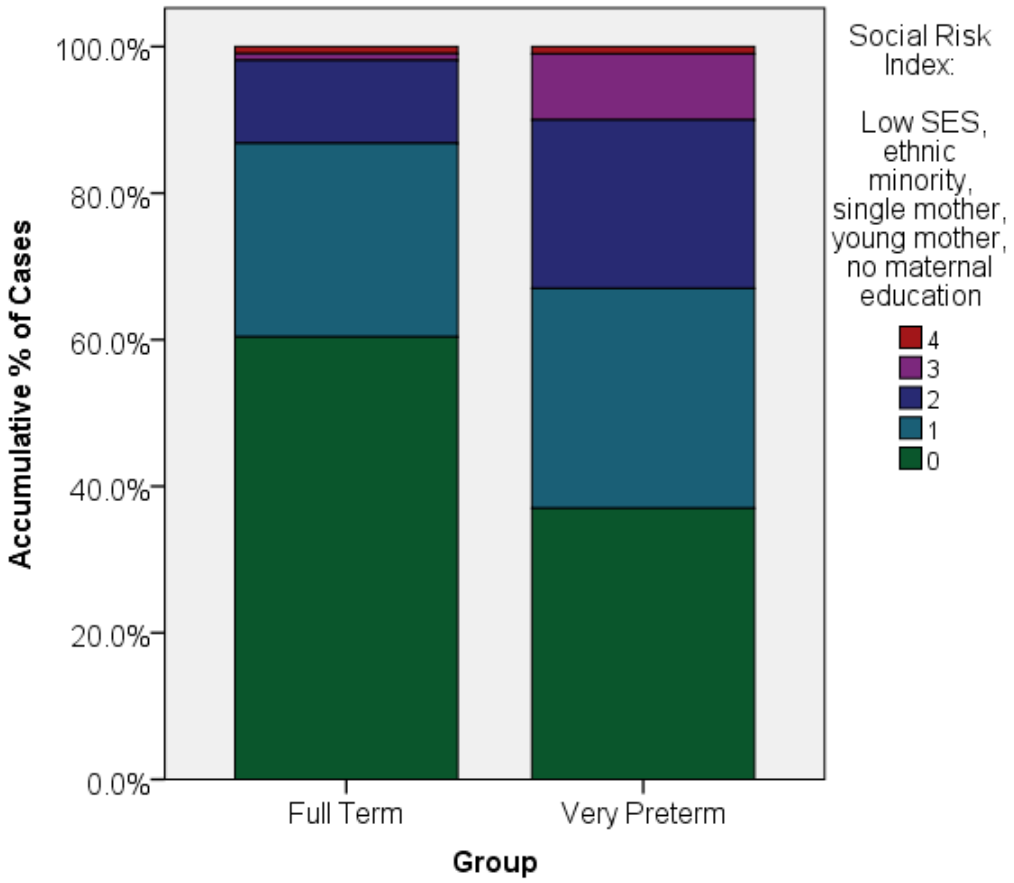


Figure 3. The distribution of multiple social risk factors between mothers of full term and very preterm infants as reported in the maternal lifestyles interview at term.

3.3.3 Developmental status at age 12 years. Table 4 shows the developmental status of the two groups at age 12 years, corrected for extent of prematurity. Developmental factors of interest included corrected age at developmental assessment, corrected age at MRI scan, general intellectual ability, and pubertal development. Retrospective factors included diagnosis of cerebral palsy by age 4 years and Attention Deficit Hyperactivity Disorder (ADHD) diagnosis by age 9 years. Very preterm and full term had a similar mean age at their developmental assessment ($p < .45$). The full term children were, however, significantly older than very preterm children at the time of their MRI scan ($p < .004$, $d = .50$)[1]. At age 12 years, very preterm children

[1] Scanning was disrupted from a series of major earthquakes resulting in civil emergency, February and June 2011.

performed less well on the shortened version of the Wechsler Intelligence Scales for Children, which measures general intellectual ability, compared to full term children ($p < .001$). In terms of neuromotor development, there was a higher incidence of cerebral palsy in very preterm children by age 4 years (16% vs. 1%, $p < .001$). At age 12 years, there were no significant differences in terms of pubertal status on the Tanner Puberty Scale, either by birth group or by sex. Very preterm children and full term children were relatively similar in terms of genital and pubic hair development in boys (ps > .05) and breast and pubic hair development in girls (ps > .05). In regards to ADHD diagnosis in childhood, there was around a three-fold increase in risk of ADHD diagnosis for very preterm children relative to full term children by age 9 years (20.6% vs. 6.4%, $p = .002$). ADHD combined appeared to be most prevalent subtype for the very preterm group (14.7%), followed by Inattentive subtype (5.9%).

Table 4
The Developmental Status of Very Preterm and Full Term Children at Age 12 years

Measure	**Full-Term (*n* = 106)**	**Very Preterm (*n* = 100)**	**t / χ^2**	***p***
Age				
At Developmental Assessment, M ± SD [b]	12.09 ± 0.10	12.07 ± 0.15	0.75	.45
At MRI Scan, M ± SD [b]	12.15 ± 0.11	12.09 ± 0.13	2.90	.004
General intellectual ability				
WISC-IV full scale IQ score, M ± SD [c]	106.93 ± 13.60	98.20 ± 14.43	4.47	<.001
Physical Development				
Cerebral Palsy diagnosis at age 4 years, %	15.7	1	14.75	< .001
Pubertal development, M ± SD [d]				
Tanner Puberty Scale Score, M ± SD	2.39 ± 0.72	2.41 ± 0.82	-0.22	.83
Boys				
Genital development	2.44 ± 0.66	2.40 ± 0.81	0.27	.79

Table 4
The Developmental Status of Very Preterm and Full Term Children at Age 12 years

Measure	**Full-Term (*n* = 106)**	**Very Preterm (*n* = 100)**	**t / χ^2**	***p***
Pubic hair development	2.44 ± 0.66	2.44 ± 0.79	-0.01	.99
Girls				
Breast development	2.37 ± 0.81	2.44 ± 0.88	-0.43	.67
Pubic hair development	2.29 ± 0.82	2.36 ± 0.85	-0.44	.66
ADHD				
ADHD diagnosis at age 9 years, % [e]				
Any ADHD	6.4	20.6	9.19	.002
ADHD inattentive	3.7	5.9	0.57	.53
ADHD hyperactive/impulsive	0.0	0.0	-	-
ADHD combined	2.8	14.7	9.65	.002

[b] Age corrected for extent of prematurity
[c] Wechsler Intelligence Scales for Children - IV: block design, similarities, coding, arithmetic (Wechsler, 2003)
[d] The Tanner Puberty Scale (Marshall & Tanner, 1969; 1970)
[e] Woodward, Bora & Moor (2012), diagnosis made from The Development and Wellbeing Assessment

3.4 General procedures. At corrected age 12 years (± 3 weeks), study children were invited to attend a comprehensive 5-hour neurodevelopmental assessment at the Canterbury Child Development Research Facility situated at the University of Canterbury, followed by a 45-minute minute magnetic resonance imaging (MRI) scan at Hagley Radiology, Christchurch. Very preterm children were evaluated at age 12 years corrected for extent of prematurity, calculated using their estimated date of delivery (*See Appendix B*). Age correction is a common method that considers biological maturation from the time of conception, independent of date birth or time spent in the extrauterine environment (Siegel, 1994). Written consent from both parent and child was obtained prior to the neurodevelopmental assessment, and consent to the MRI obtained at the same time or in-situ at Hagley Radiology. Ethical approval for all study

procedures and measures used at the 12-year follow-up was obtained from the Ministry of Health Upper South Regional A Ethics Committee (*Ethics reference*: URA/10/05/040). IRB approval was sought for all data analyses completed at Washington University in St. Louis, USA.

3.4.1 Neurodevelopmental evaluation. As part of a comprehensive neurodevelopmental assessment, several measures of cognitive functioning were administered by a clinical psychologist and postgraduate student both blind to group status. The primary measure of attention was the Test of Everyday Attention for Children (TEA-Ch: Manly, Anderson, Nimmo-Smith, *et al.*, 2001) which was administered by the author. The TEA-Ch is a standardized neuropsychological measure of attention normed against a large sample of Australian children. It is suitable for use with children aged 6 to 15 years 11 months (Manly *et al.,* 2011). For TEA-Ch analyses, raw scores are reported. Justification for taking this approach was twofold. First, raw scores are appropriate for single measure analysis when the age of the participants is narrow and when there is age equivalence between participant groups (*see* Andersen *et al*., 2011). Second, the use of raw test scores minimizes some of the methodological problems associated with outdated test norms (Aylward, 2002; Wolke, Ratschinski, Ohrt & Riegel, 1994). Comparing test performance against a regionally representative comparison group is also more desirable when there are no existing standardized test norms for the country in which the sample was recruited (Woodward, Clark, Bora & Inder, 2012).

The five selected subtests of the TEA-Ch were presented to the child in the same order with an administration time of approximately 40 minutes. All participants were tested using Version-A of the TEA-Ch. Due to a scoring error in the Sky Search Dual Task (DT) subtest, six children were retested with a parallel Version-B of the Sky Search DT at the child's home. The TEA-Ch was completed by 96% (100/104) of the very preterm children and 97% (106/109) of the full

term children. Reasons for TEA-Ch data loss in the very preterm group included severe cerebral palsy (n = 1), blindness (n = 1) and severe cognitive delay (n = 2). Reasons for data loss in the full term group included child relocated to Australia (n = 1), child task refusal (n = 1) and file misplaced (n = 1). Data is only presented for children who passed the required practice items for each subtest. Two full term children did not pass practice trials for Walk Don't Walk.

3.4.2 Structural MRI scan. After completing the neurodevelopmental evaluation, participants were met at Hagley Radiology by the senior research nurse and/or the author to undergo a 45-minute MRI scan. The MRI research manager and an MRI technician, both blind to child birth group status, executed and supervised all scans. All structural T1-weighted images were completed in the first 5-minutes of the scanning session using a GE Signa 3T HDxt scanner. Structural images were acquired with a T1-weighted, 3D inversion recovery-prepared spoiled gradient recalled echo (IR-fSPGR) acquisition (250 field of view, 256x256 acquisition matrix, 512x512 reconstruction, sagittal acquisition, 186 1mm thick slices, ~1mm^3 isotropic voxels, TE/TR=4.8/10.7ms, flip-15^o, TI=400ms). These parameters were held constant across all scans to reduce systematic bias in the data (Good, Johnsrude, Ashburner *et al.,* 2001). If motion was apparent on the first acquisition, a second or third IR-fSPGR image was acquired.

All raw structural images were visually inspected in sagittal, axial, and coronal view in iTK-SNAP by the author and post-doctoral research fellow as an additional check for motion, poor image contrast, field inhomogeneity, and artefacts. In cases where multiple T1 images were collected for a subject, the best T1 (*i.e.* motion free and adequate grey and white matter contrast) was selected. MRI scans were completed for 93% (97/104) of VPT and 89% (97/109) of FT children. Reasons for non-scans included orthodontic braces (*n* = 4), child anxiety (*n* = 4), family unable to travel to study site (*n* = 2), and declined MRI (*n* = 9). A further eight subjects were

excluded due to unusable MRI data (motion *n* = 6, parieto-occipital shunt *n* = 1, unresolved nifti conversion failure *n* = 1) leaving a final sample of 186 children (very preterm *n* = 90, full term *n* = 96).

3.4.3 Participant gratuities. Families that that travelled a significant distance to the assessment in a private vehicle were partially reimbursed with petrol vouchers. To thank the children for their participation in the developmental evaluation, they were able to choose from a range of gift vouchers to the value of $NZ20.00. For completing the MRI, the child was thanked with a CD-Rom containing a subset of brain images from their scan to take home (viewing software included).

3.5 Measures.

3.5.1 Attention. The Test of Everyday Attention for Children is comprised of child-friendly subtests that differentially examine sustained, selective and executive domains of attention. This measure was developed to provide clinically relevant and detailed information about special populations, such as children with ADHD or those with closed head injury, who may be prone to impairment in specific domains of attention (Anderson, Feniwck, Manly & Robertson, 1998; Manly *et al,* 2011). In addition, the TEA-Ch is increasingly included in large studies not only because it is clinically useful, developmentally appropriate, and reasonably quick to administer, but also because it is a performance-based and theoretically valid measure of attention in children (Manly *et al.,* 2011).

The TEA-Ch can be a considered as a valid neuropsychological measure of attention in children for a number of reasons. First, the TEA-Ch is based on the adult version Test of Everyday Attention (TEA). The factor structure of the TEA yields a model of sustained attention, selective

attention, attentional switching, and auditory-verbal working memory convergent with Posner and Peterson's model of anatomically and functionally distinct networks and domains of attention (Himelstein, Newcorn & Halperin, 2000; Halperin & Schulz, 2006; Robertson, Ward, Ridgeway & Nimmo-Smith, 1996; Posner & Petersen, 1990; Treisman, 1998). The subtests of the TEA-Ch are designed to independently test each domain of attention and identify areas of vulnerability, making it an ideal measure for very preterm children who may have differential impairments within the attention system. Second, the TEA-Ch is an ecologically valid measure that tests children's attention capabilities with subtests that require the same attention skills as used in daily activities such as attending to lists and multitasking (Bate, Mathias & Crawford, 2001; Robertson *et al.* 1994). Third and lastly, the TEA-Ch is a somewhat 'pure' measure of attention where the demands placed on other abilities such as general intellectual ability, motor and processing speed and working memory are minimized (Bate, Mathias & Crawford, 2001; Manly *et al.*, 2011).

Of the nine available subtests, five subtests were selected for administration. Reasons for this were two-fold. First, the five selected subtests can be administered as a shortened measure of attention that does not compromise the validity of the test or the number of attention domains measured. Second, due to time constraints of the full developmental assessment, a shorter 40-minute administration time was preferable compared to a 60-minute assessment of attention. The administered subtests included Sky Search (visual selective attention), Score! (auditory sustained attention), Creature Counting (executive shifting attention), Sky Search Dual Task (executive divided attention), and Walk Don't Walk (sustained attention of response inhibition). Each subtest has two practice items that the child must pass before the remaining test items can be administered. The subtests of the TEA-Ch are described below.

3.5.1.1. Selective attention.

1) *Sky Search.* Sky Search measures visual selective attention while controlling for individual differences in motor speed. Children must visually scan and select matching pairs of target spaceships amongst rows of mismatched pairs of distracter spaceships (shown in Figure 4) while being timed. The Motor Control Condition in which the target spaceships are presented without the distracter spaceships, is then administered to control for individual differences in motor speed. The difference between the Motor Control Condition time-per-target score and the Sky Search time-per-target score indicates the extent to which a child's ability to selectively attend to target stimuli was compromised by the distraction of the irreverent stimuli. Variables of interest include number of targets identified (0 – 20), time-per-target, and the Sky Search Attention Score (1 - 9). Higher Sky Search Attention Scores reflect poorer performance.

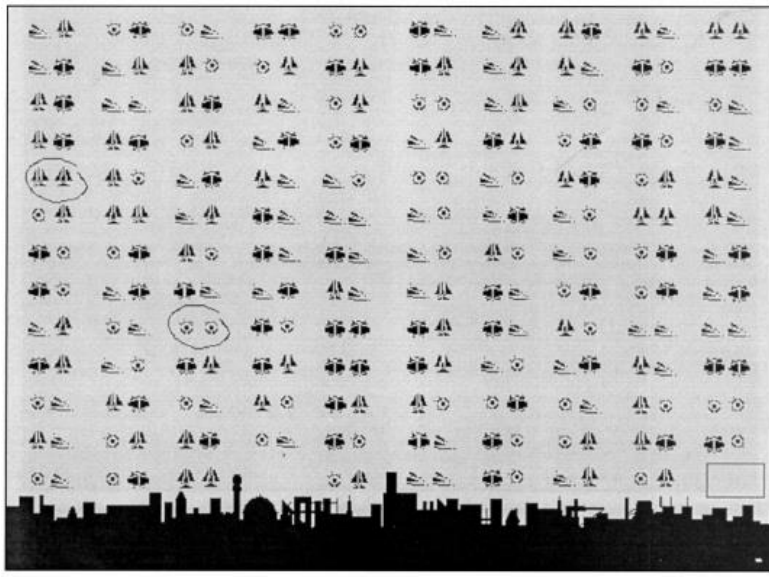


Figure 4. The Sky Search task of the TEA-Ch illustrating the pairs of target spaceships (max = 20) amongst pairs of non-target distractor spaceships, from Manly *et al*. (2001)

3.5.1.2 Sustained attention.

2) *Score!* Score! is the primary measure of sustained auditory attention. The task is comprised of ten sound games in which the child mentally counts a number of target sounds without using counting aids such as fingers or counting aloud. At the end of the sound game, the child must verbally articulate the number of tones they counted. In each trial, between 9 and 15 laser sounds (0.35 seconds each) are presented at varying and unpredictable intervals ranging from 0.5 to 5 seconds between each sound. This task requires conscious and attentive listening skills and does little to engage or stimulate the child. Higher scores (0 – 10) on this subtest suggest that the child was able to sustain attention during the goal-directed task and was less prone to short lapses of attention (Manly *et al.*, 2001).

3) *Walk Don't Walk.* The Walk Don't Walk subtest assesses sustained inhibition of responding in which children must maintain an awareness of their actions and avoid lapsing into absentminded responding, similar to Go No/Go tasks of inhibitory control. Children are presented with a printed sheet of 20 footpaths with each path containing 14 steps. Children may only progress along the foot path by marking a step with a pen stroke when they hear a 'safe' sound. They must not mark the step when they hear the 'unsafe' sound that will play anywhere between the 2nd and 12th step. The beginning of the 'safe' and 'unsafe' sounds are identical for the first 208 milliseconds, after which the 'unsafe' sound unpredictably ends with an off-key tone. The child must withhold responding until they have heard the whole sound. To facilitate speeded responding, intervals between the sounds shorten from 1500ms in item 1 to 500ms between sounds in item 20. Higher scores (0 – 20) on this task suggest that the child was able to sustain their attention to inhibiting a response until they had heard the whole 'safe' sound and avoided lapsing into an absent minded responding style.

3.5.1.3 Executive attention.

4) *Creature Counting.* Creature Counting, shown in Figure 4 below, measures attentional shifting. This task requires the coordination of switching counting direction either upwards or downwards in response to the upwards and downwards arrows. The child counts the creatures along the trail and either continues to count upwards (*i.e*. 3, 4, 5) when cued by an upward arrow, or change counting direction to downwards (*i.e.* 4, 3, 2) when cued by a downwards arrow. Seven counting games or items are completed for the Creature Counting subtest. Variables of interest include: total items correct (0 – 7), total time taken for correct items, total number of counting switches made for correct items (0 - 26) and the Creature Counting Timing score (1.7 – 7.2). The Creature Counting Score is only calculated for children who obtain at least three correct trials, and is computed by: Total time for correct items/Total switches made for correct items. Fewer correct items, slower response times, and higher Creature Counting Timing Scores suggest poor shifting flexibility and difficulty controlling attentional focus.

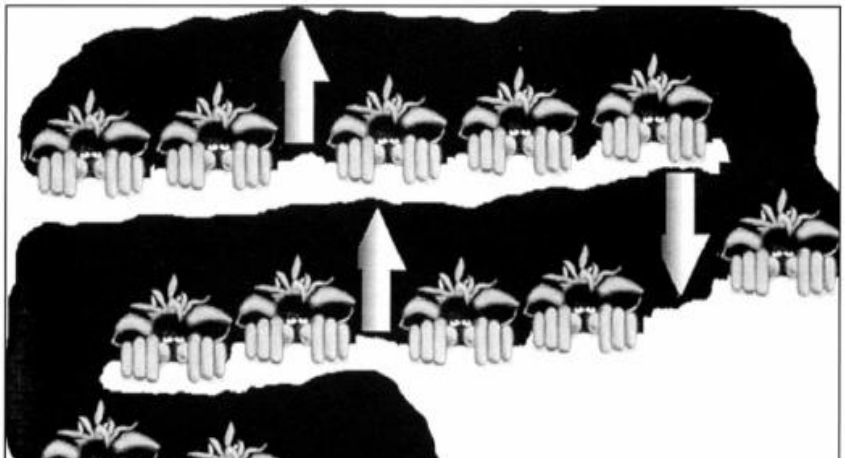


Figure 5. The Creature Counting task of the TEA-Ch illustrating the creatures are required to count and the arrows that cue a required change in counting direction, from Manly *et al*. (2001)

5) *Sky Search Dual Task (DT).* Sky Search DT tests the efficient division of cognitive resources across competing tasks, thus placing extra demands on the attentional system. In Sky Search DT, children must complete parallel versions[2] of the Sky Search measure of selective attention and the Score! subtest of sustained attention at the same time. That is, the child must identify Sky Search target spaceships while also counting Score! tones. The Sky Search DT Decrement Score is computed by subtracting the time-per-target score for the first Sky Search subtest from the weighted time-per-target score of the Sky Search Dual Task, shown in Figure 5.

