The Role of Neonatal Brain Injury and Hippocampal Development in Memory and Learning in Very Preterm 7 Year-Old Children

Submitted by

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Contents

Abstract

Children who are born very preterm (VPT<32 weeks' gestational age) are at increased risk of cognitive impairment, including memory and learning difficulties. Magnetic resonance imaging shows that VPT infants are also at high risk of focal and diffuse brain pathology. The hippocampal formations are particularly vulnerable to the complications associated with VPT, and have been associated with memory and learning. Establishing the relationship between brain pathology and memory and learning abilities is important for management and intervention.

This study aimed to investigate neonatal brain injury, memory and learning, hippocampal volume, and the relationship between hippocampal development and memory and learning in VPT children at 7 years of age. Participants included 198 very preterm (VPT) and 70 full-term born children, recruited at birth into a longitudinal study. MRI brain scans were conducted at term equivalent age and at 7 years of age and participants underwent an extensive cognitive assessment at age 7 years, which included multiple measures of memory and learning.

Regression models were used to assess differences between the VPT and full-term groups on all memory and learning outcome measures, group differences in hippocampal volumes, and whether hippocampal volume and change in hippocampal volume over time predicted memory and learning performance in VPT children. The VPT group showed reduced working memory, long term memory, and learning abilities in the verbal and visual modalities. Neonatal brain abnormality, especially deep grey matter abnormality, was associated with poorer memory and leaning in VPT children. The VPT group had reduced hippocampal volumes at age 7 years and compromised hippocampal development compared to term controls, but hippocampal volume and change in volume over time were not predictive of memory and learning performance.

Children born VPT show reduced memory and learning and compromised brain development. This study highlights the need for close surveillance and early intervention for high-risk children.

Statement of Authorship

Except where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole or in part from a thesis submitted for the award of any other degree or diploma.

No other person's work has been used without due acknowledgment in the main text of the thesis.

This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

This thesis is part of the research program from the Victorian Infant Brain Studies (VIBeS) team based at the Murdoch Childrens Research Institute, Melbourne, Australia. VIBeS is a team of researchers who conduct longitudinal studies to investigate brain and nerobehavioural development in very preterm children. As such, publications involve the contribution of multiple authors. The current candidate has made a leading and significant contribution to the data collection and production of this thesis.

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List of Figures

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism spectrum disorder
BPD	Bronchopulmonary dysplasia
BSID-II	Bayley Scale of Infant Development – Second Edition
CA	Cornu Ammonis
CGM	Cortical grey matter
CMS	Children's Memory Scale
CP	Cerebral Palsy
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
CVLT-C	California Verbal learning Test – Children's Version
DA	Developmental Amnesia
DCD	Developmental coordination disorder
DGM	Deep grey matter
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th Edition
ELBW	Extremely low birth weight
EPT	Extremely preterm
fMRI	Functional magnetic resonance imaging
FT	Full-term
GA	Gestational age
GEE	Generalised estimating equations
HB	Hippocampal body
HH	Hippocampal head

HT	Hippocampal tail
ICV	Intracranial volume
IQ	Intelligence quotient; general intellectual functioning
IVH	Intraventricular haemorrhage
LBW	Low birth weight
MABC	Movement Assessment Battery for Children
MRI	Magnetic resonance imaging
MTT	Multiple trace theory
PDA	Patent ductus arteriosus
PET	Positron emission tomography
PFC	Prefrontal cortex
PHI	Periventricular hemorrhagic infarction
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SCT	Standard consolidation theory
SD	Standard deviation
SGA	Small for gestational age
TEA	Term equivalent age
TVL	Trigone of the lateral ventricle
TVPS-R	Test of Visual-Perceptual Skills – Revised
VIBeS	Victorian Infant Brain Studies
VLBW	Very low birth weight
VPT	Very preterm
WHO	World Health Organization

WM	White matter
WMTB-C	Working Memory Test Battery for Children

Chapter 1: Preterm Birth

Infants born prematurely are at risk for higher rates of mortality and morbidity. The increasing incidence is a major public health issue (Hornby & Woodward, 2009) due to the frequent neurological, cognitive, behavioural and psychiatric difficulties faced by surviving children (P. J. Anderson & Doyle, 2003). Long-term quality of life is a primary concern for parents of VPT children. Prematurity is associated with an increased risk for early brain insult and diffuse pathology that compromises subsequent brain development (Anderson & Doyle, 2008), and may explain the neurobehavioral impairments often found in this population. Longitudinal studies that assess neurocognitive skills together with neuroimaging techniques are needed to help clarify the specific processes that contribute to cognitive impairment in preterm children. Understanding the neuromechanisms associated with specific cognitive impairments in this at-risk population may help inform new intervention methods.

This chapter will begin with a discussion of the definitions and epidemiology of preterm birth, as well as the medial complications which are thought to be associated with brain injury in preterm infants. The neuropsychological and behavioural deficits which are common to the preterm population will then be addressed.

Definitions and Epidemiology of Prematurity

Preterm birth is defined as birth occurring at less than 37 completed weeks' gestational age (GA). The World Health Organization (WHO, 2012) classifies preterm birth into sub-categories defined as: moderate to late preterm (32 to <36 weeks' gestation), very preterm (VPT: <32 weeks' gestation), and extremely preterm (EPT: <28 weeks' gestation). A present, the youngest age at which an infant born preterm can survive (i.e. limit of viability) is approximately 22 weeks' GA (Hussain & Rosenkrantz, 2003). Birth weight is linked to the GA of the infant, and was often used as a proxy for GA in the past; low birth weight (LBW) is classified as <2500 g, very low birth weight (VLBW) as <1500 g, and extremely low birth

weight (ELBW) as <1000 g (WHO, 2012). Although birth weight and GA are indicators of prematurity, the terms are not interchangeable, as infants can be born with a lower than expected weight for GA, referred to as small for gestational age (SGA) or intrauterine growth restricted. A relationship does exist however, between each additional week of gestation or gram of weight, and improvement of functional and cognitive long-term outcomes (I. S. Baron & Rey-Casserly, 2010).

In 2010, an estimated 14.9 million of all live births worldwide were preterm (Blencowe et al., 2012). Over 60% of preterm births occur in Africa and South Asia, though the countries with the highest numbers include Brazil, the United States, India and Nigeria, demonstrating its global nature (WHO, 2012). With regards to VPT birth, there has been a steady rise over the past 20, accounting for approximately 2% of births world-wide (WHO, 2012). In Australia, approximately 8.3% of birth were preterm in 2007, and 0.7% of these births were VPT (Laws & Sullivan, 2009). Further, Victoria alone had 72,103 live births, of which 552 (0.8%) were born VPT (The Consultative Council on Obstetric and Paediatric Mortality and Morbidity, 2007).

A number of factors are associated with preterm birth, and relate to three main categories (Alexander, 2007; Johansson & Cnattigius, 2010). Medical factors refer to those related to previous and current pregnancy, such as low maternal pregnancy weight, history of previous preterm birth, growth restriction, multifetal pregnancy, and uterine or cervical abnormalities. Sociodemographic factors are those related to parental ethnicity, maternal age, single marital status, and low socioeconomic status and education level. Behavioural/environmental factors include smoking, drug and alcohol abuse, caffeine, stress, poor social support and parental care, and occupational/environmental exposures (i.e. air pollution).

Mortality rates of VPT children over the past three decades have decreased substantially. For example, the Victorian Infant Collaborative Study Group (Doyle, 2004) reported survival rates for all live births across Victoria, Australia, in 1979-1980 as 6% for

infants born at 500-749 g and 37% for those born at 750-999 g. This had risen to 61% and 83% respectively in 1997. However, the proportion of preterm births remained stable in Victoria, Australia from 2000 to 2004, between 7.6% and 7.8% (The Consultative Council on Obstetric and Paediatric Mortality and Morbidity, 2007).

Increased survival rates for infants born prematurely can be attributed to advances in perinatal care, especially in the early 1990s (Noble, 2003). One of the most significant advances involved the routine administration of surfactant; a natural substance produced in the lungs from approximately 32 weeks gestation that is important for lung function. Prenatal corticosteriod administration also became more widespread in Australia during this time and had a significant impact on survival of these infants (Crowley, 1995; Soll & Morley, 2001). Additional advances included the increased use of assisted ventilation, the administration of nasal continuous positive airway pressure (CPAP), and increased rates of caesarean births (Horbar et al., 2002).

Increased survival of the highest risk infants has resulted in greater morbidity in the preterm population. These include increased frequency and severity of medical complications during the neonatal period, and poorer neuropsychological and neurodevelopmental outcomes (Stoelhorst et al., 2005). Furthermore, many children born prematurely experience multiple comorbidities, especially those with the lowest GA or birth weight.

Medical Factors and Brain Injury in the Premature Infant

VPT birth is associated with increased risk for a variety of medical complications in the neonatal period (Ward & Beachy, 2003), which can include all major systems of the body. Respiratory distress syndrome (RDS) is one of the main problems associated with VPT birth, and arises partly due to surfactant insufficiency in the lungs and may present as increased breathing rate or effort in breathing, expiration, or cyanosis (Fraser, Walls, & McGuire, 2004). Lung dysfunction in preterm infants can result in brain ischemia. With the

aim of preventing RDS, antenatal corticosteroids are used prior to birth in women who are at risk of delivering before 34 weeks' GA. After birth, the infant exhibiting symptoms of RDS is treated with surfactant replacement, mechanical ventilation or nasal continuous positive airway pressure (Fraser et al., 2004). The development and use of these therapies has almost halved the risk of RDS in preterm infants (Johansson & Cnattigius, 2010), greatly contributing to increased survival rates. In severe cases, infants may require prolonged oxygen therapy. When they still require oxygen therapy at 36 weeks' GA, they are classified as having chronic lung disease, or bronchopulmonary dysplasia (BPD) (Ehrenkranz et al., 2005).

Other medical complications associated with VPT birth include patent ductus arteriosus (PDA; abnormal blood flow between two major arteries connected to the heart), retinopathy of prematurity (ROP; an ocular abnormality), and infections such as pneumonia, meningitis, or urinary tract infection (Levy et al., 2009; McGuire, Clerihew, & Fowlie, 2004). Further, illness and infection results in inflammation, which has also been linked to brain injury in VPT infants (Volpe, 2009).

The type and extent of brain injury and altered cerebral development associated with prematurity is becoming clearer with the increased use of magnetic resonance imaging (MRI). Differing forms of brain injury can occur after VPT birth. The major neuropathologies associated with prematurity are periventricular leukomalacia (PVL), neuronal/axonal deficits, and severe germinal matrix intraventricular hemorrhage (IVH). Imaging studies show that at least 50% of infants with VLBW show PVL and apparent neuronal/axonal disease, whereas severe germinal matrix IVH occurs in approximately 5% of cases (Volpe, 2008). Furthermore, these pathologies are associated with moderate to severe cognitive and motor impairments (de Vries, van Haastert, Rademaker, Koopman, & Groenendaal, 2004; Sherlock, Anderson, & Doyle, 2005).

PVL is most common in VPT infants, involving focal necrosis (i.e. cell death) and diffuse white matter injury around the lateral ventricles (Volpe, 2001). PVL largely occurs

due to injury of preoligodendroglial cells (Haynes et al., 2003) which are most prolific when VPT birth occurs (Back et al., 2001) and are particularly vulnerable to the effects of inflammation and ischemia (Khwaja & Volpe, 2008). Injury to these cells interrupts the myelination of axons which occurs during late gestation and into early childhood. In its most severe form, focal necrosis can be accompanied by cystic infarcts deep within the white matter, differentiating cystic from non-cystic PVL (Figure 1). Cystic PVL is characterized initially by a reduction in premyelinating oligodendrocytes and then by significant astrogliosis and microgliosis (Volpe, 2009). Additionally, cystic-PVL is associated with a much larger risk of later neurological deficit than the non-cystic PVL (de Vries et al., 2004).

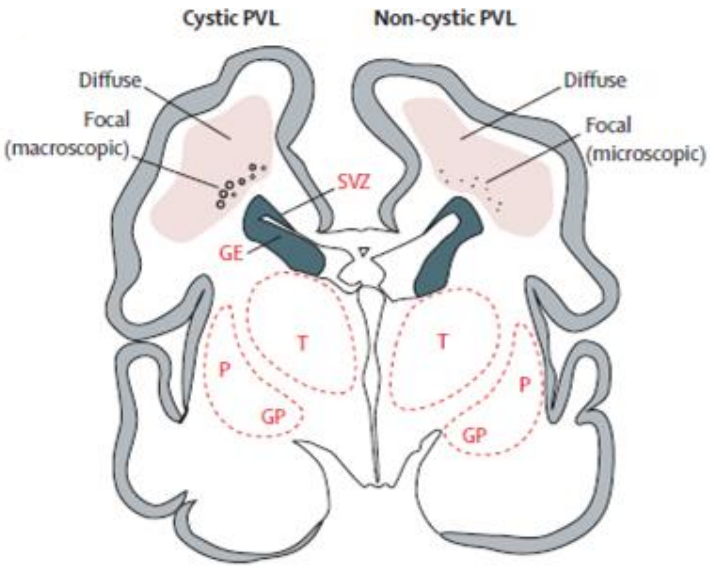

Figure 1. A coronal section of the brain in a VPT infant displaying cystic and non-cystic PVL. The dorsal cerebral subventricular zone (SVZ), the ventral germinative epithelium of the ganglionic eminence (GE), thalamus (T), putamen (P)/globus pallidus (GP). PVL is defined by both focal and diffuse injury, with macroscopic cysts evident in cystic-PVL. Adapted by (Volpe, 2009).

Recent MRI studies have demonstrated that diffuse white matter injury is common to both cystic and non-cystic PVL in VPT infants, with 20% of VPT children sustaining moderate to severe white matter abnormalities and 50% showing mild abnormalities (Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Woodward, Anderson, Austin, Howard, & Inder, 2006). Morphological changes associated with white matter injury include reduced white matter volume, delayed myelination, thinning of the corpus callosum, and enlarged ventricles (Inder, Warfield, Wang, Hüppi, & Volpe, 2005; Inder, Wells, et al., 2003). Studies show that BPD may be associated with cerebral white matter development in VPT infants (Gagliardi, Bellù, Zanini, & Dammann, 2009).

Although focal and diffuse white matter injuries are well-recognised consequences of PVL, neuronal/axonal disease is an under-recognised accompaniment of the condition. Neuronal/axonal disease can be widespread, affecting multiple brain regions. Regions most commonly affected are the cerebral white matter (axons and subplate neurons), thalamus, basal ganglia, cerebral cortex, brainstem and cerebellum (Volpe, 2009). Volumetric MRI has shown that infants with VLBW have decreased volume to these neuronal structures at term equivalent age (TEA) and in later childhood and adolescence (Volpe, 2009)

MRI studies have also found white matter damage to be a major predictor of grey matter abnormality in VPT children, including delayed gyration and decreased cerebral grey matter volume (Brown et al., 2009; Inder et al., 1999; Inder et al., 2005; Woodward et al., 2006). Grey matter typically triples in volume between 29 weeks gestational age to term (Van der Knaap et al., 1996), the period during which VPT infants are being managed in neonatal intensive care. Inder, Anderson, Spencer, Wells, and Volpe (2003) found that 65% of infants with moderate to severe white matter injury and 17% of those with mild white matter abnormality had abnormal grey matter.

The other major form of brain injury in VPT infants is IVH, which refers to a haemorrhage or bleed in the germinal matrix, which can extend into the lateral ventricles (Arthur, 2006) (Figure 2). Papile, Burstein, Burstein, and Koffler (1978) first graded IVH

according to severity; Grades I and II indicate mild injuries which resolve spontaneously, while Grade III indicates more severe injuries and the increased risk for developing hydrocephalus. Grade IV refers to a significant bleed that results in a parenchymal infarct, and is now commonly referred to as periventricular hemorrhagic infarction (PHI) (Volpe, 2009). Grades I and II IVH have been found to occur in approximately 19% of VPT children, and in only 3% for Grade III/PHI (Ancel et al., 2006).

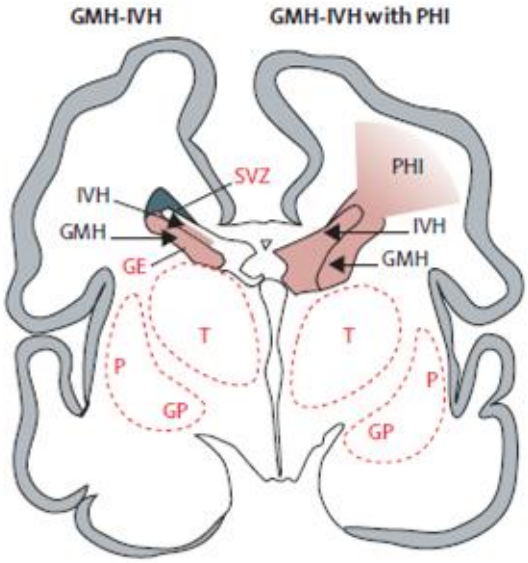

Figure 2. A coronal section of the brain in a VPT infant depicting that IVH and germinal matrix haemorrhage (GMH) can result in PHI. The dorsal cerebral subventricular zone (SVZ), the ventral germinative epithelium of the ganglionic eminence (GE), thalamus (T), putamen (P)/globus pallidus (GP). Adapted from (Volpe, 2009).

Studies have used qualitative scoring systems on MRI to define brain abnormalities into grades of severity and to derive overall abnormality scores (Inder, Wells, et al., 2003; Woodward et al., 2006; Woodward, Clark, Pritchard, Anderson, & Inder, 2011). Kidokoro, Neil, and Inder (2013) derived an MRI assessment tool to define cerebral abnormalities in the infant brain, which was an adaptation of a procedure applied previously (Inder, Wells, et

al., 2003; Woodward et al., 2006). The scoring system rates the presence and severity of white matter abnormality (WM; cystic lesions, signal abnormality, myelination delay, callosal thinning, lateral ventricular volume, white matter volume), cortical grey matter abnormality (CGM; extracerebral space, signal abnormality, gyral maturation), deep grey matter abnormality (DGM; signal abnormality, deep grey matter volume) and cerebellar abnormality (signal abnormality, cerebellar volume), and these four subscales can be summed to generate a global abnormality score. Moderate to severe abnormalities most commonly occurred in white matter, and the cerebellum, but were still evident in cortical grey matter and deep grey matter (Kidokoro et al., 2013). These findings help characterise the nature of injury commonly associated with preterm infant brain development.

Volume reduction of subcortical regions have also been reported in VPT children (Nosarti et al., 2002; D. K. Thompson et al., 2008), supporting the idea that white matter pathology may extend beyond oligodendroglial cell damage (Volpe, 2009). Studies show volume reductions in infancy to the cerebellum (Pierson et al., 2007), deep grey nuclei such as the basal ganglia and thalamus (Inder, Wells, et al., 2003), and to the hippocampus in childhood (Lodygensky et al., 2005). Further studies indicate that these reductions persist into adolescence (S. Johnson, 2007; Nosarti et al., 2002; Stewart et al., 1999) and adulthood (Lawrence et al., 2010). Importantly, these volumetric reductions are linked to global cognitive deficits (Peterson et al., 2000; Stewart et al., 1999).

Despite the recognition of brain abnormalities in VPT infants, only a limited number of studies have examined the association between neonatal brain injury and later cognitive functioning in VPT children (C. A. C. Clark & Woodward, 2010; Spittle et al., 2011; Woodward et al., 2006; Woodward et al., 2011).

Neuropsychological Impairments in VPT Children

Although severe forms of brain injury are now rare, observed in fewer than 10% of VPT infants (Volpe, 2009), studies report that up to 60% of VPT survivors are at increased

risk of experiencing a range of adverse cognitive and behavioural outcomes compared to their full term counterparts (P. J. Anderson & Doyle, 2003; Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013). Whereas preterm children with major disabilities will probably be identified at pre-school, it is more likely that those with less apparent cognitive impairments won't be recognised until later in their education when more complex skills are required (S. Johnson, 2007). Early detection is essential for the implementation of intervention aimed at reducing cognitive deficits on developmental, academic, behavioural, and social outcomes.

General intellectual functioning (IQ).

Many studies report general IQ in VPT children to be significantly lower on average than full term born peers. Bhutta, Cleves, Casey, Cradock, and Anand (2002) found that preterm children performed approximately 10 IQ points below full term children (0.66 standard deviation [SD]). In a study examining IQ results across the literature, P. J. Anderson and Doyle (2008) estimated that the mean IQ for children born between 26 and 31 week's GA was approximately 0.3 to 0.5 SD lower than term born children, and approximately 0.8 to 1.5 SD lower for children born EPT. It has been noted that IQ scores generally increase linearly with GA and birth weight (Bhutta et al., 2002). Importantly, reduced scores on both verbal IQ and performance IQ measures have been reported to continue into later childhood (Hack et al., 1994) and adolescence (Allin et al., 2008; Taylor, Minich, Bangert, Filipek, & Hack, 2004).

Rates of intellectual disability (defined as IQ<70) are also considerably higher in children born VPT. A US based study (T. M. Luu et al., 2009) reported that the rate of intellectual impairment at 12 years in children born <1250 g was approximately 14%. Roberts, Anderson, and Doyle (2010) examined developmental quotient scores in VPT or ELBW children at 2 and 8 years. At 2 years, the rate of mild, moderate, and severe cognitive delays was 20.9%, 13.4% and 13.9% respectively when compared to full term controls, and by 8 years mild intellectual disability had increased to 36.9%, while moderate and severe

disability had decreased to 10.7% and 8.6% respectively. While some of this discrepancy may reflect differences in how impairment is classified, these studies reflect the high frequency of intellectual disability in the preterm population, especially when compared with the low rate found in term born controls.

Attention and executive functioning.

Attention and executive functioning are often reported as specific weaknesses among children born preterm. Higher rates of clinically significant inattention and/or hyperactivity in preterm children have consistently been reported across studies (P. J. Anderson & Doyle, 2003; T. M. Luu et al., 2009; Shum, Neulinger, O'Callaghan, & Mohay, 2008). A meta-analysis by C.S.H. Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, and Oosterlaan (2009) investigated 26 studies focussing on executive and attention problems in children born VPT/VLBW. Parent and teacher rating of attention problems were 0.43-0.59 SD higher when compared to full term controls. In terms of executive functioning, the meta-analysis showed that VPT/VLBW children performed 0.57 and 0.49 SD lower than term controls on tasks of verbal fluency and cognitive flexibility respectively. A systematic review by Mulder, Pitchford, Hagger, and Marlow (2009) found similar results and further, that decreasing GA is associated with increased impairment to attention and executive function in preterm children.

P. J. Anderson et al. (2011) investigated a follow-up study of EPT/ELBW children and full term/normal birth weight controls at 8 years of age. When compared to controls, the EPT/ELBW group performed more poorly on measures of selected attention, sustained attention, attention encoding, shifting attention, and divided attention. No differences were identified on a measure of inhibition.

Executive dysfunction appears to be global in nature (P. J. Anderson & Doyle, 2004). Deficits to the areas of planning and organisation (P. J. Anderson & Doyle, 2004), inhibition and switching (C. S. H Aarnoudse-Moens, Smidts, Oosterlaan, Duivenvoorden, & Weisglas-Kuperus, 2009; I. S. Baron, Kerns, Müller, Ahronovich, & Litman, 2011), and impulse control

(Böhm, Smedler, & Forssberg, 2004) have been reported. A study examining executive functioning in VPT children at 4 to 12 years of age found that relative to term born children, VPT children had reduced verbal fluency, response inhibition, and planning abilities (C. S. H. Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012).

Overall, studies demonstrate generalised deficits to attention and executive functioning in children born preterm. Given that many of these abilities are considered to support later learning, impairments within these domains may partly explain poorer educational and academic outcomes commonly reported in this population (P. J. Anderson & Doyle, 2004; Loe, Lee, Luna, & Feldman, 2012).

Processing speed.

Reduced processing speed has been demonstrated in preterm cohorts throughout development, especially when compared to control samples. Importantly, slowed processing speed has been found to explain impairments in other cognitive domains in preterm cohorts, including lower IQ, language, executive function, attention, and academic achievement (Mulder, Pitchford, & Marlow, 2011b; Rose & Feldman, 1997; Rose, Feldman, & Jankowski, 2002).

Rose et al. (2002) directly assessed processing speed at 5, 7 and 12 months using a paradigm involving the presentation of a series of paired faces. One of the faces remained the same across trials whereas the other changed, and trials continued until infants displayed a consistent novelty preference. Reduced processing speed was present at 5 months of age and persisted until the first year of life, and was associated with greater medical risk, specifically RDS. A later study assessing the same cohort found that processing deficits remained evident at 24 and 36 months (Rose, Feldman, & Jankowski, 2009), indicating that reduced processing speed may be present throughout the first three years of life. The latest follow-up of this cohort at 11 years (Rose, Feldman, Jankowski, & Van Rossem, 2011) found pervasive deficits within the domains of memory, attention, processing speed, and representational competence. These findings support the authors'

theory that a large portion of cognitive development is dependent on age-related increases in processing speed (Rose & Feldman, 1997; Rose et al., 2002), and demonstrate that deficits persist across time, task, and from the non-verbal to verbal period of development.

Other VPT/VLBW studies have reported reduced processing speed at 8 years of age (P. J. Anderson & Doyle, 2003). Recently, Mulder, Pitchford, and Marlow (2010) investigated processing speed and working memory skills in relation to academic achievement in 9-10 year old children born VPT compared to controls. Processing speed explained all significant group differences on measures of academic achievement. Furthermore, motor processing speed accounted for differences on literacy tasks, whereas verbal processing speed accounted for differences in maths and literacy. In additional follow-up studies (Mulder, Pitchford, & Marlow, 2011a; Mulder et al., 2011b), reduced processing speed exhibited by the preterm children impacted attention and executive function, and was associated with the behavioural issues present in the preterm cohort. Findings from these studies further substantiate the view put forth by Rose and colleagues (Rose & Feldman, 1997; Rose et al., 2002), that age-related increases in processing speed significantly support cognitive development.

Language.

Preterm children are often reported to have compromised language development. A meta-analysis by Barre, Morgan, Doyle, and Anderson (2011) compared language skills in VPT/VLBW children examined at 24 months or older in 12 studies. The preterm group was found to perform 0.38 and 0.77 SDs below term peers on expressive and receptive language tasks respectively. The authors suggested that this finding is concerning especially since difficulties are present during primary school age or later when language skills begin to take on their adult form.

Evidence suggests that language difficulties persist throughout the primary school age and later in VPT populations. A longitudinal investigation of a single cohort of VPT/VLBW children showed poorer language expression and comprehension skills

compared with full term controls at 2 years (Foster-Cohen, Edgin, Champion, & Woodward, 2007), 4 years (Woodward et al., 2009) and 6 years (Pritchard et al., 2009). Rates of language delay in 5 year old children born VPT are reported to range from 20 to 40% (Howard et al., 2011). During the adolescent period, Rushe et al. (2001) reported that children aged 14-15 years performed more poorly than term born controls on a measure of verbal fluency. These results highlight the need for early intervention and supports to help maximise VPT children's learning opportunities as they progress academically.

Language deficits have been associated with general cognitive difficulties. Wolke, Samara, Bracewell, and Marlow (2008) found that 15.6% of children born less than 26 weeks' GA at 6 years of age had severe language difficulties compared with less than 2% of full term controls. The EPT group performed more poorly than term born controls on tasks of receptive and expressive language abilities, social communication, speech sound production, use of age appropriate language, articulation, and reading ability. Of note, differences in general cognitive scores explained specific language or phonetic awareness deficits, though not speech rating or educational difficulties. The authors concluded that the language difficulties were not specific, highlighting the global effect of EPT on brain development.

Advances in MRI have enabled the investigation of the brain networks which support language abilities in preterm cohorts. Changes in the intra-hemispheric association fibres that subserve language functioning have been identified (Ment, Hirtz, & Hüppi, 2009). For example, the use of alternative neural pathways for semantic language processing has been identified in VPT adolescents when compared to term controls (Schafer et al., 2009). These findings suggest that plasticity in network connections may foster language development in the prematurely born.

Visual-perceptual skills.

Blindness is shown by a small proportion (1% - 2%) of children born EPT (P. J. Anderson & Doyle, 2003). However, more subtle vision impairments are reported to occur

in 34% of children born less than 26 weeks' GA at age 6 years (Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000). In terms of higher-order visual-perceptual abilities (analysis and interpretation of complex visual material), the literature shows inconsistent findings.

Davis, Burns, Wilkerson, and Steichen (2005) assessed VLBW born children at ages 4-5 years using the Test of Visual-Perceptual Skills-Revised (TVPS-R) (Gardner, 1996). They reported that whilst their cohort of VLBW children displayed average IQ scores, three quarters performed well below their full term peers on all visual-perceptual tasks, with 63% and 78% of children performing below age-expectations on tests of visual closure and visual sequencing respectively. Hård, Niklasson, Svensson, and Hellström (2000) also used the TVPS-R to assess visual-perceptual processing in a sample of 7 year old children born VPT. They demonstrated that 42% of VPT children performed below the 5th percentile on tasks of visual discrimination, spatial relations, figure-ground and visual closure, compared to 12% of controls.

In contrast, some studies have failed to find impaired visual processing in preterm children. For example, Teplin, Burchinal, Johnson-Martin, Humphry, and Kraybill (1991) did not find any differences between ELBW children and controls on the original TVPS, and Goyen, Lui, and Woods (2008) found the majority of their VLBW sample performed within the average range, and as well as controls. Important methodological differences between these studies however, include varying sample sizes and preterm populations, and differences in the definition of visual-perceptual impairment. As such, whether or not visual-perceptual skills in preterm children are a particular area of concern remains an important area of inquiry.

Motor functioning.

Cerebral Palsy (CP) is the most common neurological impairment in children born preterm and is characterised by an alteration in muscle tone due to brain injury. CP has a prevalence rate between 4%-15% in VPT children (P. J. Anderson & Doyle, 2003; Platt et al., 2007; Vohr, Wright, Poole, & McDonald, 2005). One quarter to one half of preterm infants

with moderate-severe white matter abnormality have CP (Woodward et al., 2006), with high rates (57% - 85%) of infants with cystic PVL reported to have the condition (Ancel et al., 2006).

An additional 40%-50% of preterm children without CP show mild-moderate motor deficits often referred to as Developmental Coordination Disorder (DCD) (P. J. Anderson & Doyle, 2003; Williams, Lee, & Anderson, 2009). DCD has been found to have a prevalence rate of 3-4 times greater than in the general population (Williams et al., 2009). A recent meta-analysis by de Kieviet, Piek, Aarnoudse-Moens, and Oosterlaan (2009) investigated findings from 41 studies of VPT/VLBW children aged 5 to 15 years which used standardised motor assessments. VPT/VLBW children performed more poorly than term born controls, with deficits of balance, coordination and dexterity persisting into adolescence.