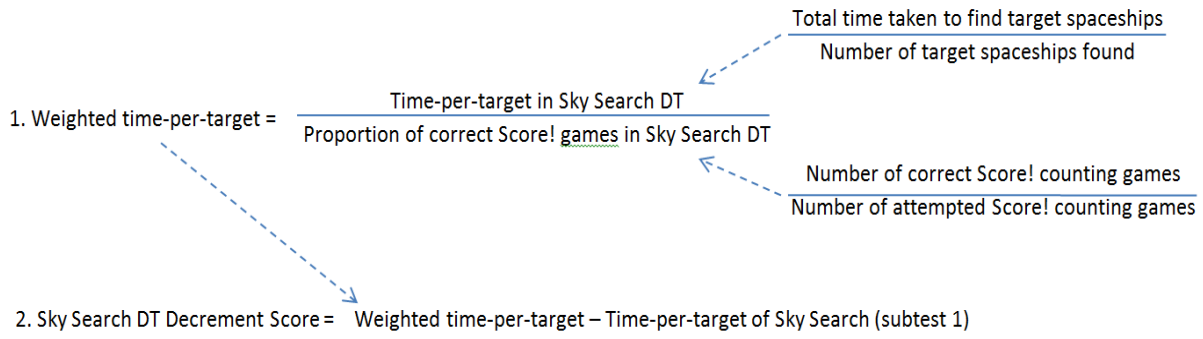


Figure 6. The equation for calculating the Sky Search DT Decrement Score for the Sky Search Dual Task of the TEA-Ch. Step 1 includes all scores from versions B presented in the dual task, and step 2 includes the time-per-target score from Sky Search version A presented in subtest 1.

The Sky Search DT Decrement Score represents the extent to which the child's performance under dual-task conditions is compromised when they must complete two equally important tasks at the same time, relative to their performance in the single task conditions. Higher positive decrement scores (-5.5 – 7.5) reflect poorer performance relative to the single task condition. While a child may have no apparent impairment when completing the selective and sustained

[2] In single task conditions, children complete version A of Sky Search and Score!. In the dual task condition, children complete parallel version B of Sky Search and Score! to minimize practice effects.

attention tasks individually, deficits in these domains may become noticeable when tested under dual-task conditions.

3.5.1.4. Reliability and validity of the TEA-Ch. The TEA-Ch is a psychometrically reliable and valid measure of attention used both typically developing and high-risk children (Anderson, Fenwick, Manly & Robertson, 1998; Manly, Anderson, Nimmo-Smith *et al.,* 2001; Manly, Robertson, Galloway, & Hawkins, 1999; Robertson, Manly, Andrade, *et al*., 1997). TEA-Ch test scores remain relatively stable over time with test-retest reliability correlation coefficients ranging from $r = .64 – .90$ for children retested 5 to 20 days after initial testing (Manly, Anderson, Nimmo-Smith *et al.*, 2001). In addition, the TEA-Ch demonstrates good levels of convergent validity with established measures of attention. TEA-Ch test scores correlate with the Stroop selective attention task ($r = .31 – .40$); Trails A ($r = .31 – .69$) and Trails B ($r = .21 – .45$) tasks of selective attention; and with the Matching Familiar Figures Test of impulsivity ($r = .20 – .35$) (Manly, Anderson, Nimmo-Smith, *et al.*, 2001). In contrast, TEA-Ch scores do not significantly correlated with prorated WISC-III IQ scores after correction for multiple comparisons, suggesting that the TEA-Ch is relatively independent from measures of general intellectual ability (Manly, Anderson, Nimmo-Smith, *et al.*, 2001). Although the association between general intellectual ability and attention was outside the scope of the current study, bivariate correlations are presented in Appendix C to acknowledge the possible relationship between IQ and attention in children born very preterm.

In terms of the discriminant validity of the TEA-Ch, boys with ADHD perform less well on both Score! And Walk don't Walk subtests relative to non-disordered controls matched for intellectual ability (Manly, Anderson, Nimmo-Smith, *et al.*, 2001). An earlier pilot version of the TEA-Ch has also demonstrated sensitivity in detecting attention impairment among children with

traumatic brain injury (Anderson, Fenwick, Manly & Robertson, 1998). Walk Don't Walk, adapted from the Sustained Attention to Response Test in adults, also predicted the extent to which clinical populations show lapses in attention (Manly, Robertson, Galloway, & Hawkins, 1999; Robertson, Manly, Andrade, *et al*., 1997). The TEA-Ch may, therefore, be sensitive to detecting impairment in children born very preterm.

3.5.2 Structural alterations in grey matter volume. Structural alterations of grey matter volume in very preterm children at age 12 years was examined using modulated voxel based morphometry which identifies structural differences in neuroanatomical regions of interest. Voxel based morphometry (VBM) is a whole-brain, semi-automatic technique that characterizes structural differences in grey and white matter volumes between large groups of subjects. It tests the voxel-wise comparison of the local concentration of grey matter between experimental and control groups whose images are spatially normalized (Ashburner & Friston, 2001; Good, Johnsrude, Ashburner *et al*., 2001) In addition to its ability to account for individual variation in total brain volume across subjects by preserving and encoding information about the absolute volume of a region prior to spatial normalization, VBM is also advantageous for examining regions that are not anatomically well defined (Ashburner, 2009; Ashburner & Friston, 2001).

Pre-processing of the acquired raw structural T1-weighted images was performed using VBM8, Template-O-Matic (TOM8), and DARTEL toolboxes for Statistical Parametric Mapping (SPM8), in Matlab (Matlab R2013a). Summarized in Figure 7, images were first downsampled (to 256x256, 1mm isotropic) and manually realigned to the anterior commissure (Ashburner *et al*., 1997) in SPM8. Using TOM8 (Wilke, Holland, Altaye & Gaser, 2008) in VBM8, subject images were initially segmented into grey and white matter images using an estimated tissue probability map based on National Institutes of Health priors matched for age and sex of the

current sample (Waber, Moor, Forbes *et al.,* 2007). Tissue probability maps provide a-priori knowledge of the spatial distribution of different tissue types to improve registration (Mechelli, Prices, Friston & Ashburner, 2005). Visual checks of the segmented grey matter images saw an additional 4 subjects excluded due to poor segmentation (very preterm $n = 89$, full term $n = 93$).

Next, grey and white matter segments from all subjects were used to create a study specific template using DARTEL (Ashburner, 2007). Structural images were intensity bias corrected, tissue classified again, and spatially normalized to the study specific DARTEL grey matter template. Grey matter segments for each subject were then modulated using non-linear components of the spatial normalisation only, thereby preserving actual tissue values locally in order to account for individual brain size globally (Ashburner & Friston, 2001; Mechelli, Prices, Friston & Ashburner, 2005). That is, SPM's estimate of the voxel tissue values in the segmented images were multiplied by the Jacobian determinants of the spatial normalization. This allows the modulated grey matter values to be interpreted as a measure of the regional difference in the absolute volume of grey matter, rather than grey matter concentration or density (Good, Johnsrude, Ashburner *et al*., 2001; Mechelli, Prices, Friston & Ashburner, 2005). Finally, the modulated, normalized grey matter segments for all subjects were smoothed using an 8mm full width half maximum Gaussian kernel. To restrict statistical analysis to grey matter voxels, a grey matter mask was created from a mean grey matter image comprised of all 89 very preterm and the first consecutive 89 full term's modulated, normalized grey matter segments (threshold = 0.15).

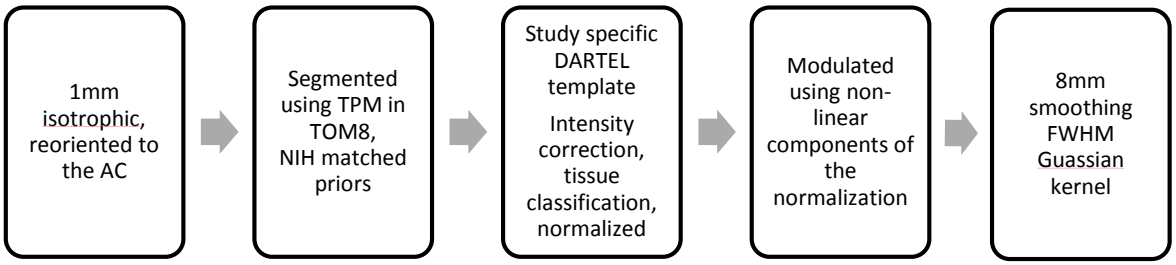


Figure 7. Summary of the preprocessing pipeline of structural T1-weighted images of very preterm and full term children at age 12 years.

After the structural T1-weighted images were pre-processed, voxel based morphometry was performed and produced the statistical parametric map (SPM) output image which shows structural between-groups differences in regional grey matter (*see* Figure 8 for an example). Outcome measures of interest included 1) the SPM output image that displays the clusters of grey matter voxels that are statistically significant, and 2) the modulated grey matter volume values that were extracted from each cluster using FSL.

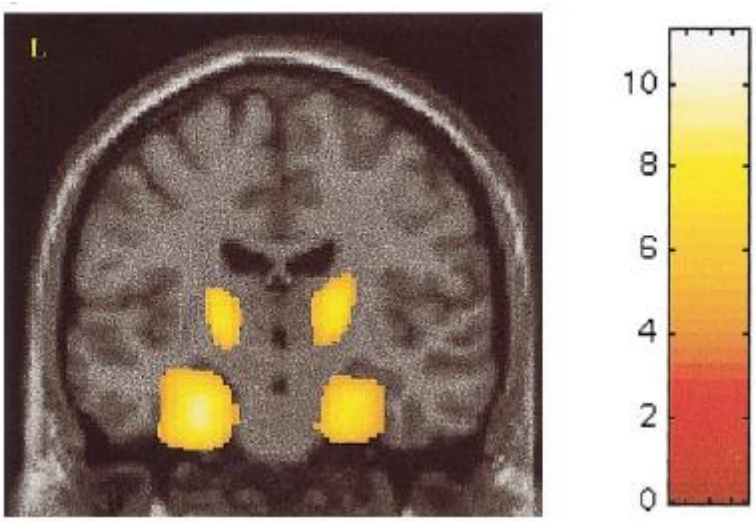


Figure 8. An example of a statistical parametric map image in which the yellow clusters represent regional between-groups differences in grey matter density or volume at the voxel level (Good, Johnsrude, Ashburner, *et al*., 2001).

3.6 Data and planned analyses.

3.6.1 Data management. Data was managed using a range of computer software programs. The TEA-Ch data was manually entered into Microsoft Access 2010 for Windows XP and subsequently imported into Statistical Package for Social Sciences (SPSS) version 17.0 for Windows XP. SPSS was used for all TEA-Ch data analysis. As previously described, structural T1-weighted images were pre-processed and analysed using VBM8 and Template-O-Matic (TOM8) toolboxes for Statistical Parametric Mapping (SPM8), in Matlab (Matlab R2013a). Modulated grey matter volume values were extracted from the SPM t-statistic image using FSL (FSL 4.1.9) and imported into SPSS for analysis.

3.6.2 Power Analysis. The sample size necessary to attain the desired power to detect an effect in the current study was satisfactory. A priori power calculations for a two-tailed independent samples t-test at the 95% significance level ($a = 0.05$) for a total sample of at least 200 children, yielded a power calculation of 0.94 to detect a desired medium effect size of $d = 0.5$. To detect an effect size of $d = 0.5$ at the 0.01 alpha level with a sample of 200, power was still adequate at 0.82 (Soper, 2011). This is considered to be sufficient to detect statistically significant between-groups differences (Cohen, 1992).

3.6.3 Data analysis. Across all analyses, the 95% confidence level (*i.e.* a significance level of $p < .05$) was used to detect statistically significant results. Where appropriate, variables were examined for violations in distribution and homogeneity of variance using visual inspection, skew and kurtosis statistics, and Levene's tests. Tolerance and VIF statistics, and condition indices of collinearity diagnostics were examined for all multivariate regression analyses. The analysis for the research aims proceeded in seven steps using both univariate and multivariate methods, which are described in detail below. All outcome variables were examined

for statistical outliers (>2 SD of group mean) and data analysis run with and without these cases[3] . As the exclusion of outliers did not alter the statistical significance of the results, these cases were retained in data analyses.

First, very preterm and full term children's performance on the TEA-Ch at age 12 years was examined for group differences with birth group being the primary grouping variable. As a continuously distributed variable, between-groups differences in mean subtest scores were examined using multivariate analysis of variance (MANOVA) which takes into account the several dependent variables in combination, thus reducing the probability of Type 1 error. If a significant effect of group was found on the multivariate F statistic, ANOVA was then used to describe group differences on the individual TEA-Ch subtests. Effect sizes were calculated using Cohen's *d*.

Second, if study children obtained a raw subtest score greater than 1 SD below the full term group mean, they were classified as having attention impairment. This classification criterion is a commonly used and well accepted definition of impairment across the neuropsychological literature (Anderson, Luca, Hutchinson *et al.*, 2011; Lezak, 1993; Nosarti, Giouroukou, Healy *et al*., 2008). Chi-square tests of independence for dichotomous variables were used to test for group-differences in the rate of impairment in selective, sustained and executive attention. Fisher's Exact Values are reported when the observed cell numbers were less than required. To measure the association between birth group and mean TEA-CH subtest scores, odds ratios with 95% confidence intervals calculated using binary logistic regression (full term = 0, very preterm = 1).

[3] One outlier was detected in Sky Search, and two outliers detected for Sky Search Dual Task.

Third, TEA-Ch analysis was then extended to include confounding factors using multivariate analysis of covariance for continuous variables, and binary logistic regression for dichotomous variables. This assessed the extent to which children's attention problems associated with very preterm birth remained after statistical adjustment for social risk index, as early exposure to socio-familial adversity modifies risk of ADHD in very preterm children (Lindstrom, Lindblad & Hjern, 2011). As previously described, the composite social risk index was created to represent cumulative social risk as a continuous variable; comprised of single and early motherhood, ethnic minority status, low socio-economic status, and no educational qualification (min = 0, max = 5).

Fourth, to examine the association between attention and the extent of prematurity, the sample was categorized into three groups: full term (36 – 41 GA), very preterm (28 – 33 GA), and extremely preterm (23 -27 GA). The classification criterion for very preterm and extremely preterm birth is a widely used clinical definition to represent the group of infants born extremely preterm and/or on the edge of viability who account for much of the reported neonatal morbidity in contemporary cohorts of preterm children (Costeloe *et al*., 2000; Markestad *et al.*, 2005; Wolke, 1998). Between-groups differences on the TEA-Ch subtest scores and rates of impairment were compared using MANOVA for continuous variables and chi-squared linear-by-linear association tests for independence for categorical variables. Cohen's *d* and odds ratios were again calculated, along with Tukey HSD post-hoc comparisons to examine pair-wise comparisons and assess the relative risk of extremely and very preterm children relative to full term children.

Fifth, voxel based morphometry (VBM) was performed on the smoothed modulated and normalized grey matter segments of very preterm and full term children using SPM8. Regional

differences in grey matter volume were tested at the voxel level using an independent samples t-test (threshold = 0.15). Smoothed, modulated, normalized grey matter segments were entered into the model with analysis restricted to areas within the grey matter mask. Two contrasts were investigated: 1) decreased grey matter volume in very preterm relative to full term, and 2) increased grey matter volume in very preterm relative to full term. Importantly, SPM results were corrected for multiple comparisons using family wise error $p < .05$ (Nichols & Hayasaka, 2003).

Sixth, to examine group differences in regional grey matter volume after covariate adjustment for a small but statistically significant group difference in age at scan ($p = .004$) and social risk index ($p < .001$) in statistical models, modulated grey matter volume values were extracted from each of the significant clusters identified in the previous VBM and examined using univariate analysis of covariance. Sex and pubertal status were considered as additional covariates, but these factors were not statistically different between the birth groups and did not affect models in preliminary analyses.

Sixth and seventh, relationships between attention impairment and grey matter volume were examined using correlational and regression methods. This analysis was restricted to the very preterm group to focus on the neuropsychology of attention for very preterm children, and because infant clinical data was not available for the full term group. First, one-tailed Pearson's product moment correlations were used to identify the regions of grey matter that were differentially associated with each component of attention and to also describe the strength and direction of these relationships. Second, multiple regression modelling was undertaken to examine the extent to which regional grey matter volume made an independent contribution to

selective, sustained and executive attention after taking into account other neonatal and social risk factors that correlated with attention in the very preterm group.

To select the infant clinical, neuropathological and social risk factors what were differentially associated with selective, sustained and executive attention, bivariate correlations matrices for all factors were created using one-tailed Pearson's product moment correlations. All factors were checked for collinearity ($r = .80$, $p < .05$). For those factors that correlated with a component of attention, the selected infant clinical factors, neuropathological factors, social risk index, and regional grey matter volumes at age 12 years were entered into forwards and backwards multiple regression models to identify the most parsimonious and best fitting model that significantly accounted for the variance in TEA-Ch subtest scores among very preterm children. At each step, the alpha level for variable inclusion in the model was set at .90 with non-significant variables ($p > .10$) sequentially removed from the model. Given the comorbidity of infant clinical and neuropathological factors (Anderson, Luca, Hutchinson *et al.*, 2011), detailed inspection of the multivariate coefficients, standard error, tolerance and VIF statistics, and condition indices of collinearity diagnostics was undertaken at each forwards step of model refinement to identify potential issues with multicollinearity.

Chapter 4. Results: Attention Outcomes

This chapter presents the results of the current study organized in the order of the research aims described in the methods. First the nature and extent of attention problems are described for very preterm and full term children at age 12 years. Second, regional structural alterations in grey matter volume are compared between very preterm children and full term children at age 12 years. Third and last, associations between regional structural alterations in grey matter volume and attention outcomes for very preterm children are examined using both correlational and regression methods.

4.1 The nature and extent of inattention in children born very preterm at age 12 years.

As outlined, the following section describes children's performance on the Test of Everyday Attention for Children (TEA-Ch) and the rates of selective, sustained and executive attention impairment for both very preterm and full term children at age 12 years. Findings are examined before and after covariate adjustment for social risk index measured at term, and the magnitude of group differences is discussed. The attention outcomes are then examined in relation to gestational age for full term, very preterm and extremely preterm children.

As shown in Table 5, the overall multivariate effect of birth group across the five TEA-Ch subtests was highly significant (F (5, 197) = 4.05, p = .002, Wilks' $\lambda = 0.91$, partial $\eta^2 = .09$). After covariate adjustment for social risk index, the multivariate effect of birth group remained significant (F (5, 196) = 3.08, p = .01, Wilks' $\lambda = 0.93$, partial $\eta^2 = .07$). The findings of the univariate tests of the effect of very preterm birth on the individual components of attention are now described.

Table 5.

The Nature and Extent of Attention Problems for all Study Children at Age 12 Years, Assessed with the TEA-Ch

Variable	**FT (*n* = 103)**	**VPT (*n* = 100)**	**95% C.I of mean difference**	**Ƒ/ X^2**	**Unadj. *P***	***d*/ OR (95% C.I)**	**Adj. *p***
Multivariate λ = 0.91				4.05	.002		.01
Selective Attention							
Sky Search Attention Score	3.49 (1.02)	3.56 (1.56)	-0.43 – 0.29	0.13	.72	.05	.98
Impaired %	16.0	12.0		0.69	.43	0.71 (0.32 – 1.59)	.34
Sustained Auditory Attention							
Score! Total Correct	8.76 (1.49)	8.18 (1.93)	0.10 – 1.06	5.71	.02	.34	.11
Impaired %	22.6	28.0		0.78	.42	1.33 (0.71 – 2.50)	.92
Sustained Response Inhibition							
Walk Don't Walk Total Correct	15.87 (2.66)	14.91 (3.66)	0.08 – 1.84	4.62	.03	.30	.13
Impaired %	16.0	29.0		4.99	.03	2.13 (1.09 – .4.17)	.04
Executive Switching Attention							
Creature Counting Total Correct	5.85 (1.48)	5.28 (1.70)	0.13 – 1.01	6.61	.01	.36	.02
Impaired %	14.2	30.0		7.75	.007	2.56 (1.30 – 6.25)	.02
Executive Divided Attention							
Sky Search DT Decrement Score	1.43 (2.36)	3.10 (4.05)	-2.59 – -0.75	13.00	<.001	.50	.002
Impaired %	9.5	24.0		7.76	.008	3.03 (0.57 – 1.35)	.02

λ = Wilks' Lambda; Impaired % for FT *n* = 106, FT *n* = 103 because MANOVA excludes cases with missing values on any of 5 the dependent variables (2 FT failed Walk Don't Walk, 1 child did not have a SS DT Decrement Score)

4.1.1 Selective Attention. Selective attention was assessed with the Sky Search subtest which requires the rapid detection of target pairs of matching spaceships that are placed amongst non-target distractor pairs of non-matching spaceships. Contrary to the research hypothesis, there was no significant between-groups difference on the Sky Search Attention Score of selective attention (p = .73), and this finding remained non-significant after covariate adjustment for social risk index (p = .98). Also shown in Table 5, a similar proportion of very preterm and full term children had mean Sky Search Attention Scores in the impairment range (p = .43).

To describe children's performance on sub-variables of the Sky Search measure of selective attention, Table 6 shows the mean scores obtained by both groups for the total number of target spaceships found, time taken to complete Sky Search, and the time taken to find each individual target spaceship. Consistent with the non-significant group difference on the Sky Search Attention Score, very preterm children identified a similar numbers of target spaceships to full-term children (p = .25) and both groups completed the task in approximately 84 seconds (p = .97). Very preterm children and full term children also had relatively similar time-per-target scores (p = .52) suggesting that both groups had comparable levels of visual search ability. When taken together, these results suggest that very preterm children had similar levels of selective attention skills relative to the full term group at age 12-years.

Table 6.

Children's Performance on the Sky Search Measure of Selective Attention at Age 12-Years, m (SD)

Sky Search	**FT (n = 106)**	**VPT (n = 100)**	**95% C.I. of mean difference**	***t***	**Unadj. *p***	**Adj. *p***
Targets identified	19.01 (1.69)	18.72 (1.93)	-0.21 – 0.79	1.15	.25	.55
Time taken (Sec)	84.50 (22.82)	84.63 (28.87)	-0.12 – 3.62	-0.03	.97	.79

Table 6.

Children's Performance on the Sky Search Measure of Selective Attention at Age 12-Years, m (SD)

Sky Search	**FT (*n* = 106)**	**VPT (*n* = 100)**	**95% C.I. of mean difference**	***t***	**Unadj. *p***	**Adj. *p***
Time-per-target (Sec)	4.47 (1.21)	4.61 (1.85)	-0.57 – 0.29	-0.65	.55	.92

4.1.2 Sustained attention. Table 5 also shows the performance of very preterm and full term children on the two measures sustained attention. Score! provides a measure of sustained auditory attention, and Walk Don't Walk provides a measure of sustained attention to response inhibition.

4.1.2.1 Sustained auditory attention. Very preterm children performed less well than full term children on Score!. Very preterm children obtained fewer correct items on Score! suggesting that very preterm children were less able to sustain a vigilant state of attention across the items in the task (p = .02, d = 0.34). After controlling for the effects of social risk, there was no longer a significant between-groups differences in the number of correct items obtained on Score! (p = .11). Despite a tendency towards poorer sustained auditory attention, very preterm children were not more likely than full term children to show significant impairment on this task (p = .42), suggesting the prevalence of impairment was relatively equivalent between the two groups.

4.1.2.2 Sustained response inhibition. In terms of sustained response inhibition, very preterm children performed less well than full term children on Walk Don't Walk. Specifically, very preterm children obtained fewer correct trials on average than full term children (p = .03, d = 0.30) and they were almost twice as likely to show impairment on this task (29 v. 16%, p = .03).

Together, these findings suggest that very preterm children were more likely to lapse into absent-minded responding and that for every full term child identified as having significant difficulty in this domain, two very preterm children were similarly identified. Although, the average number of correct trials did not remain significant after covariate adjustment for social risk index for the groups (p = .13), the rate of impairment remained significant (p = .04).

4.1.3 Executive attention. Very preterm and full term children's performance on the higher-order subtests of executive attention are also shown in Table 5. Creature Counting provides a measure of executive shifting attention[4], and the Sky Search Decrement Score provides a measure of executive divided attention. More information regarding children's performance the sub-variables of both the Creature Counting and Sky Search Dual Task measures is provided in Tables 7 and 8, respectively.

4.1.3.1 Executive shifting attention. As shown in table 5, very preterm children obtained significantly fewer correct items on the Creature Counting subtest in comparison to full term children (p = .01, d = .36). This finding suggests that very preterm children were less accurate than full term children in shifting their attentional focus when switching counting direction. Very preterm children were also twice more likely than full term children to have a total correct score in the impairment range (30 v. 14.2%, p = .007). This indicates that one third of very preterm children experience difficulty in shifting attention. The increased rate of impairment in the very preterm group remained after covariate adjustment for social risk index (p = .04), suggesting that

[4] Total Items Correct is shown as the overall summary score of executive shifting ability to retain children with very poor performance. The Creature Timing Score is only calculated for children who obtained 3 or more correct items and is prone to data loss.

difficulties in shifting attention were more likely explained by very preterm birth than social background factors.

A number of sub-variables that describe qualitative aspects of children's performance in Creature Counting are shown in Table 7. These measures include the total time taken for correct items obtained in Creature Counting; total switches in counting direction made for the total number of correct items obtained; and the summary Creature Counting Timing Score which is the proportion of total time taken for the total switches made for correct items. Together, these measures reflect overall efficiency in shifting attention ability. In terms of time taken to complete correct Creature Counting, there was no significant difference between the two birth groups (p = .93). Very preterm children did, however, obtain a significantly lower number of correct switches in counting direction for the correct items obtained compared to full term children (p = .02, adjusted p = .04). In terms of overall performance on the Creature Counting subtest of executive switching attention, very preterm children had significantly higher Creature Counting Timing Scores compared to full term children (p = .02), indicating poorer performance. This finding suggests that while very preterm children do not appear to be slower overall, the switching of counting direction in very preterm children was characterized by a greater proportion of total time taken for each switch made. This difference remained significant after covariate adjustment for family social risk (p = .01). In addition, there was around a two-fold increase in the proportion of children with Creature Counting Timing Scores in the impairment range among very preterm children relative to full term children (p = .02).

Table 7.
Children's Performance on the Creature Counting Measure of Executive Shifting Attention at Age 12-Years, m (SD)

Creature Counting	**FT (*n* = 106)**	**VPT (*n* = 100)**	**95% C.I. of mean difference**	***t***	**Unadj. *p***	**Cohen's *d*/OR (95% C.I.)**	**Adj. *p***
Time for correct items (Sec)	74.58 (29.06)	74.97 (29.86)	-8.56 – 7.78	-.10	.93	.01	.92
Total switches for correct items	21.15 (6.37)	19.05 (6.60)	0.32 – 3.88	2.33	.02	.32	.04
Number > 3 correct items	100	93					
Creature Counting Timing Score	3.49 (1.15)	3.91 (1.30)	-0.76 – -0.06	-2.34	.02	.34	.02
Any Impairment %	14.2	28.3		6.17	.02	.42 (0.21 – 0.84)	.01

4.1.3.2 Executive divided attention. Lastly, very preterm children performed less well than full term children on the divided attention measure Sky Search Dual Task (DT). The DT Decrement Score, shown in Table 5, reflects the extent to which test performance deviated under dual task conditions from performance in the Sky Search and Score! single task conditions. Higher scores indicate poorer performance. As expected, both groups showed a decrement in performance under the dual task condition and this effect was greater in the very preterm group relative to the full term group. Specifically, very preterm children obtained significantly higher mean DT Decrement Scores compared to full term children ($p < .001$, $d = .50$). Approximately one quarter of the very preterm group (24%) had a decrement score that fell into the impairment range, compared to only 10% of full term children ($p = .008$). Both the mean Sky Search DT Decrement

Scores (p = .002) and rate of impairment in divided attention (p = .02) remained significant after covariate adjustment for social risk index.

Table 8 shows the between-groups differences on the sub-variables of the Sky Search DT. Compared to the number of target spaceships found in the Sky Search single condition (p = .25, Table 6), very preterm children found fewer target spaceships than full term children (p = .03) in the dual task condition. While very preterm children tended to take longer to complete Sky Search DT, but this difference did not reach statistical significance (p = .13). However, very preterm children had a significantly slower time-per-target time compared to full term children in the dual task condition, being 0.53 milliseconds slower than full term children per target (p = .03). In terms of the Score! component in the dual task condition, very preterm children again obtained significantly fewer correct sound items compared to full term children (p < .001) and this remained after covariate adjustment for social risk index (p = .002).

Table 8.
Children's Performance on the Sky Search DT Measure of Executive Divided Attention at Age 12-Years, m (SD) at Age 12-Years, m (SD)

Sky Search DT	**FT (n = 106)**	**VPT (n = 100)**	**95% C.I. of mean difference**	***t***	**Unadj. *p***	**Cohen's *d***	**Adj. *p***
Targets identified	19.05 (1.43)	18.49 (2.13)	0.06 – 1.06	2.20	.03	.31	.08
Time taken (Sec)	79.55 (25.63)	85.45 (30.11)	-13.57 – 1.77	-1.52	.13	.21	.31
Time-per-target (Sec)	4.19 (1.39)	4.72 (1.95)	-0.99 – -0.64	-2.24	.03	.31	.11
Proportion of Score! items correct	0.91 (0.18	0.81 (0.21)	0.04 – 0.15	3.58	<.001	.51	.002

4.2 Comparison of TEA-Ch subtest effect sizes. Across the TEA-Ch subtests, small to medium effect sizes were found that favored full term children. Relatively modest effects were detected for the sustained attention measures, with Cohen's *d* ranging from .30 to .34 for the sustained auditory attention and sustained response inhibition subtests, respectively. This suggests that while very preterm children performed less well on Score! and Walk Don't Walk compared to full term children, the nature of very preterm children's difficulties in sustained attention were likely to be mild relative to the full term group. For executive switching attention, a small-medium effect size was detected of .36. A medium effect size was found between full term and very preterm children on the Sky Search Dual Task subtest of executive divided attention (*d* = .50), which suggests that very preterm children found the divided attention task relatively more difficult than the other attention tasks.

4.3 Associations between gestational age and attention. To summarize the findings thus far, very preterm children performed significantly less well on measures of sustained and executive attention compared to full term children at age 12 years. Deficits in selective attention became apparent when tested under dual task conditions. Next, the nature and extent of poor attention outcomes is examined in relation to decreasing gestational age. The sample was categorized into three groups using the clinical definition of prematurity (full term: 36 – 41 GA, very preterm: 28 – 33 GA, extremely preterm: 23 -27 GA). The mean TEA-Ch scores and rates of attention impairment across these gestational groups are shown in Table 9.

Shown in Table 9, there was a significant multivariate effect of birth group on the TEA-Ch subtests across the full term, very preterm and extremely preterm groups (F (10, 392) = 2.75, p = .003, Wilks' $\lambda = 0.87$, partial $\eta^2 = .07$). To further examine the relationship between gestational

Table 9.

The Nature and Extent of Attention Outcomes at Age 12 Years in Relation to Gestational Age at Birth, Assessed with the TEA-Ch, m (SD)

Variable	**FT (*n* = 103)**	**VPT (*n* = 60)**	**EPT (n = 40)**	**Ƒ/ X^2**	***p***	**FT v. VPT**		**FT v. EPT**	
						d/OR	***P***	**d/OR**	***p***
Multivariate λ = 0.87				2.75	.003				
Selective Attention									
Sky Search Attention Score	3.49 (1.02)	3.65 (1.86)	3.42 (0.96)	0.42	.66	.12	.74	.07	.95
Impaired %	16.0	15.0	7.5	1.81	.41	.92	.86	.42	.19
Sustained Auditory Attention									
Score! Total Correct	8.76 (1.49)	8.42 (1.86)	7.83 (2.00)	4.31	.02	.20	.44	.53	.01
Impaired %	22.6	23.3	35.0	1.87	.17	1.04	.92	1.84	.13
Sustained Response Inhibition									
Walk Don't Walk Total Correct	15.87 (2.66)	14.70 (3.66)	15.23 (3.68)	2.63	.08	.37	.06	.20	.52
Impaired %	16.0	30.0	27.5	3.51	.06	2.24	.04	1.99	.12
Executive Switching Attention									
Creature Counting Total Correct	5.85 (1.48)	5.30 (1.61)	5.25 (1.85)	3.30	.04	.36	.08	.36	.11
Impaired %	14.2	25.0	37.5	9.70	.002	2.02	.08	3.64	.003
Executive Divided Attention									
Sky Search DT Decrement Score	1.43 (2.36)	2.87 (3.58)	3.45 (4.70)	6.86	.001	.47	.02	.54	.003
Impaired %	9.5	23.3	25.0	6.72	.01	2.89	.02	3.17	.02

λ = Wilks' Lambda; Impaired % for FT *n* = 106

[a] Tukey HSD post-hoc comparison *p* value

age and the individual components of attention, the findings of univariate tests with Tukey HSD post-hoc comparisons are described in below.

Selective attention. Contrary to the research hypothesis, there was no clear linear association between decreasing gestational age and selective attention abilities. Full term, very preterm and extremely preterm children obtained relatively similar Sky Search Attention Scores ($p = .66$), with no clear tendency for very preterm and extremely preterm children to perform more poorly than full term children. In terms of the rate of selective attention impairment, there was a similar rate of impairment across full term (16%) and very preterm (15%) children while impairment was relatively less common in the extremely preterm group (8%, $p = .41$).

Sustained Auditory Attention. Also shown in Table 9 are the mean subtest scores and rates of impairment for Score! which provides a measure of sustained auditory attention. As the gestational age decreased across the three birth groups, there was a corresponding decrease in the total number of correct Score! items obtained ($p = .02$). Post-hoc comparisons indicated that extremely preterm children performed significantly more poorly than full term children ($p = .01$). Although there was an increase in the rate of impairment in sustained auditory attention across the groups, this tendency did not reach statistical significance ($p = .17$).

Sustained Response Inhibition. Contrary to the research hypothesis, there was no clear linear trend between sustained response inhibition and decreasing gestational age. Although very preterm and extremely preterm children obtained lower mean Walk Don't Walk scores than full term children, these scores did not follow a linear trajectory and group differences approached significance only ($p = .08$) A similar trend was found for the rate of impairment on Walk Don't Walk ($p = .06$). Post-hoc comparisons suggested that very preterm children showed a tendency to perform more poorly than full term children, but this difference did not reach statistical

significance (p = .08). When taken together, findings suggest that poor sustained response inhibition is somewhat associated with prematurity (p = .08), but that younger gestational age does not appear to be associated with additional increased risk of impairment in this domain.

Executive Shifting Attention. In contrast to selective and sustained attention outcomes, substantially clearer associations between executive attention and decreasing gestational age were found for shifting attention (Table 9). As gestational age decreased across the groups, there was a comparable decrease in the total number of correct items obtained in Creature Counting (p = .04) and an increase in the rate of impairment (p = .002). For every full term child identified as having an impairment in switching attention (14%), approximately two very preterm (25%) and three extremely preterm (30%) children were also identified as having a similar problem. In support of the above finding, the odds ratio for poor outcome relative to the full term group was larger for the extremely preterm group (3.64, p = .003) than for the very preterm group (2.02, p = .08).

Executive Divided Attention. Linear associations between gestational age and executive divided attention were also found for the Sky Search DT Decrement Scores (Table 9). As gestational age decreased across the groups, there was a corresponding increase in mean Decrement Scores obtained by the groups (p = .001) and an increase in the rate of impairment (p = .01). Specifically, extremely preterm children had the highest rate of impairment on this measure at 25%, followed by 23% of very preterm children and 10% of full term children (p = .01). The odds ratios further emphasized this trend, as very preterm children had increased risk of impairment compared to the full term group (OR: 2.89, p = .02) while this risk was higher still for the extremely preterm group (OR: 3.17, p = .02).

Chapter 5. Results: Structural Alterations in Grey Matter Growth and Development

The second primary objective of the current study was to describe the regional structural alterations in grey matter volume between very preterm and full term children at age 12 years. Structural T1-weighted images were analyzed using voxel based morphometry and corrected for multiple comparisons FWE $p < .05$. For this analysis, two contrasts were investigated: 1) regions in which very preterm children evidenced reduced grey matter volume compared to full term children, and 2) regions in which very preterm children evidenced increased grey matter volume compared to full term children. Mean modulated grey matter volume values were then extracted from the regions identified in the voxel based morphometry analysis and examined after covariate adjustment for age at scan ($p = .004$) and social risk index ($p < .001$) in statistical models.

5.1 Regional reductions in grey matter volume in very preterm children. Findings of the voxel based morphometry analyses suggest that very preterm children have reduced grey matter volume in a number of regions compared to full term children at age 12 years. Figure 9 displays the t-statistic image showing clusters of grey matter voxels that passed the threshold of significance after correction for multiple comparisons (FWE-corrected $p < .05$). The lighter gradient in the SPM image shown in Figure 9 represents higher t-statistic values. Figure 10 displays these same clusters in axial, coronal and sagittal view with colored overlays to distinguish each region. Together, these figures show that very preterm children have reduced grey matter volume in both cortical and subcortical regions age at 12 years compared to their full term peers. Specifically, very preterm children had reduced grey matter volume in the bilateral superior parietal cortex, bilateral temporal cortices, left prefrontal cortex, and posterior cingulate

gyrus. In terms of subcortical areas, very preterm children also had reduced grey matter volume in the bilateral thalamic and bilateral hippocampal structures.

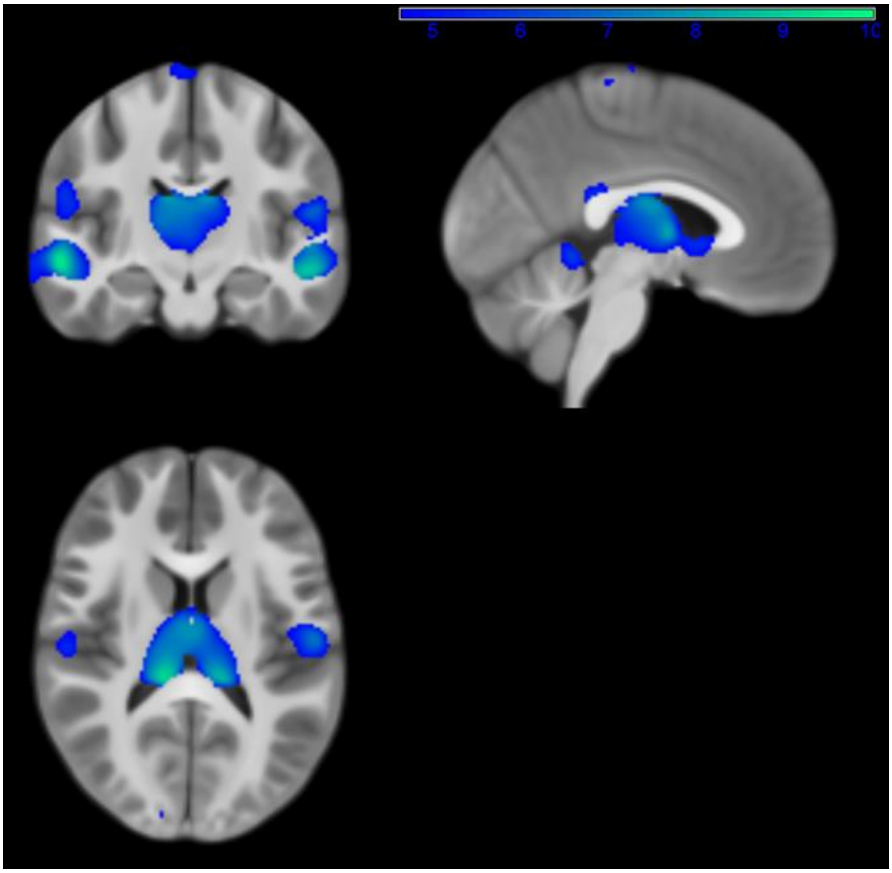


Figure 9. The SPM t-statistic output image from Contrast 1 (VPT < FT) showing the grey matter volume clusters that passed the threshold for significance, FWE-corrected $p < .05$.