Given the association between white matter injury and CP, Spittle et al. (2011) assessed whether white matter abnormalities predict all levels of motor impairments in VPT children. A large cohort of VPT infants underwent brain MRI at TEA, and white matter abnormalities were characterised as nil, mild, or moderate to severe. The motor skills of children were assessed using the Movement Assessment Battery for Children (MABC), and classified as having moderate to severe motor impairment if they performed below the 5th percentile overall. In total, 27% of the VPT group were classified as having moderate to severe motor impairment, and 50% as having mild to severe motor impairment. Mild versus no white matter abnormalities were found to increase the odds of moderate to severe motor impairment by over fivefold, and mild to severe motor impairment by twofold. When compared to no white matter abnormalities, moderate to severe abnormalities increased the odds for moderate to severe motor impairment by 19-fold, and by ninefold for mild to severe motor impairment. Thus, the rate of motor impairment increases with more severe neonatal white matter abnormalities in VPT children.

The aforementioned studies demonstrate that preterm birth has a clear and persistent impact on motor functioning. Importantly, the implications of motor impairment

are widespread, potentially affecting participation in sports, health and fitness, self-esteem, social skill development, emotional well-being, and later cognitive functioning and academic achievement (Orton, Spittle, Doyle, Anderson, & Boyd, 2009; Skinner & Piek, 2001).

Behavioural disorders and psychopathology.

A meta-analysis was conducted by Bhutta et al. (2002) examining the behavioural outcomes of school aged children born preterm or with LBW across 16 studies. Of the studies examined, 81% showed that preterm or LBW children had increased externalizing (i.e. oppositional behaviour or conduct disorder symptoms) and internalizing (i.e. anxiety and depressive symptoms) behaviours. In contrast, whilst a recent meta-analysis (C.S.H. Aarnoudse-Moens et al., 2009) of school-aged children born VPT/VLBW found children to experience higher rates of internalizing behaviours when compared to controls, higher rates of externalising behaviours were not reported. Inconsistencies between studies may reflect the screening measures used, such as the use of parent and teacher questionnaires or standard diagnostic criteria (i.e. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]).

Attention Deficit Hyperactivity Disorder (ADHD) is the most common behavioural disorder in VPT/VLBW populations (P. J. Anderson & Doyle, 2003; Botting, Powls, Cooke, & Marlow, 2006). A meta-analysis conducted by Bhutta et al. (2002) found that preterm children were on average 2.6 times more likely to have ADHD than controls. P. J. Anderson et al. (2011) found that parent questionnaires indicated an approximate two-fold increase in the rate of ADHD symptoms (especially hyperactivity and impulsivity) in EPT/ELBW children at 8 years when compared to parents of term controls. Importantly, Jaekel, Wolke, and Bartmann (2013) reported that inattention associated with ADHD in VPT and/or VLBW children aged 6 and 8 years predicted academic under-achievement at 13 years of age.

Epidemiologic studies have shown that children born preterm birth or LBW are at greater risk for Autism Spectrum Disorders (ASD) (S. Johnson & Marlow, 2011). Most recently, Karli Treyvaud et al. (2013) found that 4.5% of their VPT children met criteria for

ASD at 7 years of age. Consistently, Hack et al. (2009) reported significantly more symptoms of ASD as rated by a checklist in 8 year old children born ELBW compared to term controls, as well as higher rates of ASD diagnoses.

A number of studies have reported increased emotional problems in preterm cohorts. For example, infants born with LBW or SGA are at increased risk for emotional difficulties by age 5 than their term born counterparts (Westrupp, Mensah, Giallo, Cooklin, & Nicholson, 2012). Diagnostic studies generally indicate a specific risk for anxiety rather than depression in preterm populations (S. Johnson & Marlow, 2011). A follow-up study by Lund et al. (2012) investigated individuals born with VLBW and those born at term but SGA at 14 and 20 years of age. Compared with controls, the most frequently occurring diagnoses in the VLBW group were anxiety disorders at age 14 years, and both anxiety disorders and ADHD at age 20 years.

Furthermore, being born with VLBW is a risk factor for later psychiatric morbidity in adulthood. A recent meta-analysis (Burnett et al., 2011) examined studies which used clinical psychiatric diagnostic criteria in preterm/LBW individuals aged 10-25 years compared to term born controls. Participants born preterm/LBW were 3.5 times more likely to have a psychiatric diagnosis, and 3 times more likely to have a diagnosis of anxiety or depression in late childhood through to young adulthood than term born/normal birth weight controls. These findings suggest that the psychological well-being of preterm and LBW populations should be a key aspect of ongoing care. LBW has also been linked to Schizophrenia (Matsumoto, Takei, Saito, Kachi, & Mori, 2001).

Overall, mental health is an important topic of interest in the field of perinatal events and adult outcome. Long term follow-up studies which explore the developmental pathways that lead to adult psychopathology and the contribution from underlying neuropathology will be of significant value to the preterm literature.

Academic outcomes.

The above literature demonstrates that preterm birth can compromise performance on cognitive tasks. Such impairments might be expected to contribute to poorer academic performance (see Keller-Margulis, Dempsey, & Llorens, 2011 for a review), which is approximately three times more likely in VPT children when compared to full term controls (P. J. Anderson & Doyle, 2003). Of concern is the number of preterm children who experience difficulties that go undetected. Indeed, up to 50% of VPT children have been found to experience mild yet clinically significant problems that disrupt their school progress and related opportunities (P. J. Anderson & Doyle, 2003; Moster, Lie, & Markestad, 2008; Neubauer, Voss, & Kattner, 2008).

Children born preterm consistently show impairments on mathematics and language-based tasks. C.S.H. Aarnoudse-Moens et al. (2009) conducted a meta-analysis of academic achievement using 14 studies in VPT and VLBW children from early school-age to adolescence. VPT and/or VLBW children scored 0.60 SD lower on mathematics, 0.48 SD lower on reading, and 0.76 SD lower on spelling tests than their full term peers. A later study by C.S.H. Aarnoudse-Moens, Oosterlaan, Duivenvoorden, van Goudoever, and Weisglas-Kuperus (2011) examined the development of a range of preschool and academic skills in 4-12 year old children born VPT. In preschool, the VPT group performed comparably with term controls in early linguistics, but 0.70 SD more poorly on numerical reasoning. In primary school, they scored 0.30 SD and 0.60 SD lower in complex work, reading and mathematics/arithmetic respectively, though comparably with controls in reading comprehension and spelling. Whilst VPT had a higher grade repeat rate (25.5%), this did not result in an improvement of academic skills, indicating that VPT birth is associated with long-standing academic consequences. Difficulties with attention have also been found to be an important prerequisite for learning, and to predict later academic underachievement in VPT children (Jaekel, Wolke, & Bartmann, 2012).

Early predictors of educational outcomes have been investigated in preterm cohorts. In a longitudinal study, S. Johnson, Wolke, Hennessy, and Marlow (2011) assessed neuropsychological correlates and predictors of attainment in 11 year old children born EPT. IQ, phonological processing, attention, and executive functions assessed at 6 years were predictive of academic attainment at age 11 in the EPT children. Specifically, general cognitive ability and visual-spatial deficits or phoneme deletion at 6 years was associated with mathematical and reading attainment at 11 years in both groups. In addition to providing early indicators of academic problems, identifying deficits to neuropsychological correlates may provide potential targets for the content of early intervention programs, thus reducing the risk of later school failure in this population.

As a result of their academic difficulties, the use of special education services in preterm children (Pinto-Martin et al., 2004; H. G. Taylor, N. Klein, N. M. Minich, & M. Hack, 2000; Wocadlo & Rieger, 2007) and adolescents (T. M. Luu et al., 2009; Saigal, Hoult, Streiner, Stoskopf, & Rosenbaum, 2000) has been found to be higher than for term born controls. However, Litt, Taylor, Klein, and Hack (2005) found that although the rates of learning difficulties were higher in VLBW children compared to normal birth weight children, the number of children receiving school assistance did not differ significantly between groups (20% and 15% respectively). Results may reflect the small sample size (VLBW; n = 55, controls; n = 52) which may have limited the power for detecting group differences in rates of special assistance, as well as the failure to consider all aspects of achievement. Nevertheless, results suggest that there may be some groups of children who are born preterm that do not receive the assistance they likely need.

Memory and learning.

Research demonstrates that preterm birth is associated with compromised abilities in memory and learning throughout development (Rose, Feldman, & Jankowski, 2005; Rose et al., 2009; Rose et al., 2011). Given that memory and learning is the cognitive domain of interest in this study, a thorough examination of the literature is required. In the next

chapter, the components of memory and learning and how they relate as a cognitive model will be discussed, as well as the development of memory and learning in healthy children, and the effect of prematurity on this important cognitive domain.

Chapter Summary

Almost 8% of all births in Australia are preterm. Despite reduced mortality rates, preterm infants are at increased risk for a number of medical complications and have a high rate of morbidity. Brain injury is often associated with preterm birth, and most probably underpins many of the cognitive difficulties preterm children endure. Indeed, a broad range of behavioural and cognitive problems are associated with preterm birth, effecting domains of intellectual functioning, attention and executive functioning, processing speed, language, visual-perceptual skills, motor functioning, and memory and learning abilities.

Chapter 2: Memory and Learning

The capacity to remember and learn information is central to everyday functioning. These cognitive processes refer to one's ability to encode, store and later retrieve information from mind (Strauss et al., 2006). Memory and learning are closely related; for something to be remembered it must first be learned. Together, memory and learning are conceptualized as a hierarchical dual system involving immediate and working memory systems, and long term memory. Immediate/ working memory and long term memory systems are perceived to function independently of each other, though in parallel (A. D. Baddeley, 2003; Hodges, 2007). Figure 3 demonstrates the components of memory, though it does not depict how immediate/working memory and long term memory systems are interrelated. Memory and learning impairments can underpin academic difficulties, including reading and mathematical abilities in children (Litt et al., 2005). This section will discuss the sub-divisions of memory and learning, describe how these interact to form a coherent cognitive process, and outline the memory and learning abilities of preterm children.

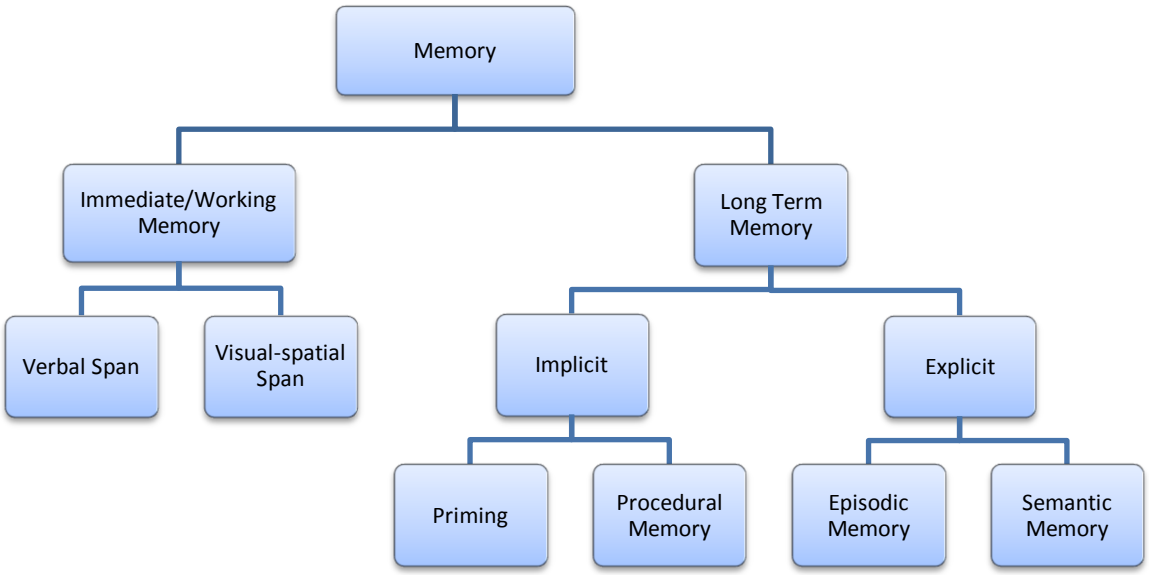

Figure 3. Memory Model. Adapted from Strauss, Sherman, and Spreen (2006).

Information initially enters a temporary storage system, or *immediate memory*. This can be distinguished from *working memory*; the capacity to process and manipulate information in immediate memory, such as during cognitive activities of planning, reasoning, problem-solving and language (Lowe, MacLean, Shaffer, & Watterberg, 2009). Processes of articulatory rehearsal (A. Baddeley, 1996) and attentional refreshment (Barrouillet & Camos, 2001) enable information to be transferred from temporary storage into the more durable *long term memory*.

The current project will refer to memory in terms of these main subdivisions (i.e. immediate memory, working memory and long term memory). Earlier models tended to group immediate and working memory systems together, using the terms 'short-term memory' (Atkinson & Shiffrin, 1968) and 'working memory' alone (A. D. Baddeley & Hitch, 1974). This will be discussed in more detail below.

Immediate and Working Memory

Researchers have long accepted the notion of a limited capacity memory store, which is quite distinct from the long-term storage system. One of the earliest and dominant models was of short-term memory proposed by Atkinson and Shiffrin (1968). It suggests that information passes through a series of sensory registers then moves into a short-term store which is accessible to consciousness. The short-term store was argued to involve a series of strategies that organize and maintain incoming material to optimize learning and subsequent recall, similar to working memory. According to this model, the longer information remained in short-term memory, the more likely it was learned and transferred into long term memory (Atkinson & Shiffrin, 1968). As such, this model proposed that memory is a unitary construct. In line with these premises, the model proposed that impaired short-term memory should result in severely impaired learning, long term memory and general cognition. However, conflicting evidence for this view came from data that supports a two-store model; patients with amnesia following medial temporal lobe damage showed profound impairment to long-term learning, but retained their short-term

store (A. D. Baddeley, 2000). The reverse pattern was also identified in some patients with normal long-term learning and memory but impaired performances on short-term memory tasks (Shallice & Warrington, 1970; Warrington & Shallice, 1972). Although this double dissociation, i.e. functional independence, appeared to support an anatomical dissociation between short-term and long term memory systems, it did not explain how patients with impaired short-term storage could learn and recall normally. Furthermore, few patients with impairments to short-term memory and long term memory had cognitive problems beyond grossly impaired short-term memory (A. D. Baddeley, 2003).

A. D. Baddeley and Hitch (1974) aimed to resolve the inconsistencies of the Atkinson and Shiffrin model by attempting to disrupt short-term memory function in normal adults. The authors used secondary or distractor tasks to deplete the availability of short-term memory in participants who were completing tasks that utilized working memory, such as reasoning or learning. Results obtained from a wide range of activities consistently demonstrated that performance was inconsistent with the Atkinson and Shiffrin model (i.e. clearly observable but far from catastrophic impairments to learning and long term memory were observed). As such, the authors proposed an alternative 'multicomponent model' based on working memory to replace the unitary short-term store described by Atkinson and Shiffrin (1968), and this has become the most influential framework to date.

According to this framework, working memory is a limited capacity system that temporarily stores and manipulates information, supporting thought processes, long term memory and action. It comprises three prominent components; an attentional control system, the central executive, and two subsidiary slave systems: the phonological loop and the visuo-spatial sketchpad. More recently, A. D. Baddeley (2000) suggested that these two slave-systems interact via the episodic buffer, which binds information from the two perceptual domains to form long term memories (Figure 4).