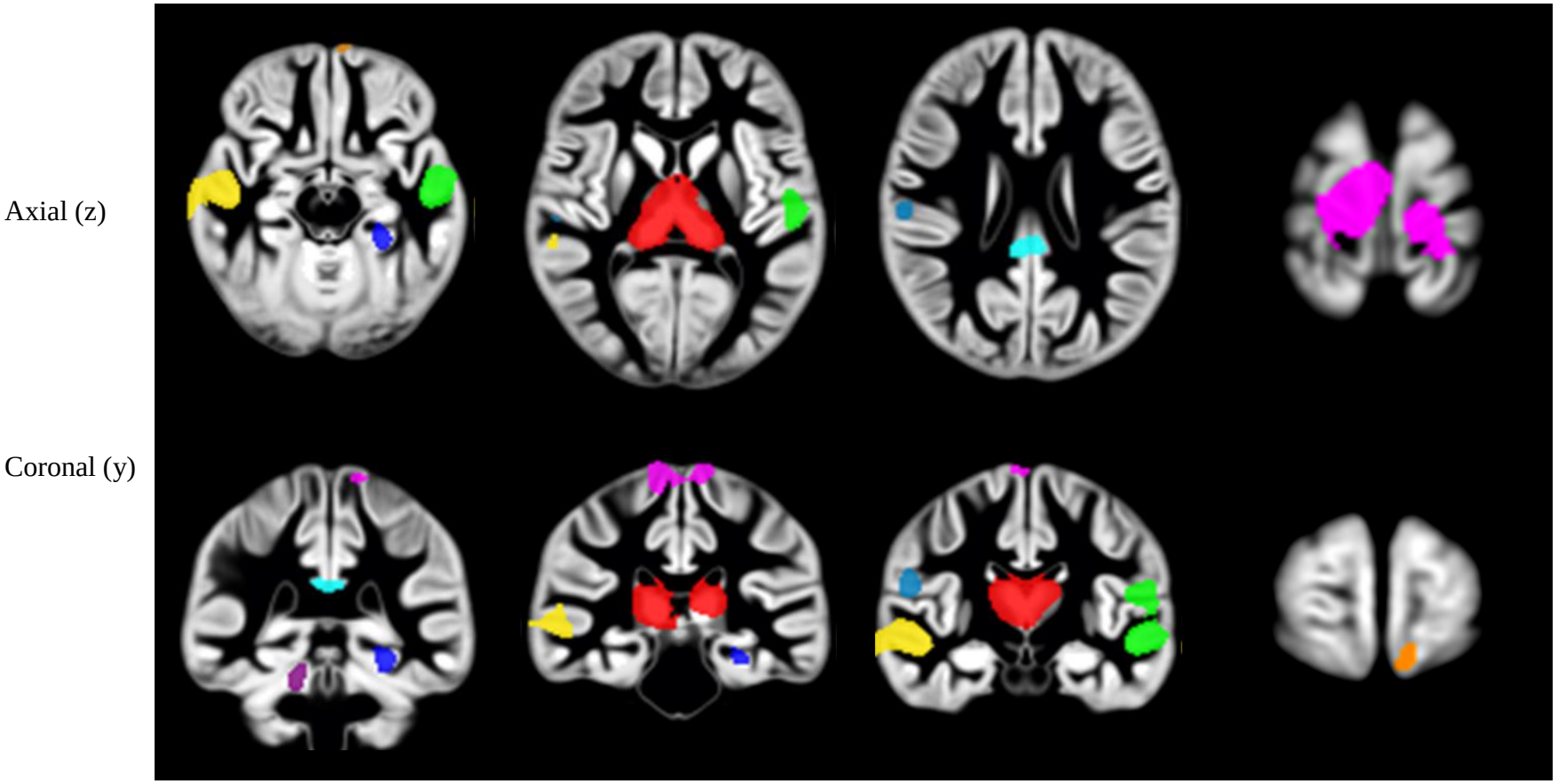


Figure 10. The SPM output image from Contrast 1 (VPT < FT) of grey matter volume, FWE-corrected $p < .05$, with colored overlays to distinguish each cluster.

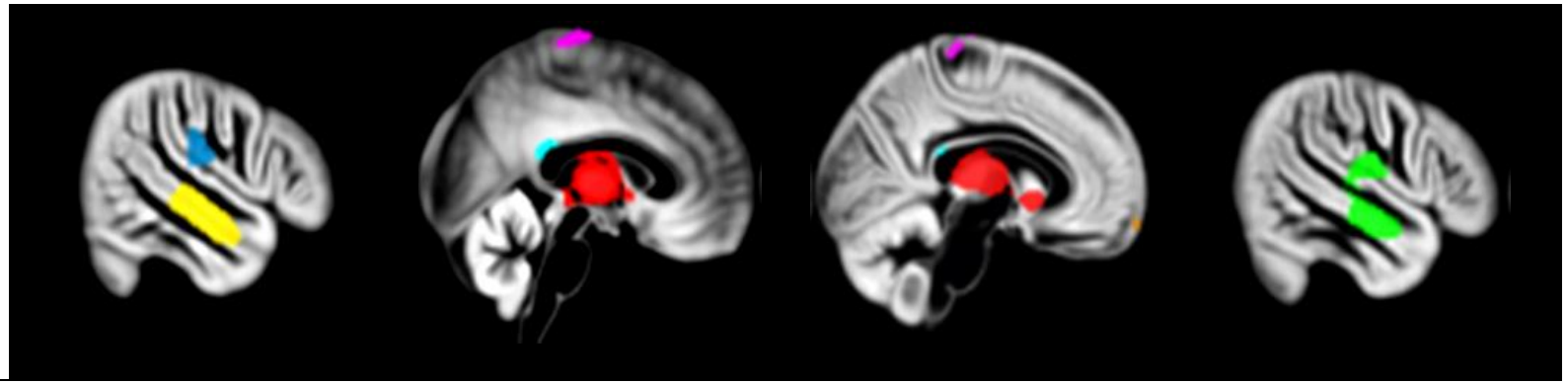
Plane	Slices
Sagittal (x)	

Figure 10 continued. The SPM output image from Contrast 1 (VPT < FT) of grey matter volume, FWE-corrected $p < .05$ with colored overlays to distinguish each cluster.

Table 10 shows the mean modulated grey matter volume values that were extracted from the clusters in the key regions identified in Contrast 1 for both groups, FEW-corrected $p < .05$. As expected, very preterm children had significantly lower mean modulated grey matter volume values in all of the identified regions compared to full term children (*p*s <.001). Taking a conservative approach, the modulated grey matter volume values were examined after covariate adjustment for corrected age at scan ($p = .004$) and social risk index ($p < .001$) to statistically control for developmental and social factors that differentiated the two birth groups (Tables 3 and 4). Sex and pubertal status were also considered as covariates, but these factors were not statistically different between the two groups and did not alter the results when included in preliminary models. As shown in Table 10, the adjusted *p* values for the modulated grey matter volume values of each region remained highly significant after adjustment for the effects of age at scan and social risk index (*p*s <.001). This suggests that regional reductions in grey matter volume in very preterm children is a robust finding that persists after consideration of social and developmental factors.

Table 10.

The Unadjusted and Adjusted Mean Modulated Grey Matter Volume Values (m, SD) of Full Term and Very Preterm Children at Age 12 Years, Contrast 1 (VPT < FT)

Region	**FT (n = 93)**	**VPT (n = 89)**	***t***	**Unadjusted *p***	***Adjusted p***
Bilateral superior parietal cortex	0.5493 (0.08)	0.4502 (0.12)	-7.03	< .001	< .001
Right superior temporal cortex	0.7668 (0.12)	0.6615 (0.10)	-6.35	< .001	< .001
Right inferior temporal cortex	0.8059 (0.08)	0.6959 (0.08)	-9.65	< .001	< .001
Left medial temporal cortex	0.7944 (0.07)	0.6708 (0.08)	-10.86	< .001	< .001
Left prefrontal cortex	0.6420 (0.15)	0.5525 (0.16)	-3.85	< .001	< .001
Posterior cingulate gyrus	0.7447 (0.10)	0.6286 (0.11)	-7.61	< .001	< .001

Table 10.

The Unadjusted and Adjusted Mean Modulated Grey Matter Volume Values (m, SD) of Full Term and Very Preterm Children at Age 12 Years, Contrast 1 (VPT < FT)

Region	FT (n = 93)	VPT (n = 89)	*t*	Unadjusted *p*	*Adjusted p*
Bilateral thalami	0.7133 (0.06)	0.6044 (0.12)	-7.83	< .001	< .001
Left hippocampus	0.8992 (0.10)	0.7844 (0.14)	-6.36	< .001	< .001
Right hippocampus	0.9372 (0.10)	0.8159 (0.14)	-6.75	< .001	< .001

5.2 Regional increases in grey matter volume in very preterm children. In addition to Contrast 1, a second contrast was also investigated to identify regions in which very preterm children had increased grey matter volume compared to their full term peers at age 12 years. Findings of the voxel based morphometry showed that very preterm children had increased grey matter volume in two regions compared to full term children. Specifically, very preterm children had higher mean modulated grey matter volume values in medial occipital cortex and anterior cingulate gyrus. These results are shown in Figures 11 and 12 below. Figure 11 displays the SPM t-statistic output image showing the clusters of altered grey matter volume that passed the threshold of significance after correction for multiple comparisons, FWE-corrected $p < .05$. The lighter gradient in Figure 11 represents higher t-statistic values. Figure 12 displays the clusters in axial, coronal and sagittal view with colored overlays to distinguish each region.

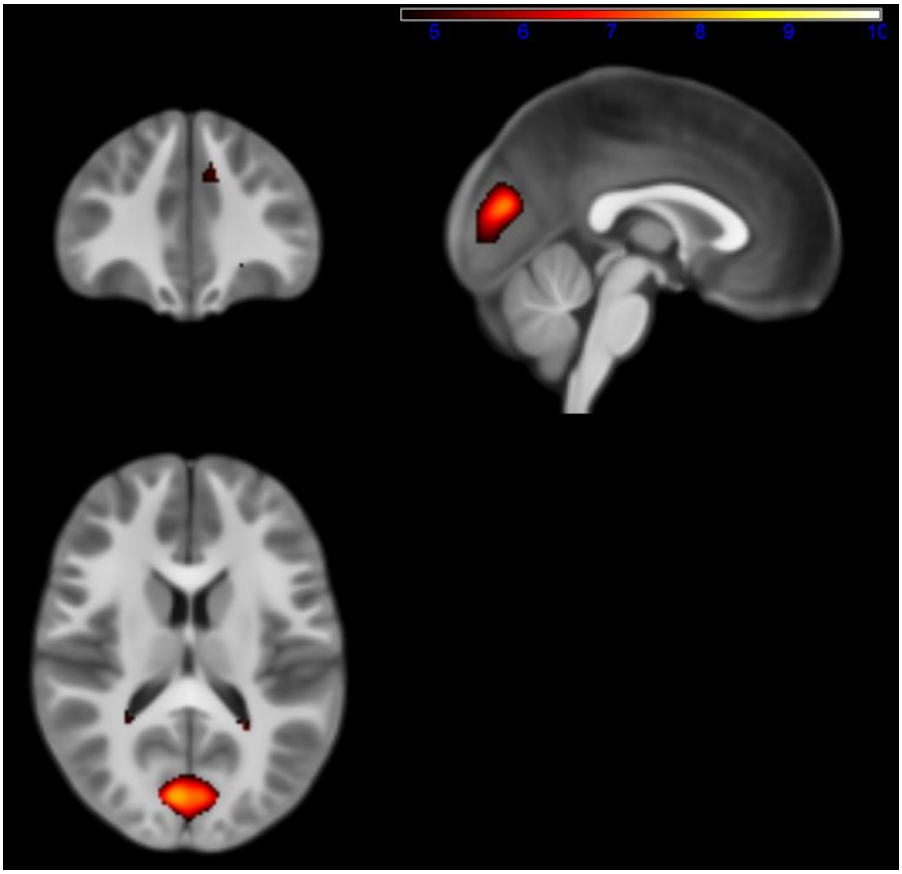


Figure 11. The SPM t-statistic output image from Contrast 2 (VPT > FT) showing the grey matter volume clusters that passed the threshold for significance, FWE-corrected $p < .05$.

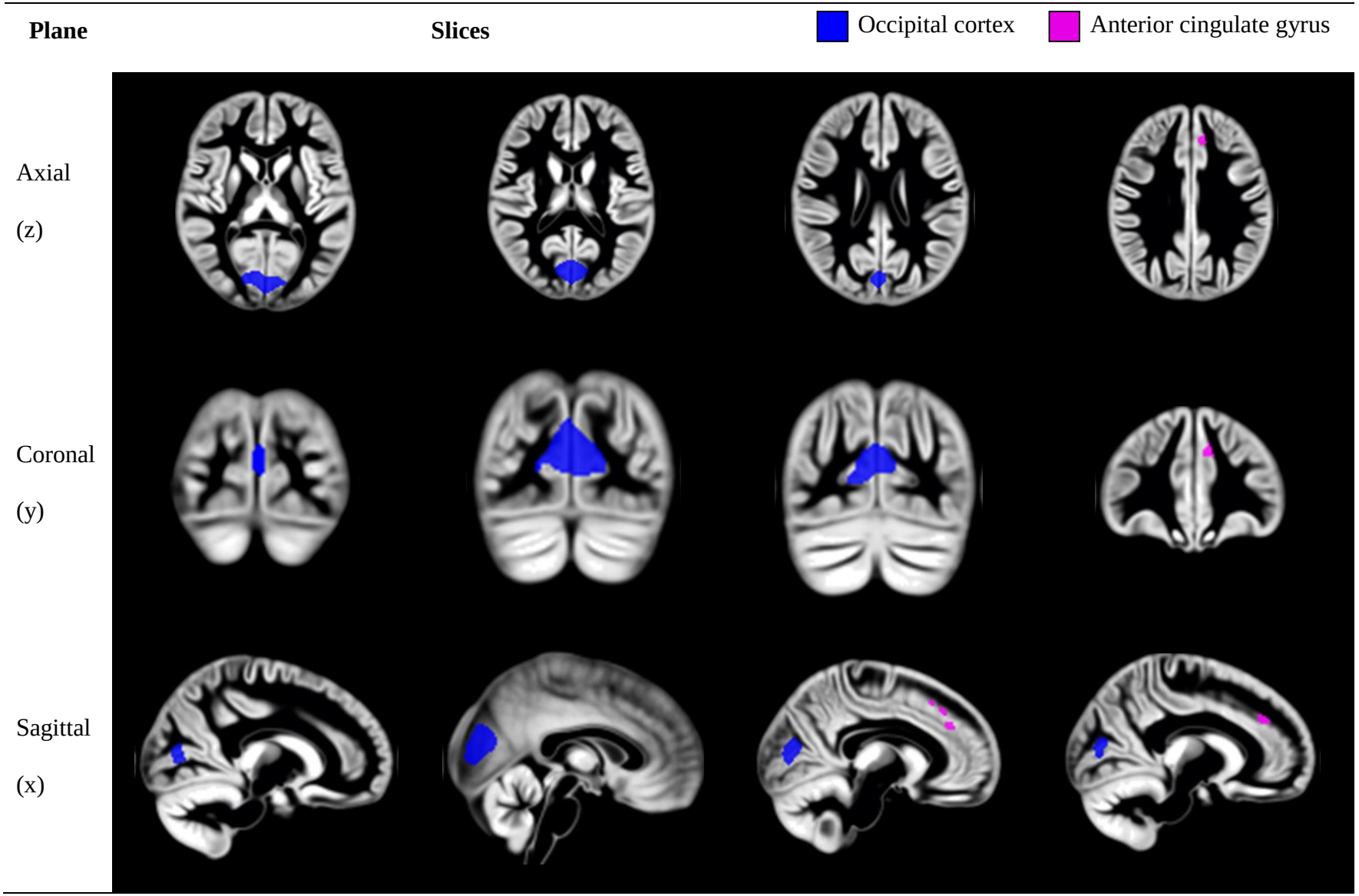


Figure 12. The SPM output image from Contrast 2 (VPT > FT) of grey matter volume, FWE-corrected $p < .05$ with colored overlays to distinguish each cluster.

Table 11 shows the mean modulated grey matter volume values that were extracted from the clusters in key regions identified in Contrast 2 for both groups. As expected, very preterm children had significantly higher mean modulated grey matter volume values in the medial occipital cortex and anterior cingulate gyrus compared to full term children (*p*s <.001). The modulated grey matter volume values were examined after covariate adjustment for corrected age at scan ($p = .004$) and social risk index ($p < .001$) to statistically control for social and developmental factors that differentiated the two birth groups (Tables 3 and 4). Importantly, the adjusted *p* values for each region remained highly significant after including age at scan and social risk index as covariate factors (*p*s <.001). This suggests that like the regional decreases in grey matter volume, regional increases in grey matter volume in very preterm children is also a robust finding that persists after consideration of social and developmental factors.

Table 11.

The Unadjusted and Adjusted Mean Modulated Grey Matter Volume Values (m, SD) of Full Term and Very Preterm Children at Age 12 Years, Contrast 2 (VPT > FT)

Region	**FT (n = 93)**	**VPT (n = 89)**	***t***	**Unadjusted *p***	**Adjusted *p***
Medial occipital cortex	0.6386 (0.08)	0.7513 (0.11)	5.88	< .001	< .001
Anterior cingulate gyrus	0.5198 (0.09)	0.6121 (0.12)	7.85	< .001	< .001

Chapter 6. Results: Associations between Attention Outcomes and Structural Alterations in Grey Matter Volume

The findings of the current study thus far suggest that very preterm children preform significantly less well on neuropsychological measures of attention relative to full term children, particularly in terms of sustained and executive attention abilities. At age 12 years, very preterm children also evidenced structural alterations in grey matter, characterized by both regional decreases and increases in regional grey matter volume relative to full term children. Importantly, these between-groups differences persisted after covariate adjustment for age at scan and social risk index. The third and final objective of the current study was to examine associations between attention and regional grey matter volume within the very preterm group, and to examine the extent to which grey matter development independently predicted attention outcomes in late childhood.

The findings relevant to this objective are reported in two sections. First, one-tailed Pearson's product moment correlations are reported to describe the direction and strength of the bivariate relationships between TEA-Ch subtest raw scores and the modulated grey matter volume values in each region of interest. Second, forwards and backwards linear regression modelling was used to identify the most parsimonious and best fitting model that show the extent to which grey matter volume at age 12 years made an independent contribution to attention outcomes after taking into account the neonatal and neurological and social factors also associated with attention.

6.1 Bivariate relationships between attention outcomes and grey matter volume in very preterm children at age 12 years.

Table 12 shows the Pearson Product moment correlations between raw subtest TEA-Ch scores and the regional modulated grey matter volume values for

very preterm children (n = 87) at age 12 years. In Table 12, the correlations relevant to the current research aim are highlighted in grey, while additional correlations showing relationships between neonatal factors, social risk index and attention are also presented in the same table to identify potential issues regarding collinearity for the subsequent regression analyses.

Selective Attention. Within preterm children, Sky Search Attention Scores of selective attention were negatively correlated with modulated grey matter volume values in the thalamic region (r = -.34, p = .001). That is, very preterm children who had reduced grey matter volume in the thalamic region were also likely to perform more poorly on the measure of selective attention. Factors that also correlated with selective attention ability in very preterm children included the presence of cystic periventricular leukomalacia (r = .56, p < .001) and extent of diffuse white matter injury (r = .22, p = .04). This factors will be taken into account when examining the independent contribution of thalamic volume to selective attention in regression analyses.