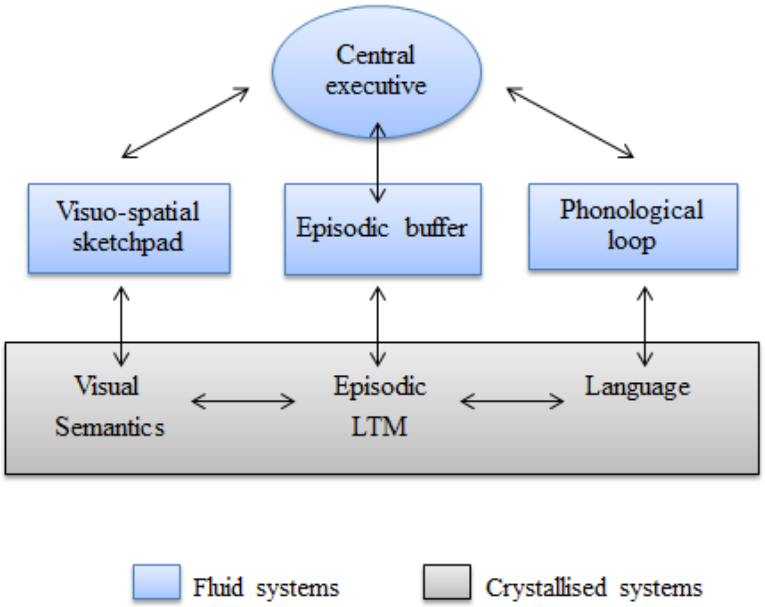

Figure 4. Multi-component working memory model. Adapted from A. D. Baddeley (2000).

The phonological loop is involved with the processing and short term storage of verbal information, and is the most researched aspect of the model. It comprises two parts; 1) the phonological store, which holds memory traces for up to a few seconds before they fade and, 2) the articulatory loop, which is involved with an articulatory rehearsal process that is equivalent to subvocal speech (A. D. Baddeley, 2003). Verbal information first enters the phonological store. To prevent this material from fading, memory traces are actively refreshed by being re-articulated, which is mediated by the articulatory loop. The word-length effect provides evidence for the role of articulation, and refers to the finding that immediate memory span declines as word length increases from one to five syllables (A. D. Baddeley, Thomson, & Buchanan, 1975). Furthermore, the two-part model of the phonological loop is supported by neuropsychological evidence of patients with phonological short-term memory deficits in the absence of more extensive language impairments (Larsen & Baddeley, 2003).

A. Baddeley, Gathercole, and Papagno (1998) proposed that the phonological loop developed to facilitate the acquisition of language. This view was based on a patient with a pure phonological loop deficit who was unable to acquire the vocabulary of a new language despite normal long term memory function. Additionally, acquisition of native vocabulary in children is well predicted by non-word repetition (i.e. the capacity to hear and repeat back pseudo-words), which is presumed to rely on the phonological loop (Gathercole & Baddeley, 1989). Children who have a specific language disability but normal non-verbal intelligence, similarly perform poorly on non-word repetition in the absence of hearing or articulatory difficulties (Gathercole & Baddeley, 1990).

The visuo-spatial sketchpad is specialized for the short term storage of visual and spatial information (A. D. Baddeley, 1983; A. D. Baddeley, 2007). Evidence for the visuo-spatial sketchpad is the phenomenon known as change blindness; when change in a visual stimulus such as to its colour or position, is unnoticed by an observer (Simons & Levin, 1997). Functions which typically involve the visuo-spatial sketchpad include; the construction, maintenance and manipulation of mental images, visual scanning, and mental rotation of objects in mind (Radvansky, 2011). Neuropsychological studies have shown double-dissociations within the visuo-spatial sketchpad between visual and spatial spans, with either a disruption of visual but not spatial short-term memory, or the opposite pattern (Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999). However, the visuo-spatial sketchpad is an under-researched aspect of the multicomponent model, and would benefit greatly from further methodological and theoretical investigations (A. D. Baddeley, 2003).

The central executive represents the most complex, and possibly the most important component of working memory (A. D. Baddeley, 2007; Gathercole & Pickering, 2000), and is thought to be closely related to executive functions (de Haan, 2010). The central executive is assumed to be responsible for a range of regulatory functions, such as the allocation of attention, and the coordination of the two slave systems (A. D. Baddeley, 1998; A. D. Baddeley & Hitch, 1974). As such, this component is critical for memory function. The

central executive is also involved in suppression, which is a method used to keep irrelevant information out of working memory or remove information that has become irrelevant (Radvansky, 2011). For example, in a span task involving people to remember the final word from each of a set of sentences read to them, people with lower spans and presumably less efficient suppression, are more likely to get the words incorrect (Chiappe, Siegel, & Hasher, 2000). Disruption to the central executive can result in the condition known as 'dysexecutive syndrome' (A. Baddeley & Wilson, 1988), which involves perseveration of behaviour or increased susceptibility to distraction.

The final component, the episodic buffer, was introduced into the model to resolve difficulty in relating working memory with long term memory (A. D. Baddeley, 2000). The episodic buffer is controlled by the central executive and is accessible to conscious awareness. It is a limited capacity, temporary multidimensional store that forms an interface between the verbal and visuo-spatial subsystems, and links these to long term memory. Being a multidimensional buffer, it enables a range of different subsystems to interact despite information within them being based on different codes. As such, a main function of the buffer is to bind together different sources of information to form episodic representations (A. D. Baddeley, 2003). Overall, this revised model differs from the original model proposed by A. D. Baddeley and Hitch (1974) in that it focuses on the processes of integrating information rather than on the isolation of the subsystems.

Neuroimaging and neuropsychological studies have also confirmed discrete neuroanatomical regions and neural networks for these memory components in adults (Hensen, 2001; Vallar & Papagno, 2002). Immediate/working memory has been associated with the prefrontal cortex (PFC), anterior cingulate, parietal and occipital regions (R. Cabeza & L. Nyberg, 2000), and the hippocampus (Piekema, Kessels, Mars, Petersson, & Fernández, 2006). The phonological loop has been associated with the peri-sylvian language areas in the dominant hemisphere, and to a lesser degree, with contributions from the non-dominant inferior parietal cortex and right premotor cortex (A. D. Baddeley, 2003). The visuo-spatial

sketchpad has been associated with functioning in the non-dominant parieto-occipital regions (A. D. Baddeley, 2003). Whilst the neuroanatomical underpinnings of the episodic buffer are yet to be established, A. D. Baddeley, Allen, and Hitch (2011) speculate that it likely involves a widely distributed system, with different forms of binding highlighting different subsystems.

Immediate and working memory development.

Understanding children's memory development is crucial for psychologists and other academic and professional groups, especially in at risk populations such as children born preterm. Whilst the multicomponent model proposed by A. D. Baddeley and Hitch (1974) is an adult-based representation of memory and learning, it has also proved to be a useful framework for characterizing the development of immediate/working memory in children (Gathercole, 2002). Studies show that almost all aspects of immediate/working memory show a stable increase from preschool to adolescence (Hulme, Thomson, Muir, & Lawrence, 1984; Elizabeth B Isaacs & Vargha-Khadem, 1989; Siegel, 1994).

With regards to the phonological loop, increased memory capacity results from a sizable increase in the rate of articulatory rehearsal as children develop, enabling children to maintain larger amounts of verbal information in the phonological store (Hulme et al., 1984). It is argued that prior to 7 years of age, spontaneous rehearsal does not occur reliably and therefore, the phonological loop only consists of the phonological store (Gathercole & Hitch, 1993). Changes in the speed of memory scanning during the retrieval process (N. Cowan et al., 1998) and of the output process (N. Cowan et al., 1992) have also been implicated with the development of phonological memory.

Whilst the development of the visuo-spatial sketchpad has received less attention, one important developmental shift has been reported. Children below 7 years of age typically rely on the visuo-spatial sketchpad to support the recall of physical aspects (or forms) of visual-spatial material (Gathercole, 1998). In contrast, older children tend to rely on the phonological loop to mediate immediate/working memory performance and

therefore, recode visual-spatial inputs into a phonological form using articulatory rehearsal (G. Hitch et al., 1983). For example, G. J. Hitch, Halliday, Schaafstal, and Schraagen (1988) reported that in a task involving the presentation of series of pictures representing nameable objects, children aged 5 years were impaired when recalling lists in which pictures of objects shared many physical features (e.g. pen, fork, comb, key). In contrast, children aged 10 years did not show susceptibility to the visual similarity of objects shown, but were impaired when the objects had longer names (e.g. umbrella, kangaroo, policeman, banana). The authors argued that whilst older children adopt a strategy of verbally recoding pictures when possible, younger children rely on their recall of visual-spatial characteristics. Consistently, studies utilizing stimuli which do not correspond to familiar items which can be recoded into phonological form indicate that visual-spatial memory increases substantially between 5 and 11 years of age (Miles, Morgan, Milne, & Morris, 1996; Wilson, Scott, & Power, 1987).

Developmental changes to the central executive have generally been assessed using complex memory span paradigms which require simultaneous storage and processing demands, such as reading, and listening and backward digit span tasks (Gathercole, 1998). Siegel (1994) demonstrated that performance on a listening span task increased steadily between 6 and 15 years of age. It has been suggested that a decrease in the processing demands of memory span paradigms allows additional resources to support storage, resulting in developmental increases in memory span and therefore, in central executive functioning from early childhood to adolescence (Case, Kurland, & Goldberg, 1982). Alternatively, it has been argued that memory span performance relies more heavily on the time which elapses between the presentation of a memory item and its subsequent retrieval rather than the processing aspect, resulting in lower span scores in younger children (G. J. Hitch, Towse, & Hutton, 2001). Additional research is needed to provide a clear explanation for developmental changes to functions conventionally associated with the central executive.

Studies examining the development of working memory have largely focused on changes which occur within individual components of the proposed framework, with less research addressing organizational changes within the system more generally. To address this issue, Gathercole, Pickering, Ambridge, and Wearing (2004) examined the structure of immediate/working memory in children aged 4 to 15 years. Children were given multiple assessments which were designed to tap each component of the original multicomponent model (i.e. not including the episodic buffer): digit recall, word list recall and nonword list recall assessed the phonological loop; block recall, the Visual Patterns Test, and mazes memory tapped the visuo-spatial sketchpad; and span measures of backward digit recall, listening recall, and counting recall were administered to assess the central executive and phonological loop. Results showed that each component underwent notable expansion in functional capacity from 4 years of age to adolescence, and that the three-factor model provided a good account for the data from 6 years of age onwards. Earlier research has demonstrated moderate associations between the central executive and phonological loop in children aged 6 and 7 years (Gathercole & Pickering, 2000), and that verbal and visual-spatial aspects of immediate/working memory are independent of one another in 11 and 15 year olds (Jarvis & Gathercole, 2003). Overall, studies highlight that the structural organisation of immediate/working memory is established around 7 years of age, and remains constant over childhood and adolescence.

Researchers are beginning to examine the development of the episodic buffer in typically developing children. Alloway, Gathercole, Willis, and Adams (2004) used a 'recall of spoken sentences' task to measure the integration of phonological memory immediate/working memory with relevant long-term language knowledge. The authors demonstrated that the task tapped the episodic buffer in 4-6 year old children, which was separable from the phonological loop and central executive (though the three components were related to an extent). Others have argued that binding mechanisms in the episodic buffer develops relatively early, possibly as young as 6 years of age (Sluzenski, Newcombe, & Kovacs, 2006).

In order to account for functional changes to immediate/working memory across development, it has been suggested that the underlying neural processes may become more differentiated with age, being less distinct in children (de Haan, 2010). Káldy and Sigala (2004) argued that visual-spatial working memory in 9-month-old infants may rely more heavily on the medial temporal lobe system, and that recruitment of areas such as the PFC may establish a more prominent role later in development. Crone, Wendelken, Donohue, Van Leijenhorst, and Bunge (2006) demonstrated that when three groups of participants aged 8-12 years, 13-17 years and 18-25 years completed an object working memory task under event-related fMRI, children aged 8-12 years performed more poorly than the adolescent and adult groups when manipulation was required. It was suggested that this may result from less efficient recruitment of the right dorsolateral PFC and the bilateral superior parietal cortices, unlike both the older age groups who showed activation in these areas.

Long Term Memory

Long term memory has been an area of wide investigation. Long term memory is typically divided into two major divisions: explicit (conscious or declarative) and implicit (unconscious or nondeclarative) memory systems (refer to Figure 3) (Squire, 1986; Strauss et al., 2006; Tulving, 1972). Explicit memory refers to the intentional or conscious recollection of one's experience. Tasks which test explicit memory are those that require patients to learn and remember a set of material, such as a series of words or pictures, and are later given a recall or recognition task (Strauss et al., 2006). In contrast, implicit memory encompasses memory for abilities, skills or procedures (e.g. procedural memory, habit formation and priming) (Strauss et al., 2006), which occur predominately without conscious awareness.

Explicit memory can be further subdivided into episodic memory and semantic memory systems (Tulving, 1972). Episodic memory refers to the process that allows conscious recollection of specific personal events or episodes and the context (time and

place) in which they occurred, such as the birth of a child (Strauss et al., 2006). Clinically, episodic memory is most commonly measured using tests of free recall, delayed recall, cued recall, and recognition measures, as these tasks require a person to consciously recollect the content and context of the experience of learning. Semantic memory refers to general knowledge about the world, such as facts, concepts and vocabulary (Strauss et al., 2006). Unlike episodic memory, semantic memory is not context dependent and therefore, specific circumstances of the learning process do not need to be recollected for information to be remembered. Examples of measures which assess semantic memory include category fluency tasks, vocabulary tests, and object naming tasks.

Studies show that the medial-temporal lobe system, particularly the hippocampus and related cortices (perirhinal, entorhinal and parahippocampal) have vital implications for the retention, storage and retrieval of information in episodic memory (Moscovitch et al., 2005; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). The contribution from medial temporal lobe structures to long term memory will be discussed in more detail in Chapter 3, which focuses on the relationship between memory and learning and the hippocampal formation. In contrast, implicit memory appears to rely on a variety of structures depending on the type of implicit memory under examination, including cortical and frontal circuits, and procedural memory has been reported to activate the basal ganglia and cerebellum (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004).

Long term memory development.

As described above, children have well-marked capacities to retain and manipulate many different forms of information in immediate/working memory, and differences in these capacities may effect children's abilities to learn in varying ways. The developmental changes associated with long term memory functioning have also been documented, though inconsistencies are present in the literature, especially within the younger age groups.

Evidence suggests that episodic memory development begins in early childhood. Findings from the following studies are some of the most influential in the literature, with

authors concluding that memory for single distant events experienced by infants and toddlers are supported by the same memory systems which subserve memory in older children and adults. Studies investigating episodic memory development in young children have typically utilised an elicited imitation paradigm. This paradigm involves the examiner using props to model a single action or action sequence to the child, after which the props are given to the child, who is then encouraged to imitate the actions. The child's ability to recall the actions is typically assessed following a delay of hours or months and is therefore, argued to provide a measure of episodic memory.

Using the elicited imitation paradigm, 14 month old toddlers have been found to recall information following a delay period of 1 week, and some 13 month old children have been reported to recall multi-step sequences after 6 weeks (Meltzoff, 1988). Patricia J Bauer, Hertsgaard, and Dow (1994) and McDonough and Mandler (1994) have also reported the recollection of action sequences presented on a single occasion in 2 year old children 8 to 12 months later. However, studies do differ somewhat in their findings of episodic memory abilities in young children (Patricia J Bauer et al., 1994; Boyer, Barron, & Farrar, 1994; McDonough & Mandler, 1994), which may reflect differences between memory sequences used across studies. To account for these inconsistencies, Nelson (1994) argued that very young children's recall abilities in the elicited imitation paradigm may be mediated by a primitive learning system based on implicit memory rather than the episodic memory system use in older children and adults. Nevertheless, findings do establish that young children can sometimes retain information for specific episodes over long periods of time.