Sustained Auditory Attention. Contrary to the research hypothesis, none of the regional grey matter volume values correlated with the raw subtest scores obtained on Score! for very preterm children at age 12-years. Instead, a number of neonatal factors showed significant associations with sustained auditory attention. These included gestational age (r = .22, p = .05), presence of retinopathy of prematurity (r = -.25, p = .02) and administration of corticosteroids (r = .23, p = .04). That is, very preterm children who were born at a younger gestational age, experienced retinopathy of prematurity from oxygen toxicity and relative hypoxia, and who required steroid administration were more likely to perform less well on the sustained auditory attention subtest. Very preterm children who were born to mothers reporting higher levels of socio-familial adversity at the time of delivery were also more likely to perform less well on Score! at age 12 years (r = -.23, p = .03).

Table 12.
Bivariate Relationships between Infant Clinical Factors, Grey Matter Volume and Attention for Very Preterm Children at Age 12 Years

		TEA-Ch subtests of attention					GM volume – 12 years			
	Factor	**SS**	**Score**	**Walk Don't Walk**	**Creature Counting**	**SS DT**	**Thalami**	**L. temporal**	**Post. cingulate**	**Occipital**
GM volume - 12 years	**Thalami**	-.34 ***			.32**	-.36***		.27*	.50***	
	Left temporal					-.35***	.27*		.32**	
	Posterior cingulate					-.36***	.50***	.32**		
	Occipital			.24*		-.30**				
Infant clinical, neurological, social background	**GA**		.22*							
	IUGR				-.38***		-.19*	-.15*		.27***
	ROP		-.25*							
	Steroid admin.		.23*							
	PVL	.56***		-.22*	-.30**	.51***	-.41***	-.24*		
	T. WMI score	.22*				.35**				
	T. social risk		-.23*	-.22*						

SS Sky Search, SS DT Sky Search Dual Task, GA Gestational age, IUGR Intrauterine growth restriction, ROP Retinopathy of Prematurity, PVL Periventricular luekomalacia, WMI White matter injury, T total
* $p < .05$, ** $p < .01$, *** $p < .001$;

Sustained Response Inhibition. Very preterm children's performance on Walk Don't Walk was positively correlated with the modulated grey matter volume values in the medial occipital region. Children who had obtained fewer correct trials on the subtest of sustained response inhibition were also had reduced grey matter volume in the medial occipital region (r = .24, p = .03). For regression analyses, children who were identified as having cystic periventricular leukomalacia (r = -.22, p = .04) and who were from higher social risk backgrounds (r = -.22, p = .04) also showed lower levels of sustained response inhibition ability at age 12 years.

Executive Shifting Attention. Within preterm children, the total number of correct items obtained in Creature Counting was positively correlated with modulated grey matter volume values in the thalamic region (r = .32, p = .003). That is, very preterm children who had reduced grey matter volume in the thalamic region were also likely to perform more poorly on executive shifting attention subtest. Neonatal factors that also correlated with executive switching attention included intrauterine growth restriction for sex and gestational age (r = -.38, p < .001) and presence of periventricular leukomalacia (r = -.30, p = .005); which will be considered in multiple regression analyses.

Executive Divided Attention. Of the five TEA-Ch subtests included in the current study, Sky Search Dual Task (DT) was associated with multiple grey matter regions. Higher Sky Search DT Decrement Scores indicating poorer test performance were associated with lower mean modulated grey matter volume values in the thalami (r = -.35, p = .001) and the left temporal (r = -.35, p = .001), posterior cingulate (r = -.36, p = .001) and occipital cortices (r = -.30, p = .005). In consideration of regression analyses, higher Sky Search DT Decrement Scores also correlated with the presence of periventricular leukomalacia (r = .51, p < .001) and the extent of diffuse white matter injury (r = .35, p = .001).

6.2 Predictors of attention for children born very preterm at age 12 years. Children born very preterm were significantly more likely to have poorer attention outcomes compared to full term children, and these attention outcomes were significantly correlated with regional grey matter volumes at age 12 years. Thus, multiple regression models were developed to examine the extent to which regional grey matter volume made an independent contribution to attention outcomes of very preterm children after taking into account the neonatal and social factors that also correlated with attention at age 12 years.

For each component of attention, factors were entered into the linear regression models to investigate which infant clinical, neurological and social background factors, and grey matter volume at age 12 years predicted TEA-Ch scores at follow-up. Five individual models were developed to predict each selective, sustained and executive attention subtest of the TEA-CH, acting as the dependent variables. The neonatal risk factors and social risk index that were associated with attention outcomes in childhood were identified and selected from earlier correlational analysis (Table 12). Infant clinical factors included intrauterine growth restriction for sex and gestation (IUGR), retinopathy of prematurity (ROP), requiring corticosteroids, presence of cystic periventricular leukomalacia (PVL), and extent of diffuse white matter injury (WMI)[5]. The independent variables with two dichotomous levels included IUGR, ROP, PVL and steroid administration (0 = absent, 1 = present). The remaining independent variables included white matter injury score (0 – 6), social risk index (0 – 5) and modulated grey matter volume values, which were retained in their continuous form as described in the method section.

[5] No significant correlations were found between attention outcomes and neonatal confirmed sepsis result, infant respiratory distress requiring oxygen supplementation at 36 weeks, dexamethasone administration, presence of necrotizing enterocolitis, or intraventricular hemorrhage grade 3/4. These factors were not entered into regression models.

Forwards and backwards linear regression models were developed to identify the best fitting and most parsimonious models of attention outcomes in very preterm children. To develop the models, infant clinical factors of interest were entered into each model first, followed by infant neuropathological factors, social risk index, and regional grey matter volumes. Variables that did not significantly contribute to the model ($p \geq .12$) were removed in a forced fashion to improve the precision of the model. To minimize potential issues related to multicollinearity among the infant clinical and neurological factors, detailed inspection of all multivariate coefficients, standard error, tolerance and VIF statistics, and condition indices of collinearity diagnostics was undertaken at each forwards and backwards step of model refinement. The final blocks of each model for the key components of attention are summarized in Table 13. Key statistics reported for each independent variable in each model include:

1) The unstandardized regression coefficient (B) which indicates the amount of change in the independent variable that is associated with change in the dependent variable,
2) The standard error (SE) of the estimation which is the standard deviation of the residual variance after the prediction,
3) The standardized beta coefficient (β), which is the partial prediction of the independent variable on the dependent variable when all variables are standardized,
4) The *t*-test *p* value which shows whether the independent variable is significantly associated with the dependent variable after holding all other independent variables in the model constant,
5) The overall *F* statistic which provides a measure of the ratio of the variance attributable to the independent variables versus that attributable to error,

6) The overall *p* value, indicating whether the combination of independent variables explains a significant amount of variance in the dependent variable, and
7) The unadjusted and adjusted squared multiple correlation R^2, which is the proportion of the dependent variable's variance explained by the combination of the independent variables.

Selective Attention. The final model for selective attention accounted for 31% of the variance in Sky Search Attention Scores (adjusted $R^2 = .31$, $p < .001$). The only significant independent predictor of selective attention for very preterm children was presence of cystic PVL ($p < .001$). Although the removal of the non-significant factors from block one of the model saw a 2% decrease in the variance of Sky Search Attention Scores accounted for, this was a non-significant change ($R^2 = -.01$, F change $(1,83) = 1.77$, $p = .19$). This model suggests that although grey matter volume in the thalamic region at age 12 years was correlated with selective attention, this factor did not significantly account for lower Sky Search Attention Scores at age 12 years above and beyond the presence of cystic PVL.

Sustained Auditory Attention. Although regional grey matter volume at age 12 years was not associated with sustained auditory attention for very preterm children, neonatal factors instead predicted children's performance on Score!. The final model accounted for 12% of the variance (adjusted $R^2 = .09$, $p = .006$) in sustained auditory attention outcomes. The significant independent predictors of sustained attention for very preterm children from the neonatal period included ROP ($p = .02$) and social risk index ($p = .03$). The removal of corticosteroid administration ($p = .25$) from block one of the model saw a 1% decrease in the variance

Table 13.

The Clinical, Neuropathological and Social Risk Predictors of Attention in Very Preterm Children (*n* = 86) at Age 12 Years

	Coefficients				Model Summary			
	Unstandardized		Standardized					
	B	**SE**	β	***p***	**R^2**	**Adj. R^2**	***F***	***p***
Selective Attention								
PVL[¥]	3.56	0.69	0.51	<.001	.31	.31	20.24	<.001
Sustained Auditory Attention								
ROP[¥]	-0.97	0.40	-0.25	.02	.12	.09	5.43	.006
Social risk index[¥]	-0.43	0.19	-0.23	.03				
Sustained Response Inhibition								
Occipital volume[ǂ]	6.27	3.14	0.21	.05	.13	.10	4.18	.008
Social risk index[¥]	-0.66	0.34	-0.20	.05				
PVL[¥]	-2.71	1.66	-0.17	.11				
Executive Shifting Attention								
IUGR[¥]	-2.05	0.52	-0.38	<.001	.27	.24	10.22	<.001
PVL[¥]	-1.93	0.78	-0.26	.015				
Thalamic volume[ǂ]	2.25	1.45	0.16	.12				
Executive Divided Attention								
PVL[¥]	8.22	1.75	0.42	<.001	.42	.39	14.68	<.001
Posterior cingulate volume[ǂ]	-9.72	3.42	-0.26	.006				
Occipital volume[ǂ]	-7.90	3.22	-0.21	.016				
Left temporal volume[ǂ]	-8.12	5.07	-0.15	.11				

[¥] Factor from neonatal period; [ǂ] Factor from 12 Years; PVL: cystic periventricular leukomalacia, ROP: Retinopathy of Prematurity; IUGR: Intrauterine Growth Restriction (> 2 SD for gestation and sex)

accounted for in the correct trials obtained for Score!, but this was a non-significant change (R^2 = -.01, *F* change (1,82) = 1.32, *p* = .25). The model suggests that oxygen toxicity and relative atrophy leading to ROP in addition to early exposure to socio-familial adversity predicts poorer sustained attention outcomes in children born very preterm. However, the model accounted for just 12% of the variance in sustained attention outcome, suggesting that factors not considered by the current study may also be contributing to the risks of inattention observed among very preterm children.

Sustained Response Inhibition. In addition to sustained auditory attention, higher social risk index was also identified as a significant predictor of sustained attention to response inhibition (*p* = .05). The presence of neonatal cystic PVL also showed some predictive association with the number of correct trials obtained for Walk Don't Walk, although this finding approached significance only (*p* = .11). When taking social risk index and PVL into account, grey matter volume in the medial occipital region was the strongest independent predictor of sustained response inhibition (β = .21, *p* = .05). This finding suggests that poor grey matter growth and development in the occipital cortex is an important risk factor for lower levels of sustained attention to inhibitory control in very preterm children at age 12 years. However, these factors explained 13% of the variance in outcome for very preterm children (adjusted R^2 = .10, *p* = .008) which is a relatively modest proportion of variance accounted for and highlights the need to consider other developmental factors for this domain of attention.

Executive Shifting Attention. The final model predicting executive shifting attention accounted for 27% of the variance in Creature Counting scores (adjusted R^2 = .24, *p* < .001). The significant independent predictors of for executive switching attention for very preterm children included IUGR at birth (*p* = < .001), neonatal cystic PVL (*p* = .02), and to some extent, grey

matter volume in the thalamic region at age 12 years (p = .12). This finding suggests that IUGR and PVL are important predictors of poor executive switching attention abilities in very preterm children at age 12 years, and that suboptimal grey matter growth and development in the thalamic region may also play a tentative role in this domain of attention.

Executive Divided Attention. Of the factors that correlated with Sky Search DT Decrement Scores, the significant independent predictors of executive divided attention included neonatal cystic PVL (p < .001), and reduced grey matter volume in the posterior cingulate (p = .006) and occipital (p = .02) cortices. Reduced grey matter volume in the left temporal cortex approached significance only (p = .11). This model for executive divided attention accounted for 42% of the variance (adjusted R^2 = .39, p < .001) in Sky Search DT Decrement Scores for very preterm children. Non-significant factors of executive divided attention included the extent of white matter injury in the neonatal period (p = .20) and grey matter volume in the thalami at age 12 years (p = .88). The removal of these factors in block two of model refinement did not significantly affect the model (R^2 = -.01, F change (1, 80) = 1.70, p = .20). Importantly, these findings suggest that after taking neonatal cystic PVL (p < .001) into account, reduced grey matter volume in the posterior cingulate (p = .006) and occipital cortices (p = .02) were significant independent predictors of poorer executive divided attention.

Chapter 7. Discussion

7.1 Overview of the current study. Children born very preterm represent a vulnerable group of children at increased risk of adverse neurodevelopmental outcomes. While very preterm birth is associated with higher rates of ADHD, little is understood regarding the nature and extent of these attention problems or the mechanisms that place very preterm children at increased risk of poor attention outcomes. Previous research suggests that grey matter growth and development, a secondary marker of neural abnormality and maladevelopment following preterm birth, may show stronger associations with attention impairments in very preterm children compared to diffuse white matter abnormalities (Bora, Pritchard, Chen *et al*., 2014; Murray, Scratch, Thompson *et al.*, 2014). However, no existing study has examined concurrent associations between attention and volumetric MRI measures of grey matter growth and development in very preterm children at school age. To bridge this gap in the literature, the current study assessed the selective, sustained and executive attention abilities of very preterm children and related these outcomes to regional grey matter volume at age 12 years.

A number of important methodological features of the current study allowed for the detailed description of attention problems in children born very preterm, and to examine the clinical, neurological and social factors that place very preterm children at increased risk of attention impairment. First, the detailed collection of infant clinical, neuropathological and social background characteristics during neonatal period enabled the current study to consider a wide range of factors associated with attention outcomes in childhood. To date, just one study has included cumulative social risk index at term as a covariate for attention analyses (Murray, Scratch, Thompson *et al*., 2014). Second, the neuropsychological measure of attention included in the current study differentially tested the selective, sustained and executive components of

attention in very preterm children. This approach provided information concerning the nature of attention impairments that may be domain specific in very preterm children, as well as providing individual test sub-variables to gauge qualitative aspects of performance such as accuracy and timing (Anderson, 1998). Third, a unique feature of the current study was the inclusion of concurrent measures of attention and grey matter volume at school age. Structural alternations in regional grey matter volume at age 12 years reflects the extent to which grey matter growth and development is adversely impacted by the trophic and maturational disturbances in brain development following very preterm birth (Giedd, Blumenthal, Jeffries *et al*., 1999; Volpe, 2009). Findings relating to each of the study aims are now discussed in light of previous literature.

7.2 The nature and extent of attention problems in children born very preterm.

7.2.1 Selective attention. At age 12 years, very preterm children had similar levels of selective attention abilities in relation to full term children. Specifically, both groups obtained equivalent mean Sky Search Attention Scores on the TEA-Ch. There was also a comparable rate of impairment in selective attention across the two birth groups. Microanalysis of individual test variables in Sky Search also showed that very preterm children identified a similar number of target spaceships and completed the task in a similar time frame as full term children. Although these findings were in contrast to the research hypothesis, they support previous studies suggesting that the selective attention problems in very preterm children may be relatively mild compared to nature and extent of impairments found in other domains of attention (Bayless & Stevenson, 2007; Mulder, Pitchford & Marlow, 2011; Shum, Neulinger, O'Callaghan & Mohay, 2008). It is important to note, however, that poor performance on Sky Search was found for very

preterm children when tested under dual task conditions of Sky Search Dual Task; suggesting that deficits in selective attention might be observable under increased cognitive load.

Nonetheless, the findings of the current study in regards to selective attention in very preterm children is generally in opposition to the findings of Anderson, Luca Hutchinson *et al.* (2011). While the current study did not find an effect of birth group on either the mean subtest scores or the rate of impairment on the Sky Search subtest, Anderson, Luca Hutchinson *et al.* (2011) reported that their preterm sample identified significantly fewer target spaceships compared to the full term group, and that 34% of the preterm sample had an impairment in this domain (OR 2.4). It is possible that this discrepancy may be attributable to the nature of the study samples. Although the samples of very preterm infants recruited by Anderson, Luca Hutchinson *et al.* (2011) and the current study had a similar mean gestational age of 26.5 ± 2.0 and 28 ± 2.4 weeks respectively, the gestation criteria for study inclusion differed between the two studies. Anderson, Luca Hutchinson *et al.* (2011) recruited infants born less than 28 completed weeks gestational age whereas the current study included very preterm infants born up to 33 weeks gestational age. Thus, deficits in selective attention may be more apparent in groups of children collectively born at younger gestational ages. It is unlikely the difference in selective attention abilities was due to other perinatal factors across the two studies as both samples were born in close temporal proximity (*i.e.* 1997 – 2000) at regional level-III perinatal facilities and were characterized by a relatively similar set of clinical and medical factors.

7.2.2 Sustained attention.

7.2.2.1 Sustained auditory attention. A second key outcome of interest included sustained auditory attention. In this domain of attention, very preterm children performed significantly less well on the Score! subtest of the TEA-Ch compared to full term children at age 12 years. The

extent of impairment in this domain, however, was similar between the two groups. In terms of the attention profile of very preterm children, this finding might suggest that of those who do show an impairment in sustained auditory attention, the nature of these problems are likely to be relatively mild. This finding is somewhat consistent with previous research. For example, Shum, Neulinger, O'Callaghan *et al.* (2008) and de Kieviet, van Elburg, Lafeber *et al.* (2012) reported that very preterm children were more prone to lapses of attention during timed measures of sustained attention. Anderson, Luca, Hutchinson *et al.* (2011) also found that very preterm children performed less well on Score! and the magnitude of the group-difference (d = .32) in Anderson, Luca, Hutchinson *et al.* (2011) was very similar to the magnitude reported by the current study (d = .34).

In contrast, Bayless and Stevenson (2007) and Mulder Pitchford and Marlow (2011), who also included Score! in their assessment of sustained attention, did not report any significant birth group-differences on this measure. While this might collectively suggest that the sustained auditory attention problems of very preterm children are mild in nature and extent, these null findings might also be attributable to methodological limitations of Bayless and Stevenson (2007) and Mulder, Pitchford and Marlow (2011) regarding smaller and more selective samples in comparison to the current study. Specifically, the participant response rates at follow-up for these two studies ranged from 30% to 75% which are substantially lower rates than what was achieved by the current study (~98%). Therefore, it is possible that the detection of a significant, albeit mild, effect of birth group on measures of sustained attention may be more likely detected in larger and more representative samples of very preterm children.

7.2.2.2 Sustained response inhibition. At age 12 years, the attention profile of very preterm children differed to full term children both in terms of the nature and the extent of their

sustained response inhibition problems. The results showed that very preterm children performed significantly less well on Walk Don't Walk and this tendency persisted after covariate adjustment for social-background factors. This finding concurs with Bayless and Stevenson (2007) who reported that on average, very preterm children obtained mean Walk Don't Walk scores approximately half a standard deviation lower than the scores obtained by full term children. More generally, this result is also consistent with reports showing very preterm deficits on other neuropsychological measures of sustained attention to response inhibition and inhibitory control, such as Go/No-Go tasks (Aarnoudse-Moens, Smidts, Oosterlaan *et al.,* 2009).

While group differences on Walk Don't Walk suggest that very preterm children are less able to sustain their attention to the inhibitory control of behavioral responses than full term children, group differences on non-motor measures of sustained attention to inhibitory control are less clear (Anderson, Luca, Hutchinson *et al.,* 2011; Mulder Pitchford & Marlow, 2011). Given that Walk Don't Walk has a strong motor component similar to other Go No-Go paradigms, coupled with the possibility that very preterm children's performance on this task may be compounded by mild to moderate impairments in fine and gross motor skills (Woodward, Moor, Hood *et al*. 2009), Walk Don't Walk may be biased to detecting impairment in very preterm children compared to other measures of sustained attention to inhibitory control. This highlights the importance of task selection in future studies that examine sustained attention and inhibitory control in very preterm children. Nonetheless, it is important to note that very preterm children in the current study had twice the odds of being identified with impairment on Walk Don't Walk compared to their full term peers, indicating that this remains an area of concern for this high-risk group.