A striking developmental dissociation between implicit and explicit memory systems has been reported in children. In a review of the literature, Murphy, McKone, and Slee (2003) reported that while explicit memory is consistently found to improve into adolescence, the majority of studies showed that implicit memory is stable across a broad age range (3 years to adulthood). Improvement on explicit memory tasks was related to a combination of four factors (i.e. the four-factor model) - an increase in 'basic-capacity' for

long term memory, age-related improvement in 'knowledge base', and two factors associated with strategic processing – 'memory strategies' (such as the use of rehearsal or semantic organisation) and 'metamemory' (i.e. the awareness of one's own memory abilities).

Murphy et al. (2003) conducted a number of experiments investigating this four-factor model in explicit and implicit memory development in participants aged 5 years to adulthood. The main factors contributing to explicit memory development beyond 5 years of age were improved knowledge base and strategic processing, but not an increase in basic-capacity. Furthermore, in contrast to previous literature, this study demonstrated that implicit memory exhibited further development due to an enhanced knowledge base. The authors argued that this novel finding may reflect the use of material which likely had little or no change in the knowledge base across the age range assessed in earlier studies.

Neuroimaging techniques have been used to assess the neuroanatomical underpinning of long term memory functioning in children. Thomas et al. (2004) also challenged the long-held view that implicit memory function matures early in infancy or childhood, while explicit memory development is prolonged across childhood. They compared implicit sequence learning (using a standard serial reaction time task) in children and adults (aged 7 to 11 years) to determine possible developmental differences in the recruitment of fronto-striatal circuitry. Adults demonstrated a larger sequence learning effect and learned more quickly than children. Moreover, age related differences in activity on fMRI between children and adults were observed in the premotor cortex, putamen, hippocampus inferotemporal cortex, and parietal cortex. The authors argued that the results provided contrasting evidence for developmental invariance in learning and memory of implicit information. However, these findings are confined to sequence learning and may not support the development of other forms of implicit learning in children, such as priming and procedural memory.

Using fMRI, Ofen et al. (2007) examined the normal development of explicit memory function in individuals aged 8-24 years. Participants were shown indoor and outdoor scenes whilst undergoing scanning, and were later given a recognition memory test including both the previously studied scenes and new unseen scenes. The researchers examined whether brain activations associated with correct memory formation changed from childhood to adulthood. Significant increases in recognition accuracy between 8 and 24 years of age were reported. Whilst this was associated with age-related increases of activations in the dorsolateral PFC, memory-related activations in the medial temporal lobe were stable across the age span. Furthermore, activations in the PFC cortex, but not medial temporal lobe, correlated with developmental increases in memory for detailed experiences. The authors concluded that there is a steady increase in dorsolateral PFC activation with the normal development of explicit memory systems.

In summary, memory and learning functioning shows substantial qualitative changes from infancy though the preschool and early school years. Beyond about 7 years of age however, memory and learning appears adult-like in organisation and strategies generally, demonstrating only gradual quantitative developments through to early adolescence.

Memory and Learning in Prematurity

Research demonstrates that preterm birth is associated with compromised abilities in immediate memory and/or working memory, learning, and long term memory throughout development. Indeed, deficits in memory have been identified in preterm children very early in their development. For example, Rose et al. (2005) reported episodic memory deficits using a paradigm involving the reproduction of action sequences and recognition of pictures in preterm infants at 12 months of age. On subsequent testing at 24 and 36 months of age, this cohort continued to perform more poorly than a group of term born controls on measures of immediate and episodic memory (Rose et al., 2009). Finally, Rose et al. (2011) showed that the same sample performed more poorly than term controls

on measures of immediate visual and spatial memory, and visual episodic memory at 11 years of age. These findings suggest that visual-spatial immediate and episodic memory deficits in preterm children may persist beyond early childhood. Findings may also reflect difficulties with attention however, as it has been suggested that recall is dependent on sustained attention particularly during initial processing (P.J. Bauer, Wenner, Dropik, Wewerka, & Howe, 2000).

Immediate memory.

Deficits to immediate memory have been frequently identified in preterm cohorts. Immediate memory within the visual-spatial modality has consistently been reported as impaired in individuals born preterm at preschool age (Rose et al., 2009; S Vicari, Barbara, Carlesimo, Casadei, & Allemand, 2004; Woodward, Edgin, Thompson, & Inder, 2005), school age (C. S. H. Aarnoudse-Moens et al., 2012; Curtis, Lindeke, Georgieff, & Nelson, 2002; E. B. Isaacs et al., 2000; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Rose et al., 2011), and adolescence (Saavalainen et al., 2007). These findings suggest that immediate visual-spatial memory may be particularly vulnerable to the effects of preterm birth.

With regards to immediate verbal memory impairment in preterm children, studies show inconsistent findings. Digit span and word/non-word repetition tasks are typically used to assess this domain in preterm children. A meta-analysis conducted by C.S.H. Aarnoudse-Moens et al. (2009) of children born VPT/VLBW found this population to perform 0.36 SD below full term peers on a digit span task. Böhm et al. (2004) reported that 5.5 year old children born with VLBW performed more poorly than term controls on both digit span and word span tasks, and E. B. Isaacs et al. (2000) found reduced verbal immediate memory on multiple recall tasks in VPT children aged 7 to 8 years. In contrast, Fraello et al. (2011) did not find significant group differences on non-word repetition and digit span tasks in a small sample of 12 year old children born with VLBW. In addition, G. H. Taylor, N. Klein, N. M. Minich, and M. Hack (2000) and Sansavini et al. (2007) also failed to detect group differences between controls and children born LBW and VPT respectively on

verbal/auditory word span measures, suggesting that word span may be less compromised in preterm children.

Working memory.

Working memory deficits have also been frequently reported in preterm cohorts. Deficits in visual-spatial working memory have been identified in preterm cohorts from early childhood through to adolescence (Jongbloed-Pereboom, Janssen, Steenbergen, & Nijhuis-van der Sanden, 2012). Beauchamp et al. (2008) found impaired visual-spatial working memory skills in 2 year old children born VPT and/or VLBW, defined as perseverative behaviour on a delayed alternation task. Visual-spatial working memory has also been reported to be poorer than term controls in preschoolers aged 3- 4 years born with VLBW (Cossu, Antonucci, & Nava, 1999; Kagan, 1981; S Vicari et al., 2004) on a task involving different spatial configurations (Cossu et al., 1999; Kagan, 1981), and 6 year old children born with VLBW have been found to show impaired performances on the backwards component of the Knox's Cube Test (Ni, Huang, & Guo, 2011). Moreover, adolescents born with VLBW have demonstrated reduced visual-spatial working memory on the Spatial Span component of the Cambridge Neuropsychological Testing Automated Battery (C. S. H. Aarnoudse-Moens et al., 2012; T.M. Luu, Ment, Allan, Schneider, & Vohr, 2011) and the Backward Spatial Span subset of the Wechsler Memory Scale, Third Edition (T.M. Luu et al., 2011) when compared to term born controls. These studies reflect evidence of weakness to visual-spatial working memory systems in individuals with a history of prematurity.

There is evidence that children born preterm have deficits to verbal working memory. Reduced verbal working memory for numbers and words using span tasks has been reported in VLBW children at 5.5 years of age (Böhm et al., 2004). C. S. H. Aarnoudse-Moens et al. (2012) reported that VPT children aged 4-12 years performed 0.3 SD below term controls on a verbal working memory task compared to full term controls. P. J. Anderson and Doyle (2004) similarly found that 8-year-old children born ELBW/VPT had

impaired verbal working memory ability. Other studies reporting on older preterm cohorts have reported similar findings (Luciana et al., 1999; Sansavini et al., 2007; S Vicari et al., 2004). On the other hand, both Ni et al. (2011) and Fraello et al. (2011) failed to detect group differences on backward digit span tasks between full term children and those born with VLBW at 6 and 12 years of age respectively.

Long term memory.

Fewer studies have examined long term memory abilities in children born preterm, and have generally used measures tapping episodic memory. Within the visual-spatial modality, 12 month old preterm infants have shown deficits in the reproduction of action sequences (Rose et al., 2009), with similar deficits persisting into late childhood (Rose et al., 2011), and children born with ELBW/VPT have demonstrated poorer location memory compared to term born controls at 6 years (I. S. Baron et al., 2012). In the verbal domain, children with VLBW have shown reduced list learning, delayed recall, inaccurate recall (Taylor et al., 2000) and visual recall (Taylor, Minich, Klein, & Hack, 2004) compared to term controls. Poorer everyday memory (Isaacs et al., 2000) has also been reported in preterm children with a mean age of 13 years. Finally, using a elicited imitation task to assess episodic memory de Haan, Bauer, Georgieff, and Nelson (2000) reported a linear relationship between the degree of prematurity and performance in 19 month old children born 27-34 weeks' GA, 35-37 weeks' GA, and 38-42 weeks' GA.

Overall, there is some evidence which suggests that prematurity has an impact on immediate memory, working memory, and long term memory and learning in both the verbal and visual modalities. This can have negative consequences on the development, academic and vocational success of the individual born preterm. Research investigating the underlying aetiology of these impairments is needed for the early detection of at-risk children.

Neonatal Brain Injury, Memory and Learning in Prematurity

Despite the recognition of brain abnormalities associated with prematurity, fewer studies have examined the association between neonatal brain injury and later memory and learning functioning in children born preterm. Woodward et al. (2005) examined whether early brain injury predicted performance on an object working memory task (a measure of visual-spatial immediate memory) in VPT children at 2 years. Poorer encoding on the task was related to qualitative measures of white matter injury identified on MRI at TEA. In a further follow-up of this group, C. A. C. Clark and Woodward (2010) investigated whether neonatal brain abnormalities predicted verbal and visual-spatial working memory at 6 years of age using the Digit Span and the Corsi Block tasks. The VPT cohort had reduced working memory in both the verbal and visual-spatial modalities, though significant results were only reported on the visual-spatial task. Verbal working memory impairments were largely confined to children with moderate-severe white matter abnormalities. In contrast, mild and moderate-severe white matter abnormalities predicted visual-spatial working memory impairment.

Studies investigating the relationship between neonatal brain injury and later memory and learning abilities in preterm cohorts highlight the potential role for the qualitative assessment of MRI brain scans in the neonatal period. Research investigating abnormalities in wider networks are needed to better understand the long term consequences of preterm birth on memory and learning outcome. The contribution of specific structural abnormalities to later memory and learning abilities is equally important and together, will improve our understanding of the underlying mechanisms that subserve memory and learning impairments in preterm children and aide the development of intervention.

Chapter Summary

Memory can be conceptualised into components of immediate memory, working memory, long term memory and learning in both the verbal and visual-spatial modalities. Memory was originally argued to be a unitary construct (Atkinson & Shiffrin, 1968), however, substantial evidence supports the notion that memory is a complex system involving relatively independent yet related subdivisions.

Immediate/working memory functioning has been reported in healthy children from 6 years of age, with sizable expansion in functional capacity from the early school years. Anatomically, recruitment of the PFC in immediate/working memory appears to become more efficient with age. With regards to long-term memory development, there is some evidence for episodic memory in toddlers, suggesting it may present from a young age. Although most development occurs before 7 years of age, explicit memory has consistently been found to improve into adolescences and despite previous conceptions, there is evidence for some improvement of implicit memory across development. The medial temporal and prefrontal cortices have been implicated with explicit and implicit memory development respectively.

Evidence suggests that preterm children experience impairments to immediate memory, working memory, and long-term memory in both the verbal and visual-spatial modalities. The few studies which have examined the association between neonatal brain injury and later memory and learning functioning in children born preterm support this relationship.

Chapter 3: The Hippocampal Formation

The hippocampal formation has a well-established and central role in memory and learning (Moscovitch et al., 2005; Nadel et al., 2000; Zola & Squire, 2000). Damage to this region early in life impacts the ability to learn and acquire information. This has subsequent effects on neurocognitive outcomes, academic and vocational success later in life. Given evidence for memory and learning difficulties in children born preterm, this section will focus on the hippocampal formations, their growth and development, and the effects of prematurity on this structure. Throughout this chapter, the hippocampal formation will be referred to in singular though it is recognized that one hippocampal formation exits in each hemisphere.

The Hippocampal Formation

The hippocampal formation is an important component of the limbic system. The limbic system includes diverse cortical and subcortical structures located in the medial and ventral areas of the cerebral hemispheres (Blumenfeld, 2002). Limbic functions can be categorized into four basic functions; 1) olfaction, 2) memory, 3) emotion, and 4) homeostatic functions. Numerous limbic structures contribute to each of these important functions and form a complex network. Structures other than the hippocampal formation which support memory functioning, including the thalamus, basal ganglia, mammillary bodies, and cortical structures will be briefly mentioned.

Broca (1878) divided the limbic lobe into the limbic gyrus and the intralimbic gyrus. This discussion will focus on the subdivisions of the limbic gyrus, the cingulate gyrus, and the parahippocampal gyrus. The parahippocampal gyrus can be divided into two components; 1) the posterior segment, which consists of the subiculum in the superior surface (separated from the hippocampus by the hippocampal sulcus), and 2) the anterior segment or piriform lobe, which comprises the uncus and entorhinal cortex (Duvernoy, 2005).

The hippocampal formation lies in the medial and dorsal continuation of the parahippocampal gyrus, in the medial temporal lobe (Blumenfeld, 2002). It is comprised of three components. The first component is the *hippocampus proper (or hippocampus)*, which includes the cornu Ammonis and the dentate gyrus. The cornu Ammonis can be divided into six layers; the alveus, stratum oriens, stratum pyramidale, stratum radiatum, stratum lacunosum, and stratum moleculare (Duvernoy, 2005). Additionally, the cornu Ammonis has been described as having four fields names; CA1-CA4 (Lorente de Nó, 1934). The dentate gyrus is less complex than the cornu Ammonis in structure. It is separated from CA1-CA3 by the hippocampal sulcus, but encloses the CA4 segment of the cornu Ammonis. The second component of the hippocampal formation is the *subiculum*, or the "bed" of the hippocampus, which is separated from the cornu Ammonis by the end of the stratum radiatum of region CA1. Finally, the third component is the *hippocampal complex,* which includes the anterior segment of the parahippocampal region (i.e.entorhinal, perirhinal and parahippocampal cortices) (Amaral & Lavenex, 2007; Moscovitch et al., 2005) (figure 5).