7.2.3 Executive attention.

7.2.3.1 Executive shifting attention. Also of interest to the current study was the extent to which very preterm children evidenced difficulties in higher-order components of attention such as the shifting of attentional focus and dividing attention across competing tasks. The effect of birth group on these aspects of attention at age was particularly prominent at age 12 years, and was largely consistent with previous research. In terms of shifting of attention, very preterm children achieved fewer correct Creature Counting items than full term children. Excluding children who obtained fewer than three correct Creature Counting items, very preterm children also had poorer Creature Counting Timing Scores compared to full term children which suggests that very preterm children took longer to complete each switch of counting direction for each correct item. Although the effect of birth group on this measure was modest (d = .36) compared to larger effects reported in this domain of attention by other very preterm studies (Anderson, Luca, Hutchinson *et al.*, 2011; Bayless & Stevenson, 2007; Mulder, Pitchford & Marlow, 2011), impairment in executive shifting attention was the most common type of attentional impairment found in the current study. Specifically, one third of very preterm children had a Creature Counting score in the impairment range and this was approximately twice the rate found in the full term group. This finding is very consistent with the proportion of very preterm children (27%) identified by Anderson *et al.* (2011) as having a similar impairment. Children born very preterm, therefore, are less efficient in their shifting of attentional focus when switching counting direction in comparison to their full term peers, with problems in this domain being common.

7.2.3.2 Executive divided attention. In addition to executive shifting of attention, very preterm children also evidenced poorer executive divided attention outcomes at age 12 years. Compared to full term children, very preterm children obtained higher Sky Search Dual Task (DT) Decrement scores on the Sky Search DT subtest of the TEA-Ch. That is, the extent to

which children's performance on the Sky Search selective attention subtest was adversely impacted by the added Score! component was greater in the very preterm group than in the full term group. The magnitude of the group difference on the Sky Search DT (d = .50) was larger than reported for the other TEA-Ch subtests, suggesting that very preterm birth was most associated with poor divided attention skills. Worryingly, for every full term child identified as having an impairment in this domain of attention, four very preterm children were similarly identified. The prevalence of impairment for divided attention was comparable to the rate reported by Anderson, Luca, Hutchinson *et al.* (2011), who identified two to three very preterm children within the impairment range for every full term child. In addition, analysis of covariance suggested that the deficits observed in divided attention were robustly associated with very preterm birth. Specifically, group differences in both mean subtest scores and odds of impairment persisted after covariate adjustment for social risk index, a finding also reported by Murray, Scratch, Thompson *et al*. (2014). Unlike sustained attention, very preterm difficulties in executive attention do not appear to be well explained by early exposures to socio-familial adversity.

7.3 Relations between social risk and sustained attention. While the findings of the current study suggest that children born very preterm are at increased risk for poorer sustained and executive attention outcomes in childhood, it is possible that socio-economic and family factors correlated with preterm birth might account for the associations observed thus far. In an effort to disentangle the effects of very preterm birth and early exposure to socio-familial adversity, the relationship between very preterm birth and children's performance on the TEA-Ch was examined after adjustment for a wide range of confounding social background

factors. These factors included maternal age at delivery, single motherhood, no high school educational achievement, low socio-economic status, and ethnic minority status.

Children born very preterm were typically born into families characterized by higher levels of socio-familial adversity compared to families of full term children. On average, mothers of very preterm children had higher cumulative social risk index scores than mothers of full term children and more commonly reported two to three risk factors. More importantly, covariate analysis showed that social risk index at term accounted for the association between very preterm birth and sustained attention outcomes at age 12 years. Subsequent regression analyses also indicated that higher levels of social risk significantly predicted poorer performance on the sustained auditory attention and sustained response inhibition subtests for very preterm children. Thus, early environmental exposures may be an important mechanism for developing sustained attention skills in very preterm children.

The reported association between higher levels of socio-familial risk and poorer sustained attention outcomes supports previous research that highlights the importance of environmental context on child neuropsychological development. For example, the classic population-based epidemiological study by Rutter and colleagues (1975) suggested that the accumulative effect of multiple social risk factors was more strongly related to parent and teacher ratings of child psychopathology compared to the effects of individual risk factors. The impact of cumulative social risk on child psychological outcomes was replicated in a more recent study linking increased family psychosocial and economic adversity at term to the likelihood of child psychiatric disorder, including ADHD, in very preterm children at age 7 years (Treyvaud, Ure, Doyle *et al*., 2013). In light of the complex interactions between socio-familial risk factors that co-exist and shape the home environment, very preterm children may arrive at poor sustained

attention outcomes due to the limited opportunities that mothers of low socio-economic and strained households have to provide children with the learning experiences that support development of sustained attention skills (Lang, Kirkwood, Bowker, *et al*., 1999; Lindstrom, Lindblad & Hjern, 2011).

Although previous research has linked higher levels of cumulative social risk index to neuropsychological outcomes in children born very preterm, very few studies have examined the impact of specific social risk factors and attention outcomes in very preterm children. In the current study, very preterm children were approximately two times more likely to be born to mothers who did not have a high school educational qualification, and three times more likely to be born to mothers from a low socio-economic household at the time of delivery compared to full term children. While the current study did not examine relationships between individual risk factors and attention outcomes, previous research suggests that there might be associations between specific risk factors and inattention in very preterm children. For instance, mothers without a high school qualification are at increased risk of having a very preterm child who meets diagnostic criteria for ADHD than are mothers with higher levels of education (Galera, Cote, Bouvard *et al*., 2011; Lindstrom, Lindblad & Hjern, 2011). Lower socio-economic status, in contrast, appears to vary in its association with inattention among very preterm children. Some studies have found evidence for an association between lower socio-economic status, very preterm birth and inattention (Indredavik, Vic, Evensen *et al.*, 2010) while others have not (Loe, Lee, Luna & Feldman, 2011). Although the current study considered a wide range of social background factors, future research should examine the extent to which specific social risk factors might account for the association between cumulative social risk and sustained attention in children born very preterm. Additional consideration could also been given to factors such as

prenatal drug exposures and maternal mental health problems as these risk factors have been linked to inattention in the general obstetric population (Galera, Cote, Bouvard *et al*. 2011; Linnet, Dalsgaard, Obel *et al.*, 2003).

7.4 Relations between gestational age and attention. The current study found mixed evidence in terms of corresponding relationships between gestational age and inattention. While decreasing gestational age did not appear to be associated with poorer selective attention outcomes, clearer relationships were found in terms of executive attention outcomes. All study children were categorized into three narrow gestational age bands (Bayless & Stevenson, 2007) with clinical definitions used to group full term (38 – 41 weeks), very preterm (<33 weeks), and extremely preterm (<27 weeks) children. Findings showed that as gestational age decreased across the groups, there was a corresponding increase in poor TEA-Ch subtest scores and rates of impairment for both executive shifting attention and executive divided attention. There also appeared to be a stepwise increase in the odds of impairment in association with younger gestational age. Both the odds ratios for impairment in executive shifting attention and executive divided attention were larger for extremely preterm children compared to full term children (OR 3.64 and 3.17, respectively), relative to very preterm children compared to full term children (OR 2.02 and 2.89, respectively).

To the knowledge of the author, this is one of the few studies that have been able to demonstrate a gradient effect of gestational age in relation to poorer attention outcomes in late childhood (Bul & van Baar, 2012). Specifically, Anderson, Luca, Hutchinson *et al*. (2011) did not find any gradient effects within their extremely preterm sample, either by comparing gestational age groups (< or > 26 weeks) or birth weight groups (< or > 750g). However, Bayless and Stevenson (2007) suggest that compared to within-group analysis, gradient effects may become apparent

when two narrow bands of gestational ages, such as very preterm and extremely preterm, are examined. The findings of the current study appear to support this premise. Although the current study found significant between-groups differences across the birth groups, gestational age was not strongly related to attention at the bivariate level. This finding is not unexpected given that a wide range of perinatal risk factors more commonly characterize extremely preterm children, and it may be these factors heterogeneously associated with extreme prematurity that places this group at increased risk of poor outcomes relative to older born peers, rather than decreasing gestational age per se (Anderson, Luca, Hutchinson *et al*. 2011; Wilson-Ching et al. 2013; van de Weijer-Bergsma, Wijnroks & Jongmans).

7.5 Regional structural alterations in grey matter volume in very preterm children at age 12 years. The findings of the current study suggest that children born very preterm perform more poorly on measures of sustained and executive attention compared to full term children at age 12 years. Notably, findings showed that there was a two- to three-fold increase in the rate of executive attention impairment among very preterm children, which also appeared to be associated with extreme prematurity. The tendency towards poor executive attention in very preterm children remained after covariate adjustment for social risk index. To better understand the neurological mechanisms that place very preterm at increased risk of poor attention outcomes, the second objective of the current study was to identify the regional structural alterations in grey matter volume among children born very preterm at age 12 years. These findings of this study aim are discussed below.

7.5.1 Regional reductions in grey matter volume. At age 12 years, very preterm children were characterized by structural alterations in regional grey matter volume in both cortical and subcortical areas. Compared to full term children, very preterm children had lower

mean modulated grey matter volume values in the bilateral parietal and temporal cortices, left prefrontal cortex and posterior cingulate cortex (FWE-corrected $p<0.05$). Subcortical reductions in grey matter ere also found in the bilateral thalamus and bilateral hippocampus (FWE-corrected $p<0.05$) for very preterm children. These results are highly consistent with previous studies that have also reported volumetric reductions in these regions for children and adolescents born very preterm (Kesler, Reiss, Vohr *et al.* 2007; Nagy; Ashburner, Andersson *et al.* 2009; Peterson, Vohr, Staib *et al*., 2000; Soria-Pastor, Padilla, Zubiaurree-Elorza *et al*., 2009). One exception was found in regards to grey matter volume in the parietal cortex (*cf.* Ment, Kesler, Vohr *et al*. 2009; Kesler, Ment, Vohr *et al.* 2004).

The findings of the current study suggested that grey matter abnormalities were present in the parietal cortex of very preterm children at age 12 years, shown by the lower modulated volume values in this region compared to full term children. While this finding is consistent with Nagy Ashnurner, Andersson *et al.* (2009) who also found reduced grey matter in the parietal cortex in very preterm children aged 12 to 17 years; it is in direct contrast to the findings of Ment, Kesler, Vohr *et al*. (2009) and Kesler, Ment, Vohr *et al*. (2004). At both the 8 (Kesler, Ment, Vohr *et al*., 2004) and 12 year (Ment, Kesler, Vohr *et al*., 2009) follow-up evaluations of the Yale prospective longitudinal study that utilized serial MRI scanning, the grey matter volume of the parietal cortex was approximately 4 – 5% lager in very preterm children compared to the full term children at both time points. Two factors that may account for the discrepancy in study findings relating to the growth and development of grey matter in the parietal cortex, concerning the incidence of intraventricular hemorrhage (IVH) and the MRI analysis methods employed by each study. First, the sample recruited by Ment and colleagues was enrolled as part of a randomized controlled trial of low dose indomethacin administered in the perinatal period (*see*

Ment, Oh, Ehrenkranz & Phillip, 1994 *for the original study*). As such, this sample was characterized by a lower incidence of IVH grades 3 and 4 in comparison to the current study sample. This sample difference might partially account for the discrepancy in results as the presence and severity of neonatal IVH is strongly associated with individual variations in regional brain morphometry among very preterm children (Kesler, Ment, Vohr *et al*., 2004).

A second important difference to consider is the MRI analysis methods employed by each study. Both the current study and Nagy Ashburner, Andersson *et al.* (2009) used modulated voxel based morphometry to investigate volumetric differences in regional grey matter volume, and found similar results. In contrast, Ment and colleagues used an automated Talairach parcellation approach for their analysis of brain development in preterm children (*approach described in* Kates, Warsofsky, Jeffries *et al*., 1999). The key difference between these volumetric MRI methods lies in the fact that volumes derived from regional parcellation measures the gross anatomy of a structure, while VBM is a cluster based approach that is sensitive to local differences in tissue composition at the voxel level (Mechelli, Price, Friston & Ashburner, 2005). In other words, voxel-based approaches are highly sensitive to local changes in volume which may not be captured by global approaches, and vice versa (Broadman, Counsell, Rueckert *et al*. 2006). Subsequently, it is somewhat difficult to compare the findings of the current study with Kesler, Ment, Vohr *et al*. (2004) and Ment, Kesler, Vohr *et al*. (2009) as both may be adequately capturing local and global aspects of grey matter abnormality in the parietal cortex for children born very preterm. Nonetheless, the validation of current volumetric findings using other complimentary MRI approaches will be important to better understand grey matter development in the parietal cortex for children born very preterm.

7.5.2 Regional increases in grey matter volume.

In addition to regional reductions in grey matter volume among very preterm children at age 12 years, the current study also identified regions in which very preterm children showed increased grey matter volume compared to full term children. In the very preterm group, increased grey matter volume was found in the anterior cingulate and medial occipital cortices (FWE-corrected $p<0.05$). In terms of the cingulate cortex, Nosarti, Giouroukou, Healy *et al.* (2008) similarly found increased grey matter volume in this region for very preterm adolescents aged 14 – 15 years old, born at a comparable gestational age of 29 weeks. Nosarti, Giouroukou, Healy *et al.* (2008) also reported volumetric differences between very preterm and full term adolescents in the occipital cortex. However, this difference was in the opposite direction to that reported by the current study, as Nosarti, Giouroukou, Healy *et al.* (2008) found that their very preterm sample had reduced grey matter volume in the occipital region. The sample recruited by Nosarti, Giouroukou, Healy *et al.* (2008) was born approximately 20 years earlier than the current sample and only limited neonatal data was reported. Thus, it is unclear whether differences in infant clinical characteristics and/or risk might account for the discrepancy in findings regarding the occipital cortex.

However, a more recent re-analysis of the Nosarti *et al*. (2008) sample did identify structural differences in the medial occipital region that were more consistent with the current study (Nosarti, Mechelli, Herrera, Walshe. Shergill *et al.*, 2011). Specifically, Nosarti *et al*. (2011) found that increased volume in the left medial occipital gyrus in very preterm children co-varied with volumetric alterations in the left cingulate gyrus. It is possible, therefore, that the morphometric difference found in the occipital cortex for the current study is dependent upon the morphometry of the cingulate gyrus in the in very preterm children, thus accounting for

similarity in findings with Nosarti *et al*. (2011) rather than Nosarti *et al.* (2008). This issue warrants further investigation of this region.

7.6 Maturational disruption of grey matter following very preterm birth. The findings of the current study generally concur with previous research showing altered grey matter growth and development following very preterm birth. Structural alterations were found in the parietal, cingulate, temporal, frontal, and occipital cortices, and subcortical regions including the hippocampus and thalami. In addition to consistency with results from existing follow-up studies of very preterm children at school age (Kesler, Ment Vohr *et al*., 2007; Nosarti *et al.*, 2008; Peterson, Vohr, Staib, *et al*., 2000), it is also interesting to note that the structural alterations found in these regions has also been identified on term-equivalent MRI (Boardman, Counsell, Rueckert *et al*., 2006; Inder, Warfield, Wang *et al*., 2005; Peterson, Anderson, Ehrenkranz *et al.*, 2003; Thompson, Warfield, Carlin *et al*., 2007; Thompson, Wood, Doyle *et al.*, 2008). The relative continuity between the regions identified in the neonatal period and at follow-up highlights 1) the persistence of grey matter abnormalities beyond infancy into childhood, and 2) the regional vulnerability of grey matter following very preterm birth.

First, the neuroanatomical regions showing structural alterations in grey matter volume identified by the current study were similar not only to other longer term follow-up studies, but also studies that focus on the neonatal period (Inder, Warfield, Wang *et al*., 2005; Thompson, Warfield, Carlin *et al*., 2007). The consistency found between the regions identified in both infant and child literatures suggests that early and regionally specific alterations in grey matter volume persist for children born very preterm. Akin to the current study, reduced grey matter volume has also been identified on term equivalent-age MRI in the parieto-occipital, sensorimotor, hippocampus, and thalamus in very preterm neonates (Boardman, Counsell, Rueckert *et al*.,

2006; Peterson, Anderson, Ehrenkranz *et al.*, 2003; Thompson, Wood, Doyle *et al.*, 2008). Temporal grey matter also appears to be compromised by premature birth, as recent study by Engelhardt, Inder, Alexopoilos *et al*. (2015) found that very preterm birth had a significant impact on the sulci depth and cortical shape of the superior temporal sulcus; and increased gyrification in this area negatively correlates with volume (Kesler, Vohr, Schneider, Katz *et al.*, 2006). When taken together, these findings collectively suggest that very preterm birth has specific impacts on grey matter structures, with current study findings showing that these impacts are likely to be observed at long term follow-up.

Second, although voxel-based morphometry does not provide information regarding tissue composition at the voxel level in terms of cell cytoarchitectural structure (Good, Johnsrude, Ashburner *et al.*, 2001; Mechelli, Price, Friston & Ashburner, 2005), we can speculate that cerebral alterations of grey matter volume found in very preterm children reflects the longer term effects of off-time very preterm birth and subsequent disruption to the neurobiological processes or mechanisms that underlies the development of the central nervous system (*See Appendix A*). The observation of both regionally specific reductions and increases in grey matter volume among very preterm children relative to full term children supports the premise that there are two independent but interrelated neurobiological mechanisms contributing to the pathogenesis of grey matter in very preterm children (Leviton & Gressens, 2007; Nosarti *et al.*, 2008). The first process concerns early disease and injury to pre-oligodendrocytes and axons resulting in failure of tissue growth, and the second concerns inefficient synaptic pruning.

In terms of volumetric reductions in grey matter for very preterm infants and children, it is hypothesized that growth failure in grey matter stems from the primary disease sustained to pre-oligodendrocytes; a form of neuroglia that are active from 24 weeks gestational age onwards and

are critical for the myelination of axon sheaths and subsequent axonal differentiation (Boardman, Counsell, Rueckert *et al*., 2006; Ment, Hirtz, Huppi, 2009; Volpe 2009). Extensive inflammation and ischemic-hypoxic related events following the trauma of very preterm birth causes injury to pre-oligodendrocytes, while also adversely impacting the development of subplate neurons that support axonal growth and cortical connections from 24 to 32 weeks gestation (Salmaso, Jablonska, Scafidi *et al.,* 2014). The vulnerability of pre-oligodendrocytes is further compounded by excitotoxicity of the glutamate receptors and generation of free radicals at the cellular level (Peterson, 2003; Volpe 2009). Together, these mechanisms adversely impact the development of the central nervous system in the very preterm neonate, likely resulting in growth failure of grey matter tissue (Boardman, Counsell, Rueckert *et al*., 2006; Leviton & Gressens, 2007).

Coupled with the neurobiological disturbances that underpin grey matter growth failure, a second neurobiological mechanism is thought to be responsible for atypical increases in grey matter volume in very preterm children relative to their full term peers. Although the genetically programmed migration of interneurons from the subplate to the cortical plate is adversely impacted by very preterm birth, altered cortical connections are formed nonetheless (*see Appendix D*, Leviton & Gressens, 2007; Volpe, 2009). As part of an expected recessive event in healthy brain development, regional reductions in brain volume occur when synaptic connections that are surplus to what is deemed necessary by genetic programming and environmental experience are typically pruned away (Berk, 2011). Current perspectives suggest that this process may be impaired in the very preterm brain. Synaptic pruning during childhood may be delayed or inefficient in very preterm children, thus altering the expected non-linear decrease in regional grey matter volume that is otherwise seen in healthy populations and accounting for larger grey

matter structures in this group (Murner-Lavanchy, Steinlin, Nelle *et al*., 2014; Nosarti *et al.*, 2008).

In summary of the discussion above, very preterm birth was associated with poorer sustained and executive attention outcomes. There was also evidence of increased risk of executive attention impairment in relation to extreme prematurity. While social risk index appeared to be important in explaining the sustained attention outcomes in very preterm children, the association between very preterm birth and executive attention was not fully accounted for by early exposure to higher levels of socio-familial adversity. The consideration of other factors associated with prematurity may therefore help to explain relations between very preterm birth and attention. Forming the final objective of the current study, it was hypothesized that grey matter growth and development may be an important mechanism for inattention in children born very preterm (Bora, Pritchard, Chen *et al*. 2014; Murray, Scratch, Thompson *et al*., 2014).

7.7 Associations between attention abilities and grey matter development in very preterm children at age 12 years.

7.7.1 Associations between attention and grey matter volume.

The third and final objective of the current study was to relate the attention outcomes of very preterm children to regional grey matter volumes at age 12 years. Bivariate analysis showed that there were significant relationships between poor performance on the subtests of the TEA-Ch and reduced grey matter volume in number of regions within the preterm group. Specifically, poorer selective and executive switching attention was correlated with reduced volume in the thalamus, while poorer sustained response inhibition was associated with reduced grey matter volume in the medial occipital cortex. Poorer executive divided attention was associated with

reduced grey matter in multiple brain regions including the thalami, left temporal cortex, posterior cingulate cortex and the medial occipital cortex. While the strength of the correlations was modest, they nonetheless suggest that the regional reductions in grey matter were differentially related to the components of attention in manner that is theoretically consistent with neuropsychological models of attention.

Selective attention. First, poorer selective attention in very preterm children was associated with reduced volume in the thalamus at age 12 years. This task-region association fits well with previous descriptions of the role of the thalamus (Cohen, 2014; Kastner, Saalmann & Schneider, 2012). The thalamus acts as a gateway between subcortical and cortical structures, playing a primary role in the selection of goal-relevant information and sending that information to the appropriate areas in the cortex for further processing (Cohen, 2014; Peterson & Posner, 2012). As part of the frontostriatal network, the thalamus is particularly important for the selection of visual information for action-selection processes and, conversely, the gating of non-relevant information (Cohen, 2014; Kastner, Saalmann & Schneider, 2012). The Sky Search subtest is a measure of visual selective attention that requires the detection of target stimuli as quickly and accurately as possible while discounting non-relevant stimuli; a task that appears to map onto the proposed functions of the thalamus. In addition to Sky Search, volume in the thalamus was also associated with Creature Counting which provides a measure of shifting attention. In this task, visual cues index new task-relevant information that must be selected and acted upon to effectively change counting direction when required, which also aligns with the preferentially selective nature of the thalamus.

Sustained response inhibition. Second, poorer performance on Walk Don't Walk, the measure of sustained attention to response inhibition, was associated with reduced volume in the medial

occipital region in children born very preterm at age 12 years. Imaging studies linking inhibitory control to the occipital cortex in children are sparse outside of the ADHD literature (*e.g.* Ma, Lei, Jin *et al*., 2012; Tamm, Menon & Reiss, 2002), but the reported finding is consistent with adult-based studies that have demonstrated robust links between inhibitory control tasks and recruitment of the medial occipital cortex (Mostofsky, Schafer, Abrams *et al*., 2003; Simmonds, Pekar & Mostofsky, 2008). For example, in a sample of young adults born very preterm aged 17 to 23 years, task-based fMRI showed that there was a decreased blood-oxygen-level-dependent effect in the middle temporal/occipital gyrus compared to full term control adults during a Go/No-Go task of inhibitory control that is similar to Walk Don't Walk (Lawrence, Rubia, Murray *et al*., 2009). Within-task analysis has also shown that the occipital cortex is specifically recruited during Go trials, whereas the dorsolateral prefrontal cortex is implicated in No-Go trials among adults (Mostofsky, Schafer, Abrams *et al*., 2003). Thus, the association between Walk Don't Walk and the occipital cortex is theoretically consistent with previous adult-based studies, which might suggest that grey matter abnormality in the occipital region is linked with poorer maintenance and employment of stimulus-response behavior for children born very preterm.

Executive divided attention. As a higher-order component of attention, children's performance on Sky Search Dual Task (DT) was correlated with a number of grey matter regions. These regions included the thalamus, occipital cortex, left temporal cortex and the posterior cingulate cortex. Executive divided attention is a complex component of attention that involves both lower level processes such as selective and sustained attention, and the top-down executive control of attention to shift and allocate attention across competing tasks (Cohen, 2014). Subsequently, executive attention draws upon a wide distribution of cortical networks to support the multimodal nature of this component of attention (Posner & Peterson, 1990). It is theoretically

plausible, therefore, that poor performance on the Sky Search DT would be associated with grey matter abnormalities in multiple brain regions for children born very preterm.

Higher-order cognitive processes, including executive divided attention, are hierarchically organized in that lower-level functions and structures are integrated into a higher-order precept (Stuss, 1992). The association between grey matter abnormality in the thalamus and the occipital cortex and lower Sky Search DT Decrement Scores might reflect 1) poorer selective processing of information in the thalamus and 2) weaker manipulation of stimulus-response associations in the occipital cortex that, when taken together, fail to provide the appropriate foundation for divided attention abilities in very preterm children. Furthermore, the temporal cortices are postulated to support the maintenance of sustained attention and integration of lower-level stimuli into unitary percepts for higher-level cognition (Sowell, Thompson, Welcome *et al.*, 2003). The posterior cingulate cortex, characterized by dense connections to a large number of neuroanatomical structures, primarily integrates information that has been processed in other brain regions (Leech, Braga & Sharp, 2012). The compounding effects of poor grey matter development and abnormality in the information-integrating regions of the brain might suggest very preterm children are less able to process and integrate multiple sources of information when multitasking, leading to poorer divided attention outcomes. It is important to note, however, that the interpretations of these task/region relationships are based on correlational analysis alone. Future studies utilizing task-based fMRI in very preterm children will be necessary to validate the functional recruitment of these regions in relation to domain-specific subtests of attention.

7.7.2 Regional grey matter volumes as independent predictors of attention. While the findings of the current study suggest that the attention abilities of children born very preterm are associated with regional reductions in grey matter volume in childhood, it is possible that the

infant clinical, neuropathological and socio-familial factors associated with preterm birth might also account for the associations observed thus far (Anderson, Luca, Hutchinson *et al*. 2001; Wilson-Ching, Molloy, Anderson *et al*. 2013). In an effort to disentangle the effects of neonatal risk and grey matter growth and development on attention outcomes, multiple linear regression models were used to take confounding factors into consideration.

The results of the multiple linear regression models indicated that regional reductions in grey matter volume made independent contributions to the attention outcomes of very preterm children after taking into account factors such as intrauterine growth restriction (IUGR), periventricular leukomalacia (PVL), and early exposure to socio-familial adversity. Specifically, reduced medial occipital volume significantly predicted sustained response inhibition ability (p = .05), and volumes in the posterior cingulate cortex (p = .006) and medial occipital cortex (p = .02) significantly predicted executive divided attention abilities within the very preterm group. There was some suggestion that after taking into account PVL and IUGR, thalamic volume was somewhat associated with executive switching attention (p = .12) and the left temporal cortex associated with shifting attention (p = .11), but their contributions to their respective regression models did not reach the threshold for statistical significance. Nonetheless, these findings support and validate the previous correlational analysis highlighting the role of grey matter growth and development in the posterior cingulate cortex and occipital cortex for attention outcomes in very preterm children at age 12 years.

The inclusion of concurrent regional grey matter volumes as predictors of attention in school aged children born very preterm was a novel feature of the current study. However, two previous studies have examined a similar set of infant risk factors as predictors of attention in very preterm children and adolescents with modest results (Anderson, Luca, Hutchinson *et al*. 2001;

Wilson-Ching, Molloy, Anderson *et al*. 2013). Thus, the inclusion of regional grey matter volumes at age 12 allowed for an improvement in the predictive value of regression models for attention outcomes in very preterm cohorts. For example, Anderson, Luca, Hutchinson *et al*. (2001) reported that the presence of PVL and necrotizing enterocolitis (NEC) in very preterm infants predicted 26% of the variance in selective attention at the 7 year follow-up, while other factors explained between 4 – 11% of the variance in sustained and executive shifting and divided attention measures. The current study found that a similar proportion of variance in selective attention was explained by the presence of PVL (31%). In contrast, the proportion variance accounted for in the remaining measures of attention was higher in comparison to the findings of Anderson, Luca, Hutchinson *et al*. (2001). Specifically, current models including regional grey matter volume at age 12 years were able to explain 13% of variance in sustained response inhibition outcomes and 42% of the variance in executive divided attention outcomes. Furthermore, regional occipital volume was the strongest predictor of sustained attention to response inhibition ($\beta = .21$) in preterm children, followed by social risk index ($\beta = -.20$) and to some extent PVL ($\beta = -.17$). In contrast, PVL was the strongest predictor of executive divided attention ($\beta = .42$), followed by posterior cingulate cortex volume ($\beta = -.26$) and occipital cortex volume ($\beta = -.21$), and to some extent, left temporal volume ($\beta = - .15$). Regional grey matter growth and development, therefore, appears to be an important neurobiological mechanism that is independently associated with sustained and executive attention abilities in children born very preterm at school age.

Although the current study identified regions in which grey matter growth and development was differentially and independently related to the sustained and executive attention outcomes of very preterm children at age 12 years, a range of infant clinical and social factors were also important

in explain attention outcomes. As previously mentioned, the presence of PVL was a strong predictor of selective attention outcomes (Anderson, Luca, Hutchinson *et al*., 2001). Neonatal PVL is particularly associated with abnormalities in the thalamus following very preterm birth (Boardman, Counsell, Rueckert *et al*., 2006; Boardman, Craven, Valappil *et al*. 2010), which in turn, is associated with grey matter lesions and damage to thalamocortical tracts (Ball, Boardman, Reuckert *et al*. 2011; Pierson, Folkerth, Bolliards *et al*. (2007). This might account for the strong predictive validity of the presence of neonatal PVL over and above thalamic volume at age 12 years for selective attention and executive divided attentions outcomes in this cohort. Further analysis is needed to determine whether there is a causal relationship between PVL and thalamic volume in childhood for children born very preterm.

As a form white matter injury, Wilson-Ching, Molloy, Anderson *et al*. (2013) found that IVH grades 3/4 significantly predicted executive shifting attention, although this finding was not replicated by the current study. Instead, IUGR was the strongest predictor of shifting attention ($\beta = -.38$), which might suggest IUGR represents the smallest babies characterized by higher levels of clinical risk and thus poorer outcomes. Although Anderson, Luca, Hutchinson *et al*. (2001) and Wilson-Ching, Molloy, Anderson *et al*. (2013) did not identify IUGR as a risk factor for poor attention, other findings more generally link IUGR to subtle deficits in attention and alterations in the brain networks recruited for attentional control (Geva, Leitner & Harel, 2012; Reveillon, Urben, Barisnikov *et al*. 2013). Another unique finding was retinopathy of prematurity (ROP) as the strongest predictor for sustained auditory attention at school age ($\beta = -.25$), which reflects oxygen toxicity effects from intensive oxygen supplementation in the NICU. Oxygen complications and lung disease in the neonatal period has been identified as a risk factor

for poor attention in younger groups of very preterm children (van de Weijer-Bergsma, Wijnroks & Jongmans, 2008).

7.8 Implications of study findings. A number of research and clinical implications can be made from the findings of the current study. These implications include 1) the timely identification of sustained and executive attention problems in children born very preterm, 2) concerns for the longer term neurological development of very preterm children, and 3) the predictive value of grey matter growth and development for attention outcomes in children born very preterm.

The first implication of study findings concerns the timely identification of attention problems in very preterm children at school age. At age 12 years, very preterm children were significantly more likely to perform less well on tasks that required sustained attentional focus, shifting attention, and multitasking. One third of very preterm children evidenced a deficit in shifting attention, while multitasking or dividing their attention across competing tasks was a particular weakness in very preterm children relative to full term children. Both basic and higher order attention skills appear to be affected by preterm birth. These findings raise important questions regarding possible relationships between these attention problems and other areas of functioning, especially in terms of educational achievement. At the time of preschool entry, very preterm children already evidence socio-emotional, behavioral and attentional problems compared to their full term peers (Reijneveld, de Kleine, van Baar *et al*., 2006). As very preterm children progress through their formative school years, they are also more likely to show educational underachievement in math and literacy (Johnson, Hennessy, Smith *et al*., 2009; Mulder, Pitchford, Marlow, 2010). While visual selective attention is a predictor of reading ability in school aged children born extremely preterm (Johnson, Wolke, Hennessy & Marlow, 2011), the

extent to which problems in other domains of attention, such as those measured by the current study, relate to academic achievement remains unclear. This raises important questions surrounding how attention problems might contribute to educational underachievement and highlights the need for the timely identification of attention impairments as these children transition into secondary school education during their early teenage years. The development of tailored educational support programs that take into account the nature of their attentional difficulties and aid in their transition to higher education is also important.

Second, the findings of the current study raises concerns for the longer term neurological development of children born very preterm. As previously discussed, very preterm birth appears to have regionally specific impacts on cortical and subcortical grey matter structures in the neonatal period (Boardman, Counsell, Rueckert *et al*., 2006; Engelhardt, Inder, Alexopoilos *et al*., 2015; Peterson, Anderson, Ehrenkranz *et al.*, 2003; Thompson, Wood, Doyle *et al*., 2008) and poor growth and development in these regions was observed the 12 year follow-up (*see also* Kesler, Reiss, Vohr *et al.* 2007; Nagy; Ashburner, Andersson *et al.* 2009; Peterson, Vohr, Staib *et al*., 2000; Soria-Pastor, Padilla, Zubiaurree-Elorza *et al*., 2009). Importantly, Ment, Kesler, Vohr *et al*. (2009) found that the rate grey matter growth in terms of volume change between 8 to 12 years was delayed in very preterm children, highlighting the continuous nature of poor grey matter development in this group. In line with previous studies (*e.g* Kesler, Ment, Vohr *et al.* 2004; Peterson, Vohr, Staib *et al*., 2000), the current study speculated that the cascading effects of early neuronal injury following the trauma of very preterm birth contributed to the findings related to grey matter volume at age 12 years. This brings to light the importance of preventative and early interventionist procedures in the NICU in an effort to alleviate the myriad of medical complications that so often affect the neurological development of premature babies. Follow-up

of contemporary groups of very preterm infants will remain important to examine the extent to which more recent advances in neonatal care might ameliorate the development of structural abnormalities in the very preterm brain, as found by the current study.

The third and last implication of study findings relates to the predictive value of grey matter growth and development and pathways to risk of attention impairment in very preterm children. To the knowledge of the author, this is the first study to examine the attention outcomes of very preterm children in association with concurrent structural MRI measures of grey matter volume. While current study findings indicate that the inclusion of volumetric MRI measures of regional grey matter volume at school age improves the amount of variance accounted for in predictive models of attention outcomes (*cf.* Anderson, Luca, Hutchinson *et al*. 2001; Wilson-Ching, Molloy, Anderson *et al*. 2013), there was not a high degree of overlap found in terms of the risk profiles for poor sustained and executive attention outcomes in very preterm children.

Across the sustained attention subtests Score! and Walk Don't Walk, a common predictor of outcome included social risk index at term. In contrast, the presence of PVL was predictive of children's performance on both Creature Counting and Sky Search Dual Task. This might suggest that children born very preterm who are exposed to higher levels of socio-familial adversity early in life are more likely to develop problems in sustained attention (Lang, Kirkwood, Bowker, *et al*., 1999; Lindstrom, Lindblad & Hjern, 2011). In contrast, children who evidence PVL on neonatal ultrasound might be at particular risk of damage to the thalamus and thalamocortical tracts (Ball, Boardman, Reuckert *et al*. 2011; Boardman, Counsell, Rueckert *et al*., 2006) and subsequent poorer executive attention outcomes. Furthermore, poorer executive attention outcomes also showed clear relationships with decreasing gestational age and was associated with multiple grey matter regions, collectively suggesting that executive attention may

be more greatly impacted by adverse biological events than other domains of attention (summarized in Figure 13). Given the complex relationships between PVL, thalamic injury and structural alterations in cortical development in the neonatal period (Ball, Boardman, Reuckert *et al*. 2011; Boardman, Counsell, Rueckert *et al*., 2006), future research should examine the extent to which PVL mediates or moderates the relationship found between regional grey matter volume and attention outcomes in school aged children born very preterm.

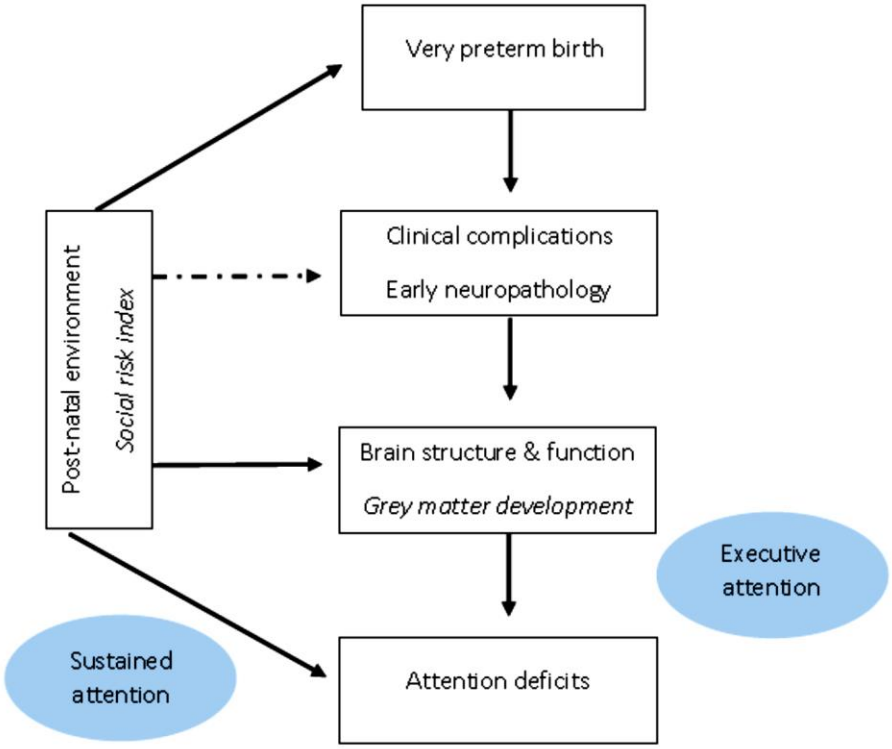


Figure 13. Differential pathways to risk for sustained attention and executive attention outcomes in children born very preterm at school age. Adapted from Halperin *et al*., (2012).

Chapter 8. Concluding Remarks

8.1 Limitations of the current study. Although the current study was able to detect significant associations between very preterm birth, attention, and grey matter volume at age 12 years, a number of methodological limitations should be taken into account when interpreting the findings of the current study. These limitations included not imputing TEA-Ch data for children who demonstrated extremely poor test performance, limitations inherent to voxel based morphometry methods, and not including motion parameters from structural MRI scans as a covariate for non-detected motion.

First, the current study only reported attention data for children who passed the practice items for each TEA-Ch subtest. Therefore, the results do not represent the highest-risk participants who had major cognitive impairment (n = 2), could not pass practice items (n = 2), or who had behavioral difficulties leading to task refusal (n = 1). This might account for the lack of a significant finding in selective attention outcomes. One approach to remedy this type of data loss is to assign the lowest possible subtest score to such cases, thereby retaining subjects who are characterized by extremely poor performance in data analyses. Murray, Scratch, Thompson *et al*. (2014) included secondary analysis in their study in which children with cognitive impairment were assigned the minimum possible TEA-Ch score. The authors found that initial associations between deep grey matter abnormality at term and inattention at age 7 years became stronger after including the imputed data. As the current study did not impute scores for extremely poor performance, it is possible that the extent of inattention and its association with grey matter volume in very preterm children at age 12 years may be slightly underestimated. Future re-analysis of this data set should consider the inclusion of imputed scores to supplement the data presented in the current study.