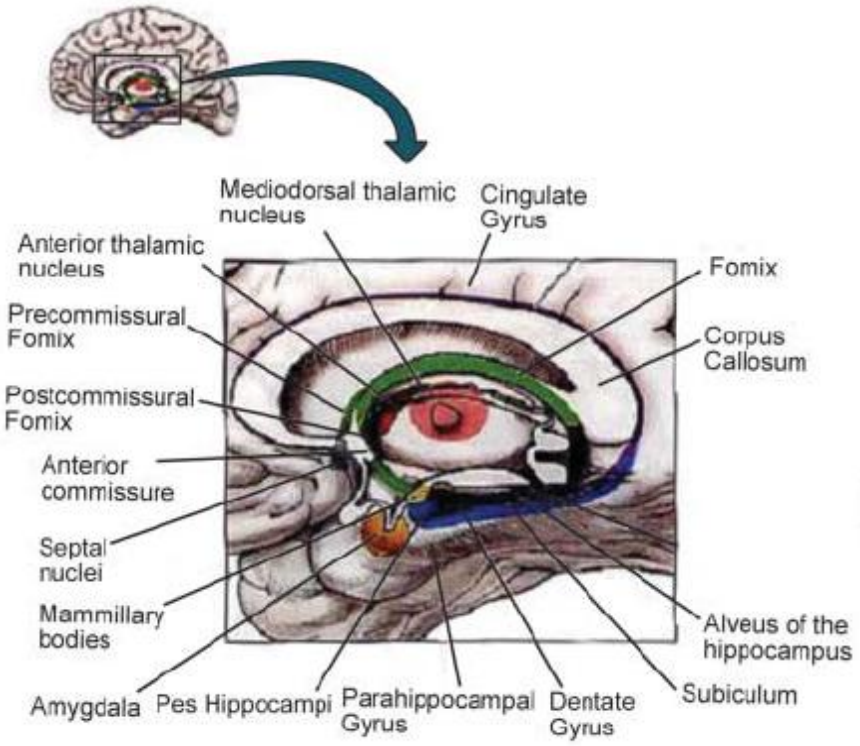

Figure 5. Saggital section of the medial temporal lobe structures. Adapted by Blumenfeld (2002).

According to anatomical criteria, the hippocampal formation can be divided into three sections: 1) the anterior part, or *head*, 2) the middle part, or *body*, and 3) the posterior part, or *tail* (Duvernoy, 2005). It has an overall length of approximately 4-4.5 cm; the body is on average 1 cm wide and the head is 1.5-2 cm wide (Dejerine, 1980). Unlike the six-layered neocortex, which comprises approximately 95% of the cortex in humans, the hippocampal formation has only three layers and is referred to as the archicortex.

The circuitry of the hippocampal formation has been extensively investigated because of its vital role in memory (Figure 6). Nerve fibers carrying information arising from neocortical areas converge to the entorhinal area, through the hippocampal formation, and back to the entorhinal cortex (Blumenfeld, 2002; Duvernoy, 2005). The entorhinal cortex serves as the major input and output relay between association cortices and the hippocampal formation (Zola & Squire, 2000). Inputs to the hippocampal formation arrive from the frontal, parieto-occipital, and temporal lobes, however, storage is believed to occur in the neocortex (Duvernoy, 2005). As a result, an important hippocampal projection is from the subiculum to the entorhinal cortex, and back to the association cortices (H. J. Markowitsch, 1995; H.J. Markowitsch, 1995).

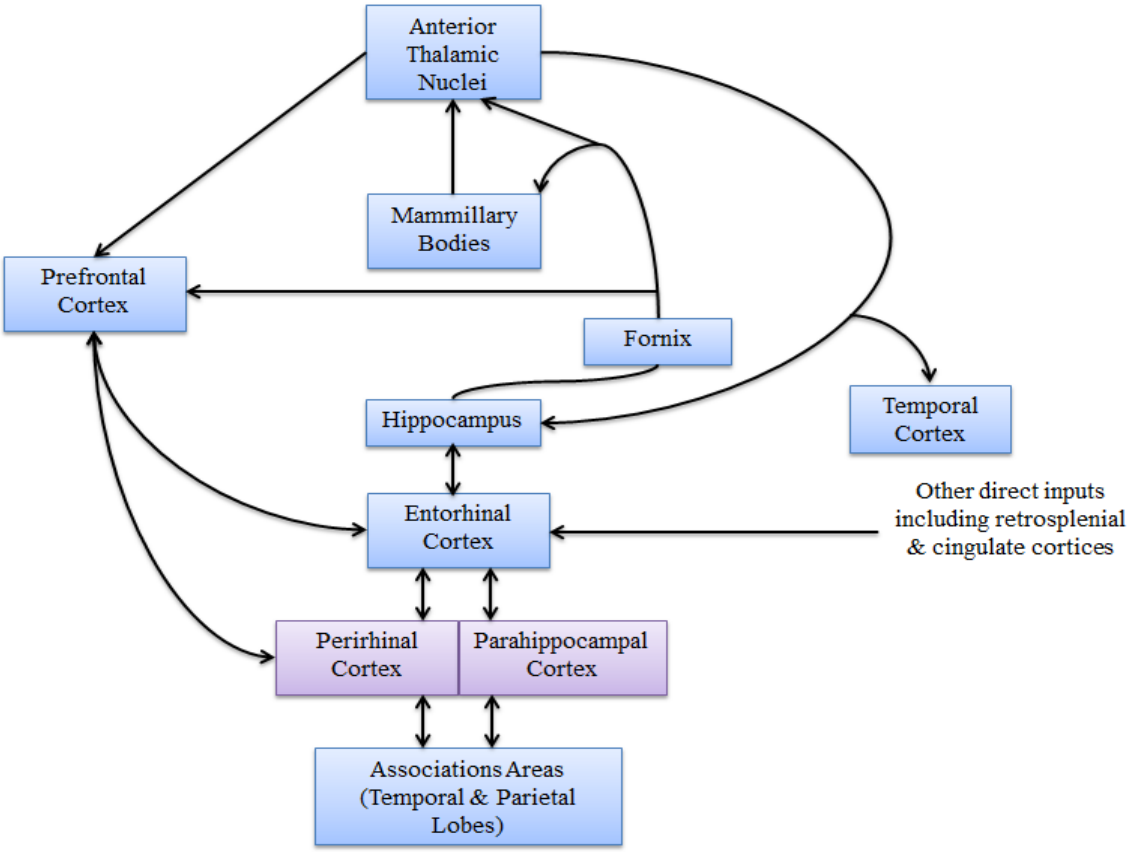

Figure 6. The extended hippocampal system showing connections between the medial temporal lobe structures and thalamic nuclei and frontal lobes. Connections represent the principal pathways that are involved with encoding of episodic information and underlie recollection. Those involving the perirhinal and parahippocampal cortices represent particularly important connections within the network. Adapted from Aggleton and Brown (1999).

In vivo measurement and volumetric analyses of the brain utilising MRI have become key components of neuroimaging research. This technique has become a popular method to study the growth and development of the hippocampal formation, and assess the impact of disease processes and conditions. Manual delineation, semi-automated and automated methods are used to outline the hippocampal formation. Semi-automated methods require a human operator to firstly introduce landmarks, seedpoints or bounding

boxes (Chupin et al., 2007; Perez de Alego et al., 2003), whereas fully automated methods are based on statistical-based models and atlas registration (Barnes et al., 2007; Carmichael at al., 2005; Svarer et al., 2005). Other methods can also be combined with atlas registration, such as intensity-based voxel-classification or learning-based optimization (Hammers et al., 2007; Zhou & Rajapakse, 2005). Manual delineation is recognized as the 'gold standard' and is most commonly conducted in the coronal plane (Konrad, Ukas, Nebel, Arolt, Toga & Narr, 2009).

A standard protocol for the delineation of the hippocampal formation does not exist. As a result, there is considerable variation among research studies. Differences in protocols can be attributed to a number of discrepancies in acquisition, post-acquisition processing, and a wide variety of definitions and landmarks for anatomical guidelines (Geuze, Vermetten, & Bremner, 2005). In their review of 423 studies, Geuze et al. (2005) found that approximately 60 different anatomical guidelines were used for hippocampal segmentation. Konrad et al. (2009) reported that the major points of discrepancy in anatomical boundaries between studies are; 1) the inclusion/exclusion of the alveus and fimbria (i.e. hippocampal white matter), 2) the definition of the anterior hippocampal-amygdala border, 3) the definition of the posterior border and amount of hippocampal tail included, 4) the boundary of the inferior medial border, and 5) the use of arbitrary lines to aide delineation guidelines. This has resulted in inconsistent findings across laboratories and conditions (Konrad et al., 2009; Van Leemput, Bakkour, Benner, Wiggins, Wald, Augustinack et al., 2009).

In addition to the hippocampal formation, Aggleton and Brown (1999) outline other structures that are important for memory function. Specifically, the anterior thalamic nuclei receive direct projections from the hippocampus via the fornix and indirect hippocampal projections via the mammillary bodies and mamillo-thalamic tract. This extended hippocampal system is essential for effective encoding and retrieval of episodic information, and damage to these structures can result in anterograde amnesia (i.e. an inability to create new episodic memories from the time of injury) (Aggleton & Brown, 1999; Moscovitch et al.,

2005). Although the basal ganglia have long been implicated with motor function, evidence supports its role in memory and learning, where simultaneous activation of its structures and the medial temporal lobe systems have been identified during learning tasks (Packard & Knowlton, 2002; Seger, 2006).

Prenatal and Postnatal Development of the Hippocampal Formation

The hippocampal formation undergoes a period of rapid growth and development prenatally. The hippocampal sulcus is first visible in the prenatal period, at 10 weeks' gestation. By 18-20 weeks' gestation, the dentate gyrus and CA regions have folded into the medial temporal lobe and the hippocampal sulcus obtains a horizontal orientation (Okada et al., 2003). At this point, the hippocampal formation has most of its adult characteristics, and at 24-25 weeks' GA the layers of the hippocampus are formed (Seress, 2001). The hippocampal cytoarchitecture, or cellular composition, is well formed at 34 weeks' GA (S. E. Arnold & J. Q. Trojanowski, 1996).

Some morphological abnormalities of the hippocampal formation are believed to occur during this period of early prenatal development, such as incomplete in-folding (or inversion) of the structure (Kier, Kim, Fulbright, & Bronen, 1997). This is found in approximately 19% of the general population (Bajic, Ewald, & Raininko, 2010). Abnormal hippocampal morphology may also result from abnormalities of corticogenesis, including disruption of cortical-hippocampal connections (Bernasconi, Kinay, Andermann, Antel, & Bernasconi, 2005). Indeed, some of the first hippocampal connections are those within the entorhinal cortex, which connect the hippocampus to the cortex (Hevner & Kinney, 1996). It is possible that early disruptions to cortical-hippocampal connections subserve impairments to memory and learning in preterm children.

Volumetric analyses of the hippocampal formation at distinct time points have been conducted in healthy cohorts post-mortem and in vivo. Kretschmann, Kammradt, Krauthausen, Sauer, and Wingert (1986) conducted the most influential post-mortem study

which examined normal male participants from mid-gestation to 99 years of age. Term infant hippocampi were on average 1.5 cm^3 and approximately 3 cm^3 by adulthood. In contrast to post-mortem estimates, in vivo measurement tends to underestimate hippocampal volume due to varying segmentation protocols. Furthermore, rightward asymmetry has been reported in children (Giedd et al., 1996; Pfluger et al., 1999; Utsunomiya, Takano, Okazaki, & Mitsudome, 1999) and adults (Uematsu et al., 2012; Watson et al., 1992). For example, D. K. Thompson et al. (2008) found that right hippocampal volumes were on average 1.19 cm^3, and left hippocampal volumes were 1.16 cm^3 in healthy neonates, and Pfluger et al. (1999) reported that volumes ranged from 1.04-3.47 cm^3 for the right hippocampus, and 1.09-3.05 cm^3 for the left in children aged 1 month to 15 years of age.

A handful of studies have investigated the volumetric trajectory of the hippocampus. These provide additional information regarding the way neural and function development occurs over time. Kretschmann et al. (1986) demonstrated that hippocampal volumes increased significantly between one and two years. Volumetric MRI techniques also show increases in hippocampal volumes during these early years. Utsunomiya et al. (1999) reported maximum hippocampal growth between one and two months, with continued rapid growth up to two years of age and slow growth thereafter in individuals aged 3 weeks to 14 years. Similarly, Knickmeyer et al. (2008) reported a 13% increase in hippocampal volume between 1 and 2 years of age, though there was relatively little growth after controlling for total brain volume.

Different regions of the hippocampus have been shown to grow at different rates. Between ages 4-5 and 25 years, the posterior sub-regions (i.e. the body and tail of the hippocampus) appear to show enlargement whereas the anterior regions (i.e. the head portion) decrease in volume (N. Gogtay et al., 2006; Insausti, Cebada-Sanchez, & Marcos, 2010). N. Gogtay et al. (2006) suggested that these distinct developmental trajectories of hippocampal sub-regions may correspond with differences in functional development.

The volumetric trajectory of the hippocampal formation has also been investigated with regards to gender, although studies show inconsistent findings. Giedd et al. (1996) demonstrated that right hippocampal volume correlated with age in females, but that the left hippocampal volume did not increase with age in males or females between 4 and 18 years. Most recently, Uematsu et al. (2012) showed significant non-linear age-related hippocampal volume changes during the first few years of life, regardless of gender and after adjustment for intracranial volume in a cohort of healthy subjects aged 1 month to 25 years of age. Additionally, rightward laterality was evident in both males and females (Uematsu et al., 2012). The robust growth of the hippocampal formation prenatally and during infancy highlights the potential vulnerability of neural networks in this period.

Adult hippocampal morphology is thought to be reached at approximately 5 years of age (Insausti et al., 2010), although further organization, dendritic branching and myelination continues into adolescence (Insausti et al., 2010). Uematsu et al. (2012) reported peak hippocampal volume at 9-11 years of age, suggesting that critical periods for neural development are those occurring during infancy and preadolescence. Hippocampal volume shows progressive loss with age in healthy adults. For example, Jernigan et al. (2001) reported that in normal controls aged 30 to 99 years, age-related losses in the hippocampus were significantly accelerated relative to grey matter losses in other brain regions. Moreover, it was estimated that on average, there is a 35% volume loss in the hippocampus between the ages of 30 and 90.

The Hippocampal Formation, Memory and Learning

Lesion and surgical studies provide strong evidence for the role of the hippocampal formation in explicit memory and learning. Since the classic works of Penfield and Milner (1958) and Scoville and Milner (1957), it has been established that bilateral lesions to the medial temporal lobes that include the hippocampi, results in profound anterograde amnesia characterized by impaired long term memory, with preserved intelligence, perception, short-term memory, and older autobiographical and semantic memories

(Corkin, 1984). In addition, patients have been reported to have temporally graded retrograde amnesia (i.e. the inability to recall events prior to brain injury) from the point of surgery. An example of such impairment was recorded in patient RB (Zola-Morgan, Squire, & Amaral, 1986), who experienced a cardiac arrest and subsequent ischemic episode. RB developed marked anterograde amnesia, temporally graded retrograde amnesia of 1-2 years, and showed no signs of other cognitive impairment. Neuropathological analyses indicated that RB had sustained bilateral lesions restricted to the CA1 regions of the hippocampi.

Following the work of Zola-Morgan et al. (1986), Rempel-Clower, Zola, Squire, and Amaral (1996) investigated neuropsychological and neuropathological findings in three cases with differing degrees of bilateral medial temporal lobe damage. The authors reported three key points: 1) bilateral damage confined primarily to the CA1 region was sufficient to produce moderately severe anterograde amnesia, 2) bilateral damage that extended further than CA1, but still limited to the hippocampal formation, produced more severe anterograde amnesia, and 3) bilateral damage limited to CA1 caused minimal retrograde amnesia (1 or 2 years), whereas damage to the hippocampal formation resulted in extensive, temporally graded retrograde amnesia of up to 15 years or more.

Historically, the aforementioned pattern of deficits has been interpreted in terms of the standard consolidation theory (SCT) (Burnham, 1904; Muller & Pilzecker, 1900). This theory states that the formation of durable long term memories, originating from transient short-term memories, is part of a time-dependent process (Hebb, 1949). It argues that retention and retrieval of long term memories initially rely on the hippocampus, but become independent of it as memories consolidate in extra-hippocampal structures (presumably the neocortex). Furthermore, a process of prolonged (or system-level) consolidation is thought to occur, which may last for months or decades (Dudai, 2004; Frankland & Bontempi, 2005). The SCT also proposes that memories which are consolidated in extra-hippocampal regions retain the same characteristics as when they were initially represented in the hippocampus.