Second, voxel-based morphometry (VBM) is one of many readily available tools to analyze structural MRI data. Although this semi-automatic approach is useful to characterize local differences in grey matter composition between large groups of subjects, a number of methodological considerations need to be acknowledged. First, VBM is a statistical heavy approach that produces modulate grey matter volumes values for regions in which grey matter composition differs between the two groups at the voxel level, displayed as statistically significant clusters on a statistical parametric map (SPM) output image (Thacker, 2008). Crucially, modulated volume values are not quantitative units of measurement that can be easily interpreted in cubic dimensions. The extent to which VBM provides informative information about true volumetric differences between subjects is therefore controversial (Thacker, 2008). To make accurate interpretations of the SPM output, VBM also relies on a number of assumptions. The most important of these is that the quality of the output data is dependent upon near-perfect tissue classification and registration of the raw image in native space to the template in stereotaxic space during spatial normalization (Good, Johnsrude, Ashburner *et al.*, 2001). Areas of misregistration can take on the appearance of significant structural difference in grey matter on the SPM output image, particularly in areas around the ventricles where grey and white matter boundaries less certain (Thacker, 2008). Although this is a valid limitation of VBM, the current study included a pediatric brain atlas of NIH matched priors, spatially normalized grey matter segments to a DARTEL study-specific grey matter template, and visually inspected the data at each preprocessing stage to identify and minimize misregistration effects.

It is more likely, however, that the current study was affected by two other limitations related to VBM. First, VBM is not an ideal tool for subjects who show gross anatomical abnormalities. Such cases often fail tissue segmentation and registration to a common template as VBM aligns

subjects based on voxel signal intensities rather than major anatomical sulci or gyri landmarks (Kimberg, Coslett &Schwartz, 2007). In relation to this, MRI data for four subjects was excluded on the basis of poor initial grey and white matter segmentations due to gross structural abnormalities, thereby reducing the representativeness of the data for high-risk very preterm cases. Second, VBM is less sensitive to detecting structural differences in regions when the variability is high across participants (Good, Johnsrude, Ashburner *et al.*, 2001; Thacker, 2008). It is reasonable to speculate that this may be the reason that the current study did not find stronger results for the pre-frontal cortex, a region known to be 1) impacted by very preterm birth (Anderson, Jacobs & Harvey, 2005; Nosarti, Giouroukou, Healy *et al*., 2008), 2) implicated in the neural circuitry of attention (Alvarez & Emory, 2006), and 3) maturing from early adolescence and onwards (Giedd, Blumenthal, Jeffries *et al*., 1999). In light of these considerations, replication of current findings using a complementary region-of-interest parcellation approach will be important to validate VBM results.

Third and last, recent perspectives suggest that movement parameters, traditionally acquired for diffusion tensor imaging, should also be acquired for structural MRI scans and included as a covariate in statistical analyses. This is particularly important when the population of interest is characterized by developmental disorder or poor motor ability, as are very preterm children (Woodward, Moor, Hood *et al*. 2009; Yendiki, Koldewyn, Kakunoori *et al.*, 2014). A recent study by Reuter, Tisdall, Qureshi *et al.* (2015) suggested that even after thorough inspection of T1-weighted structural images for motion artefacts, morphometric differences in brains structures may still be overestimated if motion parameters for structural scans are not included as a covariate. Unfortunately, scanning protocols for the current study did not include the collection of movement parameters specifically for structural scans. While this information was available

for resting state fMRI and diffusion scans, it was unclear whether either of the movement parameters for those scans would be suitable for inclusion in this dissertation at the time of data analysis. This remains an important issue to consider in the future.

8.2 Strengths of the current study. As previously outlined, past studies are limited by methodological problems including the inadequate reporting of infant clinical characteristics (Bayless & Stevenson, 2007), small and selective samples attributable to low participant response and retention rates (Bayless & Stevenson, 2007; Mulder, Pitchford & Marlow, 2011; Shum, Neulinger, O'Callaghn *et al*., 2008). The current study employed a range of methodological strategies to remedy these issues. The current study was prospective longitudinal, included a large non-selective sample of very preterm children and a regionally representative and matched control group, and high rates of sample retention with relatively minimal data loss, as well as detailed reporting of infant clinical factors (Aylward, 2002; Siegel, 1994; Wolke, 1998).

A particular methodological strength of the current study was the inclusion of the Test of Everyday Attention – Children (TEA-Ch, Manley *et al*., 2001). The TEA-Ch differentially tests the individual components of selective, sustained and executive attention, while also providing information about qualitative aspects of performance like speed and accuracy (Anderson, 1998; Mulder, Pitchford, Hagger & Marlow, 2009). This makes it an ideal measure to identify areas of weakness in the attention profile of very preterm children. As very preterm children are a complex group often with comorbid cognitive and motor issues, the was also preferable as the TEA-Ch minimizes the demands placed on these domains compared to other measures of attention (Manley *et al*., 2001; Mulder, Pitchford, Hagger & Marlow, 2009). Thus, the findings

of the current study likely represent a valid evaluation of the attention abilities of very preterm children at late school age.

In terms of the methodological strengths related to the VBM analysis, the current study utilized two recent methodological advancements in VBM preprocessing. First, the current approach aligned and spatially normalized the grey matter segments for each subject to a study-specific grey matter template created with DARTEL to derive the optimized normalization parameters which are then applied to the original structural images in native space prior to final tissue segmentation (Good, Johnsrude, Ashburner *et al.*, 2001). This is preprocessing step is an advantage over spatially normalizing to whole-brain templates as per standard VBM approaches as it reduces the likelihood of misregistration. Second, the spatially normalized segmented grey matter images for each subject were also modulated during the final steps of preprocessing. As previously outlined, modulation encodes information concerning the absolute volume of brain regions prior to registration and spatial normalization into the data, which compensates for the structural warping effects of the spatial normalization (Good, Johnsrude, Ashburner *et al.*, 2001). Therefore, the VBM of current study can be considered as a volume-based approach as opposed to being limited to making judgments about the relative grey matter concentration or density between subjects at the voxel level (Good, Johnsrude, Ashburner *et al.*, 2001; Mechelli, Price, Friston, Ashburner 2005).

8.3 Suggestions and directions for future research. The findings of the current study has contributed to the field in terms of the detailed description the nature and extent of attention problems in very preterm children and relating these outcomes of volumetric MRI measures of grey volume at age 12 years. Considerable thought was given to a wide range of infant clinical and social background factors to assess the extent to which grey matter volume at age 12 years

was associated with attention after taking into account confounding factors associated with prematurity. However, future research should also include measures of neonatal grey matter volume to examine how grey matter abnormality in infancy relates to both attention and grey matter outcomes at 12 years (Murray, Scratch, Thompson *et al*., 2014). Of greater interest is the extent to which poor grey matter growth curves from term equivalent-age to age 12 years, as a proximal measure of grey matter growth and development over time, might be associated attention at school age.

Future research could also employ alternative classification schemes to examine attention outcomes relative to other pediatric risk factors. On such factor might be ADHD diagnosed at age 9 years. Interestingly, TEA-Ch analyses identified attention impairment in approximately 12% to 30% of the very preterm group depending on the subtest in question. At age 9 years, 6% of very preterm children met the criteria for ADHD-Inattentive subtype and 15% met the criteria for ADHD-Combined subtype. Given that the TEA-Ch identified a relatively greater proportion of very preterm children demonstrating test performance impairment, the TEA-Ch may be identifying very preterm children who have subclinical ADHD symptoms. Thus, the comparison of TEA-Ch performance between very preterm children who have or do not have diagnosed ADHD at age 9 years may yield important information concerning the nature of global or differentiated attention problems within a clinically high-risk group of very preterm children. It would also be worth considering the use of a more stringent cut-point to define a clinically meaningful level of attention impairment in the sample distribution, such as 1.5 or 2 standard deviations below the mean of the full term group (Wilson-Ching, Molloy, Anderson *et al*., 2013). Future research should also consider general intellectual ability as a possible covariate in

attention analyses to adjust for the association between IQ and attention in very preterm children (see *Appendix C*).

8.4 Conclusions. The current study examined the selective, sustained and executive attention outcomes of children born very preterm at age 12 years, and related these outcomes to concurrent volumetric MRI measures of grey matter volume. Confounding factors associated with prematurity were also considered. While very preterm children showed similar selective attention abilities compared to full term comparison children at age 12 years ($p = .72$), very preterm children were characterized by poorer sustained (ps = .03) and executive attention (ps = .01) outcomes. Around one quarter to one third of very preterm children were identified as having an impairment in sustained and executive attention, which was a two- to three-fold increase in the rate of impairment found in the full term group (ps $\leq .03$). Group differences in sustained attention to response inhibition ($p = .04$), executive shifting attention ($p = .02$) and executive divided attention ($p = .02$) remained after covariate adjustment for social risk index, suggesting that poor attention was robustly associated with prematurity. Furthermore, children born extremely preterm showed the poorest executive attention outcomes compared to very preterm and full term children (ps $\leq .04$). These findings indicate that children born very preterm more commonly experience lapses in attention, difficulty shifting their attentional focus, and problems with multitasking in comparison to their full term peers at age 12 years. The nature of these problems and the extent to which inattention might contribute to academic underachievement in preterm children should be considered as they transition into higher level secondary school education, coupled with the development of educational support services tailored to meet the attentional needs of very preterm children. Given that the current study likely identified very preterm children with attention problems who did not meet the criteria for ADHD diagnosis at

age 9 years, access to educational support services should be readily available to very preterm children in schools to target children who otherwise fall below the threshold for clinical support services.

In terms of grey matter development, very preterm children had reduced grey matter volume in the bilateral parietal and temporal cortices, left prefrontal cortex, posterior cingulate cortex, bilateral thalamus and bilateral hippocampus (FWE-corrected $p < .05$) compared to full term children at age 12 years. In the very preterm group, increased grey matter volume was found in the anterior cingulate and medial occipital cortices (FWE-corrected $p < .05$). Importantly, findings remained highly significant after covariate adjustment for age at scan and social risk index ($ps < .001$). The identification of structural abnormalities in grey volume at age 12 years raises concerns for the longer term neurological development of this high-risk group. Although these cross-sectional findings suggest that disturbances in cerebral development following very preterm birth persist beyond infancy and into late childhood, further follow-up evaluation with serial MRI will be important to fully understand whether birth-group differences found at age 12 reflect a delay in grey matter growth and maturation or a static group difference that does not improve over time.

Within the VPT group, reduced grey matter volume in the thalami was correlated poorer selective attention ($r = -.34$) and executive shifting attention ($r = .32$) ability. Reduced grey matter volume in the medial occipital region correlated with poorer sustained inhibition of responding ($r = .24$), while reduced grey matter volumes in the thalami ($r = -.36$) and left temporal ($r = -.35$), posterior cingulate ($r = -.36$) and occipital cortices ($r = -.30$) correlated with poorer executive divided attention ability. The TEA-Ch task-region associations reported by the current study are theoretically consistent with neuropsychological models of attention, indicating

that regions showing poor grey matter growth and development following very preterm birth are implicated in the neural circuitry of attention. Furthermore, after taking into account the infant clinical, neuropathological and social factors associated with prematurity, reduced grey matter volume in the medial occipital (p = .05), cingulate (p = .006) cortices, and to some extent temporal (p = .11) and thalamic (p = .12) regions, made an independent contribution to attention outcomes in very preterm children at age 12 years. Together, findings suggest grey matter abnormalities, particularly in the posterior cingulate and medial occipital cortex, are an important neural mechanism for inattention in children born very preterm.

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Appendix A. The Timing of Preterm Birth for Central Nervous System Development.

Figure 14 shows the timing of the neurobiological processes (listed on the left hand-side of the figure) that underlie the development of the human central nervous system from conception to adulthood. The critical period of development that is adversely impacted by off-time preterm birth is highlighted in orange (author's emphasis). The thick bold horizontal lines represent the critical stages in which neurobiological processes are most active during gestation and vulnerable to the interruption of preterm birth. Important factors include neural proliferation and migration from the subplate, axonal and dendrite sprouting, synapse formation, glial cell proliferation, myelination, and programmed cell death.

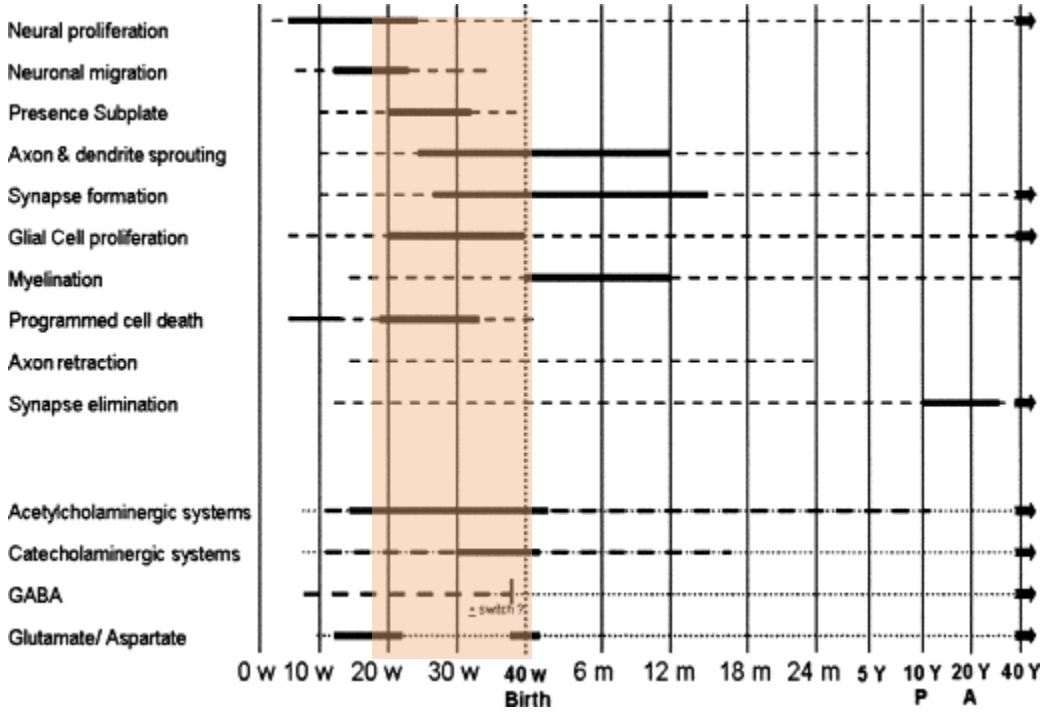

Figure 14. The timing of neurobiological processes underling the development of the central nervous system (de Graaf-Peters & Hadders-Algra, 2006).

Appendix B. Age Correction for Extent of Prematurity.

Figure 15 illustrates the distinction between chronological age and corrected age. Chronological age is measured from the date of birth and reflects and considers development in the context of the extrauterine environment. Corrected age takes into account the biological immaturity of the very preterm infants and determines the due date for follow-up evaluation from the expected date of delivery (*i.e.* when the infant should have been born).

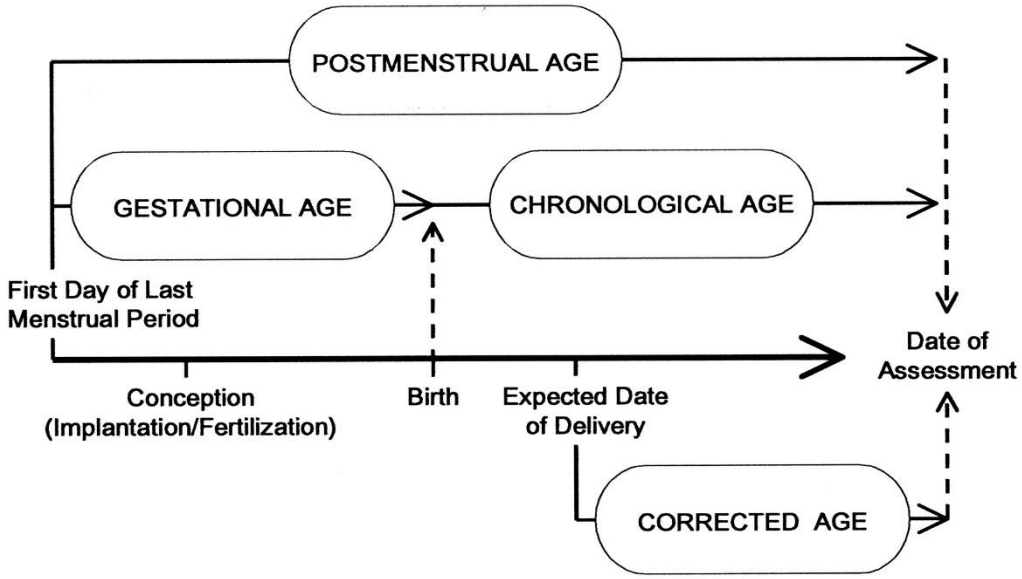

Figure 15. Distinction of chronological age and corrected age (Committee on Fetus and Newborn Pediatrics, 2004).

Appendix C. The Relationship between IQ and Attention in Full Term and Very Preterm Children at Age 12 Years.

Table 14 shows the Pearson's Product Moment correlations between children's general intellectual ability and performance on the TEA-Ch. General intellectual ability was measured with the Wechsler Intellectual Scale for Children-III.

Table 14

Association between WISC-III FSIQ scores and TEA-CH Subtest Scores for all Study Children at Age 12 Years (n = 206)

	Selective	**Sustained**		**Executive**	
	Visual	**Auditory**	**Response Inhibition**	**Shifting**	**Divided**
	Sky Search Attention Score	**Score! total correct**	**Walk Don't Walk total correct**	**Creature Counting total correct**	**Sky Search DT Decrement Score**
Full term (n = 106)					
FSIQ	-.41***	.38***	.30**	.32**	-.31**
Very Preterm (n = 106)					
FSIQ	-.53***	.42***	.50***	.50***	-.48***

FSIQ: Full Scale Intellectual Quotient ** $p < .01$, *** $p < .001$

Appendix D. Neuronal Damage that Accompanies Perinatal White Matter Damage.

Figure 16 illustrates the inflammatory and excitotoxic effects on myelinated neurons migrating from the subplate to the cortex. The right-hand side of the diagram shows the adverse effects of activated microglia that enhance inflammatory and excitotoxic processes in the intermediate zone, thus injuring neurons prior to their migration from the subplate zone. In comparison, the left-hand side shows the expected pattern of migration for neurons in normal development.

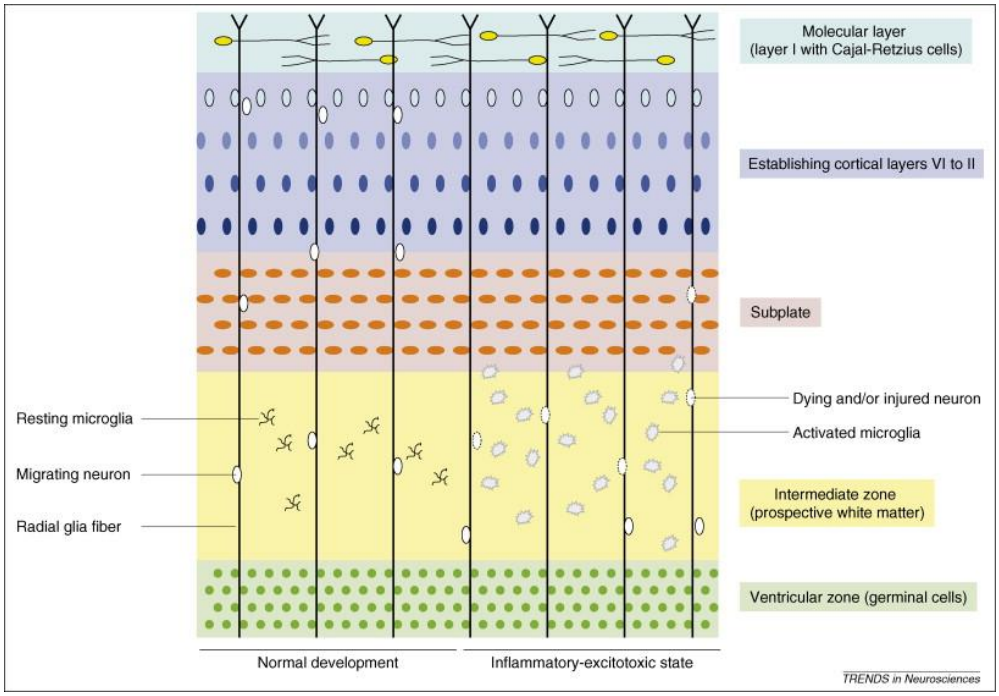

Figure 16. Impacts of inflammatory and excitotoxic effects on neuronal migration (Leviton & Gressens, 2007)