A limitation of the SCT, however, is that it is restricted to explicit memory, and cannot adequately account for the presence for retrograde amnesia following hippocampal injury (Winocur, Moscovitch, & Bontempi, 2010).

In recent years, experimental findings in both human and animal studies have not always supported the SCT (R. E. Clark, Broadbent, & Squire, 2005; Viskontas, McAndrews, & Moscovitch, 2000; Winocur, Moscovitch, Caruana, & Binns, 2005). To account for these inconsistencies, Nadel and Moscovitch (1997) proposed a multiple trace theory (MTT) of memory. According to the MTT, the hippocampal complex rapidly encodes all information that is consciously apprehended (Moscovitch, 1992), and binds neocortical neurons that represent specific experiences or episodes into a memory trace. This information is encoded into a broad network of neurons within the hippocampal complex that act as a 'pointer' or 'index' to the neurons representing the attended information (Teyler & DiScenna, 1986). Consequently, a memory trace of an episode contains a linked collection of neocortical, hippocampal and medial temporal lobe neurons.

In contrast to the SCT, the MTT does not propose a prolonged consolidation process. Rather, it suggests that each time a memory is retrieved the hippocampus re-codes the memory automatically along with the context in which it was retrieved. As such, old episodic memories are represented by stronger or more hippocampal/medial temporal lobe-neocortical traces than are new episodic memories. The neocortex mediates similar processes for abstracting the semantic aspects of episodic memory. Thus, the hippocampus is always required for representing detailed episodic memories, and facilitates the forming (in neocortical regions) of semantic memories related to the episodic event (McClelland, McNaughton, & O'Reilly, 1995).

Most recently, Winocur et al. (2010) proposed an alternative view of memory consolidation based on the 'transformation hypothesis'. Unlike the SCT, which suggests that the initially formed memory is the same as the consolidated version, Winocur et al. (2010) argue that memory characteristics change with time (i.e. a transformation process). The

framework is based on three key elements, the first two elements being derived from the MTT: 1) the originally formed memory is assumed to be episodic and contextually bound, and relies on the hippocampus while it retains its episodic features, 2) with time and experience, this memory promotes the development of a schematic version of the original memory in the neocortex, which maintains some of its characters and meaning but few contextual details, and 3) a dynamic interplay exists between these two forms of memory. As such, memories are transformed from context-dependent or episodic and represented in the hippocampus, to context-independent or semantic and represented in the neocortex. Whereas the former version of memory is lost after hippocampal damage, the latter is preserved, accounting for the temporal gradients present in retrograde amnesia. Animal studies provide evidence for the transformation view (Wiltgen & Silva, 2007; Winocur, Moscovitch, & Sekeres, 2007).

The memory models described above demonstrate the general consensus that the hippocampal formation supports the acquisition of episodic and semantic memories. Nevertheless, there is continuing debate regarding the retrieval of episodic and sematic memories, and in particular, whether the hippocampus plays a role in either or both of these retrieval processes. Generally, neuropsychological investigations from patients with hippocampal damage have supported the notion that episodic and semantic memory retrieval is dissociable, with the former but not the latter, being mediated by the hippocampus (Hoscheidt, Nadel, Payne, & Ryan, 2010; Moscovitch et al., 2005). Episodic memory retrieval was thought to rely primarily on the medial temporal lobe, whereas semantic memory retrieval was argued to utilise the lateral and anterior temporal cortex and ventro-lateral prefrontal cortex (Graham, Patterson, & Hodges, 1999; Martin & Chao, 2001; Thompson-Schill, 2003). Whilst more recent accounts by Squire, Stark, and Clark (2004) acknowledge the possibility of a division of labor within the medial temporal lobe, they argue that the hippocampus is implicated in both semantic and episodic retrieval.

Most research has focused on the relationship between hippocampal function and episodic memory retrieval (Gilboa et al., 2004; Graham, Lee, Brett, & Patterson, 2003; Hoscheidt et al., 2010; Maguire, 2001; Moscovitch et al., 2005; Rekkas & Constable, 2005; Stark & Squire, 2000). Imaging typically shows activation in the left and/or right hippocampus when episodic memory retrieval tasks are administered and compared to baseline tasks, such as reading simple sentences or sentences describing personal semantics (Moscovitch et al., 2005). Furthermore, episodic memory for verbal information (e.g. recognition of words) is considered to be mediated by left temporal lobe structures (Nyberg, Mclntosh, Houle, Nilsson, & Tulving, 1996) and non-verbal or spatial memory by the right temporal lobe structures (Lee & Rudebeck, 2010) in normal adults.

In contrast, there is inconsistency between patient cohorts and neuroimaging data for the involvement of the hippocampus during semantic memory retrieval (Manns, Hopkins, & Squire, 2003; Ryan, Hoscheidt, & Nadel, 2008). At least some amnesics have been found to show deficits to semantic memory retrieval for well-established world knowledge, especially when damage extends into other medial temporal lobe regions (Luo & Niki, 2002; Squire et al., 2004). On the other hand, neuroimaging studies of healthy individuals consistently show hippocampal activation during the retrieval of different types of well-established semantic knowledge (Bernard et al., 2004; Henke et al., 2003; Ryan et al., 2008; Ryan, Lin, Ketcham, & Nadel, 2010). Despite these findings, recent neuroimaging studies show that greater hippocampal activation occurs in conditions that involve a spatial rather than non-spatial context, in both episodic and semantic conditions (Eichenbaum & Cohen, 2001; Hoscheidt et al., 2010; Ryan et al., 2010; Winocur et al., 2010). Thus, the notion of distinct dissociations between episodic and semantic memory systems may be over simplistic in adults.

The observation that patients with selective and bilateral lesions to the medial temporal lobe have intact short-term memory and impaired long term memory has supported the distinction between the two memory systems. As mentioned in chapter 2,

short-term memory has been extended into the notion of immediate memory and working memory systems, and these functions have been implicated with the prefrontal and parietal cortices. Challenging this view, however, are recent behavioral, neuroimaging, and electrophysiological data which suggest that common functional and anatomical mechanisms may be shared by both short-term and long term memory systems (Cashdollar et al., 2009; Hannula, Tranel, & Cohen, 2006; I.R. Olson, Moore, Stark, & Chatterjee, 2006; I. R. Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Piekema et al., 2006).

Over the past decade, studies have demonstrated that in addition to its prominent role in long term memory, the hippocampus may also be required in certain aspects of immediate/working memory (Cashdollar, Duncan, & Duzel, 2011). The role of the hippocampus in relational memory (i.e. connecting or associating multiple aspects of stimulus information) has been of recent interest and investigation. Evidence supporting this suggestion comes from research examining immediate/working memory for visual-spatial relationships (Hannula et al., 2006; I.R. Olson et al., 2006; I. R. Olson et al., 2006) and topographical information (i.e. recalling where a location is) (Hartley et al., 2007). Amnestic patients with selective hippocampal atrophy have demonstrated immediate/working memory deficits for the visual-spatial configuration of objects over short-delay periods (Hannula et al., 2006; I.R. Olson et al., 2006). For example, following a brief presentation of a scene (even of just a few seconds), these patients are unable to hold in mind the configural relationships between a number of objects within the scene.

Hippocampal involvement in the active immediate/working memory maintenance of relational memory has also been demonstrated at a functional level. Using fMRI, Piekema et al. (2006) investigated hippocampal involvement in the active maintenance of visual-spatial and non-visual-spatial associations in 18 healthy university participants (mean age 25.5 years). Participants performed a delayed-matched-to-sample task which involved the maintenance of object-location associations, colour-number associations, single locations, or single colours. Findings showed right hippocampal activation during object-location

associations, but failed to find hippocampal activation for the maintenance of colour-number associations or single items. The authors suggested that processing of colour-number associations may occur at an earlier stage and therefore, does not need to be bound together for long term memory storage.

As such, it is evident that lesions selective to the hippocampus can result in deficits to aspects of immediate/working memory abilities. The majority of earlier research generally used very simplistic and overlearned clinical tests of immediate/working memory, such as the use of words or digits, in the absence of any relational memory manipulation (see Ranganath & Blumenfeld, 2005 for a review). This may explain why the notion that the hippocampus is not necessarily involved in immediate/working memory functioning has been so enduring.

The Hippocampal Formation and Memory and Learning in Children

Developmental studies following selective damage to the hippocampus provide insight into the neural development underpinning human memory and learning. In contrast to adult studies, there appears to be a greater distinction between hippocampal involvement in episodic and semantic memory function in children. De Haan, Mishkin, Baldeweg, and Vargha-Khadem (2006) argue that the medial temporal lobe supports episodic memory during the first postnatal months and memory retrieval within the first year. They also suggest that normal memory development is sequential; a form of semantic-like memory emerges first, whereas episodic memory development co-occurs with the progressive development of the hippocampus later on. Finally, the authors propose that early bilateral damage to the hippocampus disrupts this pattern of memory development, as there is relatively little developmental plasticity for episodic memory. As such, skills cannot grow past the phase of sematic memories.

Vargha-Khadem et al. (1997) investigated the effects of hippocampal pathology sustained at birth on later episodic and semantic memory abilities in three patients aged 14,

19 and 22 years. In each case, hippocampal damage and memory impairment were likely due to perinatal hypoxic-ischemia. Volumetric estimates of the hippocampi showed bilateral reductions of 40-61% in comparison to the mean value of healthy individuals. Whilst neuropsychological assessment revealed a severe loss of episodic memory in each case, speech, reading, writing and spelling abilities were at a level commensurate with verbal intelligence quotients. This pattern of memory impairment was later termed 'developmental amnesia' (DA) (Gadian et al., 2000). Findings from this study support the argument that semantic memory formation is possible after early damage that is restricted to the hippocampus (De Haan et al., 2006).

A later study by Vargha-Khadem et al. (2003) demonstrated that the age at which DA occurs (i.e. less than 1 year of age compared to 6-14 years) does not affect cognitive outcome. Similar findings were reported by Brizzolara, Casalini, Montanaro, and Posteraro (2003) and Bindschaedler, Peter-Favre, Maeder, Hirsbrunner, and Clarke (2011), who showed that anterograde amnesia following bilateral hippocampal damage occurs in the context of preserved semantic acquisition in children aged 6 and 8 years of age respectively. Furthermore, the reverse dissociation (i.e. impaired semantic memory acquisition and preserved episodic memory) was reported by Temple and Richardson (2004). These studies suggest that semantic and episodic memory systems have the capacity to develop separately in childhood.

The difference in memory and learning outcomes following hippocampal damage in children and adults possibly reflects the prospect for neural plasticity, and the continued growth of the hippocampus and related structures into adolescence (Insausti et al., 2010). This finding is encouraging, as children who sustain early hippocampal damage may escape the level of impairment endured by their adult counterparts.

The Hippocampal Formation and Prematurity

Alterations to hippocampal development are likely to occur when growth is most prolific, which corresponds to the period when preterm birth occurs. Consistent with this premise, Fuller, Guthrie, and Alvord Jr (1983) reported that at autopsy, 67% of their sample of preterm infant brains showed hippocampal abnormalities. The hippocampus is especially susceptible to many of the stressors and medical complications associated with VPT birth, including infection, hypoxia-ischemia, poor nutrition, hypoglycemia, hypothyroidism, and stress hormones (Gadian et al., 2000; E. B. Isaacs et al., 2000; Khwaja & Volpe, 2008; Sizonenko et al., 2006). These complications can result in diffuse white matter damage and reductions in gray matter volumes (Inder et al., 2005; Volpe, 2009), including pyramidal cell death, a slowing of neural migration (Rees, Breen, Loeliger, McCrabb, & Harding, 1999) and neuronal injury (Volpe, 2000) to the hippocampus. D. K. Thompson et al. (2008) showed that white matter injury and postnatal glucocorticoid exposure were the factors most likely to predict reduced hippocampal volumes in VPT infants.

As previously mentioned, inversion of the hippocampal formation should be completed by 21 weeks' gestation. One of the effects of preterm birth appears to be a high rate of incomplete hippocampal inversion. Bajic et al. (2010) examined hippocampal development in three groups of preterm neonates aged 23-24 weeks' GA, 25-28 weeks' GA, and 29-36 weeks' GA. Incomplete hippocampal inversion was found in 50%, 24% and 14% of neonatal groups respectively, with bilateral changes most common in the youngest age group. Recently, Deanne K. Thompson et al. (2013) investigated hippocampal shape in VPT infants and similarly found VPT infant's hippocampi were less infolded compared to term born controls. Additionally, white matter injury and postnatal corticosteroid administration were associated with straighter hippocampi. Nevertheless, the clinical significance of persistent changes to hippocampal shape in preterm cohorts remains unclear (Bajic et al., 2010; Deanne K. Thompson et al., 2013).

Volume reduction of the hippocampus appears to be another consequence of preterm birth. Most studies report bilateral hippocampal reductions in preterm cohorts compared to full term across developmental stages controls (Beauchamp et al., 2008; Gimenéz et al., 2004; E. B. Isaacs et al., 2000; E. B. Isaacs et al., 2003; Lawrence et al., 2010; Lodygensky et al., 2008; Nosarti et al., 2002; Peterson et al., 2000). However, select studies have reported changes to the left (Gimenez et al., 2008) or right (D. K. Thompson et al., 2008) hippocampi individually, or have failed to find significant differences (E. B. Isaacs, Edmonds, Chong, Morley, & Gadian, 2004; Lodygensky et al., 2005). Inconsistencies in findings may reflect the boundary and segmentation difficulties discussed earlier.

Preterm birth can reduce the size of the brain in general. In a recent meta-analysis, de Kieviet, van Elburg, Lafeber, and Oosterlaan (2012) investigated brain development in VPT/VLBW children and adolescents. The authors found that total brain volume was significantly reduced when compared with term born controls. On average, brain volume was more than 1.5 SD below that of term born peers. Consequently, reduced hippocampal volumes in preterm children may reflect an overall smaller brain size.

As noted above however, the hippocampal formation is particularly susceptible to inflammation and hypoxia. As a result, disproportionate reductions of the hippocampi may be expected in preterm children. Most of the aforementioned studies investigating hippocampal volume in preterm children found that these reductions persist after secondary analyses controlling for total brain volume (Gimenez et al., 2008; E. B. Isaacs et al., 2000; Nosarti et al., 2002; Peterson et al., 2000). For example, Nosarti et al. (2002) reported that in their sample of adolescents aged 14-15 years total brain volume was reduced by 6.0% when compared to term controls, and hippocampal volume reductions of 15.6% (right) and a 12.1% (left) persisted after controlling for total brain volume. Gimenéz et al. (2004) reported that only left hippocampal volume (16.7%) remained disproportionately reduced once total brain volume (a reduction of 8% compared to term controls) was controlled for in a sample of VPT 10-18 year-olds. Additionally, hippocampal

volume reductions reported by D. K. Thompson et al. (2008) in VPT infants did not remain after controlling for head size, and percentage reductions in preterm hippocampi (3.4%) were less than for total brain volume (4.7%).

Reduced total brain volume has been found to remain constant during childhood and early adolescence despite continued growth of brain volume during this time (de Kieviet et al., 2012). These findings suggest that the growth curve of brain development between childhood and adolescence is comparable for children born VPT/VLBW and at term, and therefore, complications associated with prematurity may have lasting implications for the total brain and its structures.

A number of studies have investigated hippocampal volume and its relationship to general intellectual abilities and neurodevelopmental outcomes in preterm populations. Reduced hippocampal volume in VPT neonates has been associated with poorer performance on the Mental Development and Psychomotor Development Indices of the Bayley Scale of Infant Development (BSID-II) at 2 years' corrected age (Thompson et al., 2008). Reduced hippocampal volume has also been associated with poorer full scale IQ in VPT children at 8 years of age (Lodygensky et al., 2005; Peterson et al., 2000). Moreover, left hippocampal volume reduction at 15-16 years of age has been associated with low IQ in adolescents born with VLBW (Abernethy, Palaniappan, & Cooke, 2002). Isaacs and colleagues (2004) also reported a relationship between reduced hippocampal volume and poorer Performance IQ in a cohort of adolescents born VPT and/or VLBW. In contrast, Abernethy and colleagues (2004) found little evidence for a relationship between hippocampal volume in VPT children at 7 years, and performance on the Movement ABC or full scale IQ.

Fewer studies have specifically examined the relationship between hippocampal volume and memory and learning in VPT children. This is surprising given evidence for the important role of the hippocampus in memory and learning (Moscovitch & Umilta, 1990; Cabeza & Nyberg, 2000; Nadel et al., 2000). Beauchamp et al. (2008) found that reduced

neonatal hippocampal volume was associated with poorer visual-spatial working memory on a delayed alternation task in VPT 2 year olds. Additionally, reduced hippocampal volume in adolescents aged 13 years who were born VPT/VLBW has been associated with poorer everyday memory (Isaacs et al., 2000; 2003), and left hippocampal volume reduction in those born VPT has been correlated with reduced verbal episodic memory and learning performances at age 10-18 years (Giménez et al., 2004).

In summary, children born preterm are at high risk of brain injury, which includes damage to the hippocampal formation. While these children demonstrate impairments in multiple components of memory, few studies have investigated the relationship with underlying hippocampal pathology. This relationship requires further investigation, especially given the importance of these skills for academic progress and success (Bull, Espy, & Wiebe, 2008; Hornby & Woodward, 2009; Woodward et al., 2009), and the possibility for intervening early in life.

Chapter Summary

The hippocampal formation comprises the hippocampus proper, subiculum, and the hippocampal complex. The hippocampus can be divided into the head, tail and body, and has complex circuitry involving the medial temporal lobe structures, thalamic nuclei and frontal lobes. In vivo measurement and subsequent volumetric analysis utilising MRI have become key components into hippocampal research, with manual delineation considered the gold standard technique.

The hippocampal formation undergoes rapid development prenatally and within the first 2 years of life. Studies investigating the volumetric trajectory of the hippocampal formation also support increases in volume during these early years. Although adult morphology is thought to be resembled early in childhood, continued development occurs into adolescence.

Bilateral lesions to the hippocampal formation can result in profound anterograde amnesia and temporally graded retrograde amnesia, with preserved intelligence, perception and semantic memories. The hippocampal formation has been associated with the acquisition of episodic and semantic memories, and to a lesser extent, with the retrieval of these memory processes. In contrast to adult studies, there appears to be a greater distinction between hippocampal involvement in episodic and semantic memory function in children. Furthermore, recent evidence implicates the hippocampal formations with immediate/working memory, challenging the long-held view of its exclusive role with long-term memory functioning.

Reduced hippocampal volumes have been reported in children and adolescents born preterm. Moreover, preliminary evidence suggests that reduced hippocampal volume is associated with poorer memory and learning abilities in preterm children. Further investigation is needed to clarify the nature of this relationship utilising multiple components of memory and learning in preterm cohorts.

Chapter 4: Rationale and Hypotheses

Rationale

This study is part of the 7-year follow-up of the Victorian Infant Brain Study (VIBeS); a perspective, longitudinal study of children born VPT and full term. These children were recruited shortly after birth and have had brain MRI scans at TEA (40 weeks' gestation ± 2 weeks). As outlined in the previous chapters, preterm birth is associated with widespread cognitive deficits and structural brain abnormalities that persist throughout childhood and adolescence. As such, research investigating cognitive impairment in relation to underlying neuropathology may be informative for understanding the long-term outcomes of children born preterm. Although memory and learning impairments have been recognised in preterm populations, the importance of these skills for educational development and achievement makes this an important area for further consideration. Moreover, understanding how memory and learning impairments are related to underlying neuropathology associated with VPT birth will provide further insight into the nature of these difficulties. The hippocampal formation has long been associated with memory and learning functioning, and further research examining this relationship in VPT children is needed. Prenatal injury has the capacity to compromise the developmental trajectory of brain development, including the hippocampi; however, research has not yet investigated this notion in preterm populations. Given that VPT birth occurs during a period of significant growth and development, this would seem an important area of investigation.

The current study aims to address the above issues across three papers. Overall, this will provide an improved understanding of memory and learning in VPT children, and the neurological abnormalities associated with difficulties in this domain.

Aims and Hypotheses

Paper 1.

This paper aims to characterize memory and learning in both the verbal and visual domains in 7 year old children born VPT compared with full-term controls, and secondly, to evaluate the association between brain abnormalities on neonatal MRI and memory and learning functioning at 7 years of age in VPT children.

1) It is hypothesized that in comparison to full-term children, VPT children will display generalised memory and learning difficulties in both verbal and visual modalities.
2) It is hypothesized that brain abnormalities on neonatal MRI will predict memory and learning impairments in VPT children.

Paper 2.

The second paper will compare hippocampal formation volume between VPT and term controls at 7 years. It will also evaluate the association between hippocampal volume and memory and learning functioning in the VPT group.

1) It is predicted that both left and right hippocampal volumes will be reduced in VPT children when compared to those of term-born controls.
2) It is hypothesized that reduced hippocampal volumes will be predictive of memory and learning impairments in the VPT cohort.

Paper 3.

The third paper aims to assess the developmental trajectory of the hippocampal formation, specifically the change in hippocampal volumes and morphology from TEA to 7 years in VPT and term controls. It will also evaluate whether change in hippocampal volumes and morphology between TEA and 7 years is associated with memory and learning

outcomes at 7 years of age in VPT children. For the purposes of this project however, reference will only be made to change in hippocampal volumes.

1) It is hypothesized that relative change in hippocampal volume between TEA and 7 years of age will be greater for term children when compared to VPT children.
2) It is predicted that change in hippocampal volumes between TEA and age 7 years will be associated with reduced memory and learning abilities in VPT children.

Chapter 5: Method

Participants

Participants in the present study are part of the VIBeS cohort, which were recruited into a prospective, longitudinal study examining brain abnormality and development in VPT and full term children. Initial recruitment occurred from July 2001 to December 2003 at the Royal Women's Hospital in Melbourne, Australia. Eligible infants had either a GA of <30 weeks or a birth weight of <1250 g. In total, 227 were recruited although two children died in early childhood and one was later excluded due to a late diagnosis of congenital infection, leaving 224 infants. A control group of 77 children born full term (37 to 42 weeks' GA) and of normal birth weight (≥2500 g) was also recruited; 46 children were recruited during the neonatal period from the Royal Women's Hospital and 31 were recruited at 2 years of age from maternal and child health centres. Previous follow-up assessments have been performed at ages 2 and 5 years, corrected for prematurity (Roberts, Lim, Doyle, & Anderson, 2011; D. K. Thompson et al., 2008; K. Treyvaud et al., 2012). At the 7-year follow-up, 198 of the 224 VPT children (88% of infants) and 70 of the 77 control children (91%) were assessed (see Figure 7). The 7- year follow-up is the focus of the current study.

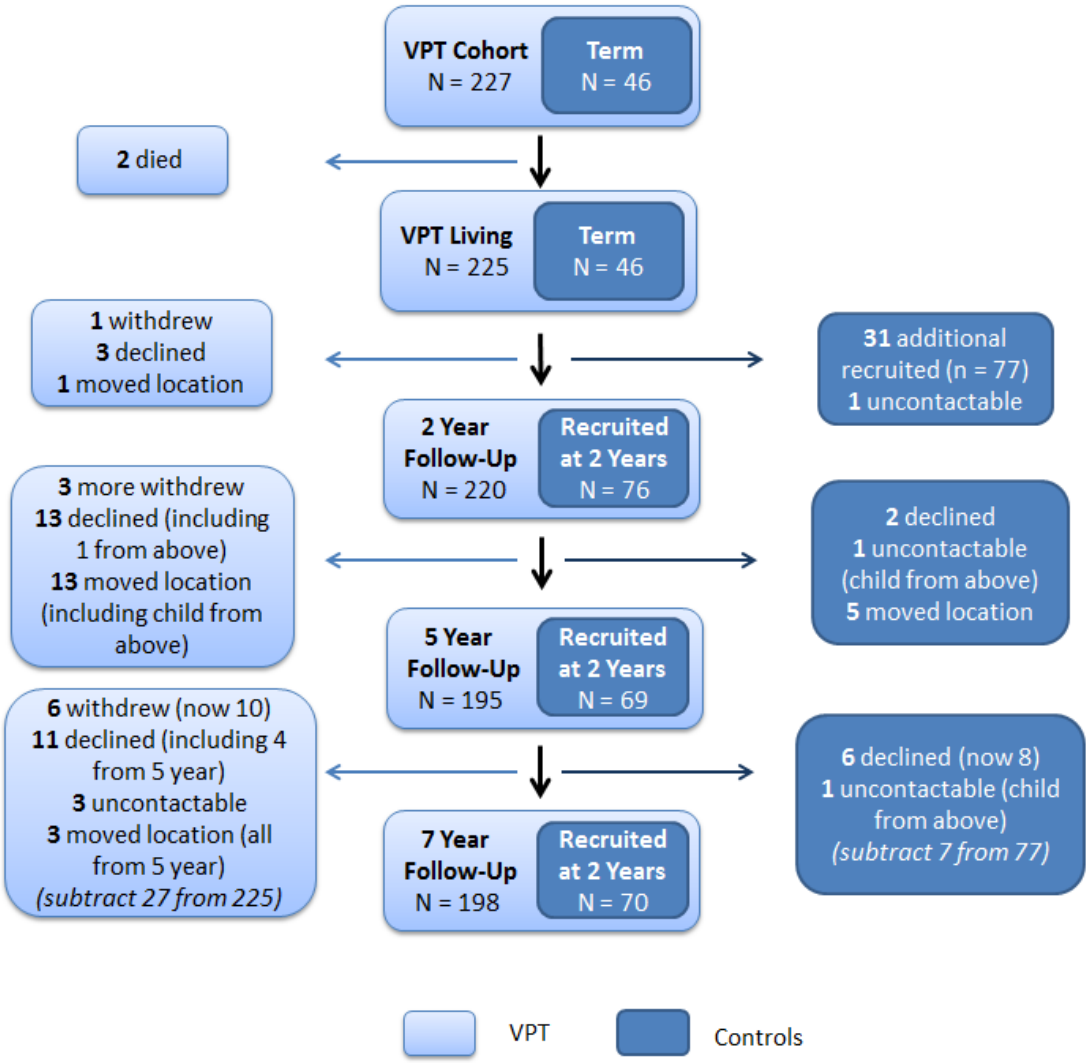

Figure 7. Recruitment and follow-up rate of VPT and term-born children in the larger study.

Procedure

Neonatal period.

The Royal Women's Hospital Human Research and Ethics Committee approved the initial VIBeS study. Families of eligible children were approached by a research nurse or neonatologist whilst in hospital. A smaller group of full-term infants (n = 46) were recruited from The Royal Women's Hospital to form the control group. Additional control children were recruited at 2 years of age (n = 31) from maternal health care centres. Written consent

was obtained from participating families, which outlined the neonatal study as well as the first follow-up planned for 2 years of age. Extensive perinatal data, including information about the pregnancy, birth and neonatal health and hospital stay, was collected by a research nurse from participant medical records.

Brain MRI scans were performed at TEA (38-42 weeks' GA) at the Royal Children's Hospital, Melbourne, Australia. After being fed, settled and fitted with earmuffs, infants were placed inside a vacuum fixation bean bag (S&S Radiograph Products, Brooklyn, New York) without sedation for scanning. Both T_1 (1.2 mm coronal slices; repetition time 35 msec; echo time 9 msec; flip angle 45°; field of view 210×158 mm; matrix 256×192) and T_2 weighted MR images (1.7-3.0 mm coronal slices; repetition time 4000 msec; echo time 60/160 msec; flip angle 90°; field of view 22×16 cm; matrix 256×192, interpolated 512×512) were acquired with a 1.5 Tesla General Electric MRI scanner.

2 year follow-up.

No data from this follow-up will be used for the purposes of the current study. Families were contacted and assessments took place at the Royal Children's Hospital. Home visits were arranged for families who were unable to attend assessments at the hospital. The follow-up involved a one and a half hour assessment of general development using the *Bayley Scale of Infant Development – Second Edition* (BSID-II) (Bayley, 1993), a parent-child interaction assessment, medical and neurological review, and parent or guardian questionnaires.

5 year follow-up.

This follow-up study aimed to assess school readiness in VPT children, though data from this time point will not be used for the present study. Families were recontacted as children approached 5 years of age. Participation was sought for both the 5 and 7 year follow-ups, although families were able to consent to only one follow-up or defer their decision for the 7 year study until that time.

7 year follow-up.

This follow-up was conducted between July 2008 and August 2011, and is the focus of the current study. Assessments occurred between children's 7th and 8th birthdays, and were coordinated by a research nurse. The protocol was completed over two days at the Royal Children's Hospital, generally no more than two weeks apart. Home visits were organised for families who were unable to get to the hospital and in some cases assessors travelled interstate or overseas for those families who had relocated.

All assessors were blinded to previous medical information and group membership (VPT or control groups). Reports summarising findings across each aspect of the follow-up were written and sent to families, and appropriate referrals were made when required. This follow-up protocol involved the following four components:

Medical and neurological assessments.

This assessment took approximately one and a half hours and was conducted by a developmental paediatrician. The standardised medical interview included vision and hearing screens. A formal neurological exam was administered in which a diagnosis of cerebral palsy was determined. The *Movement Assessment Battery for Children – Second Edition* (MABC-2) (Henderson, Sugden, & Barnett, 2007) was administered to assess motor skill development.

Mock and MRI scans.

Parents were able to decline the MRI though still participate on the remainder of the assessments. Participants that consented underwent a mock scanning session prior to their MRI in order to familiarise children to the scanning procedure and environment. This lasted between 30 and 45 minutes and was conducted by a research assistant or play therapist that was trained in the MRI familiarisation process. The child's parent was present throughout. The protocol involved a discussion of the scanning procedure using a doll and photos of the scanner. Participants were then taken to the mock scanner which was a full-size MRI

scanner shell with head coil and fully functioning gantry. The child lay flat inside the scanner with headphones on, which produced sounds to simulate the noise of a real scan. The child was monitored for signs of discomfort or over-activity that would compromise scan quality. If the mock scan was passed, the child's MRI appointment was confirmed. The MRI scan was not conducted for any child that did not successfully complete the mock session or moved excessively throughout it, or asked not to follow through with the real scan (often due to anxiety).

No sedation, anaesthetic or contrast was used for MRI scans. Six imagining sequences were conducted, including T1 (0.85mm sagittal slices, flip angle = 9°, repetition time = 1900ms, echo time = 2.27ms, field of view = 210 x 210mm, matrix= 256 x 256) and T2 (0.90mm sagittal slices, repetition time = 3200ms, echo time = 447ms, field of view = 240 x 215mm, matrix = 256 x 230) sequences. The mock and MRI sessions were conducted at the Children's MRI Centre in the RCH.

Of the children at the 7 year follow-up, 160 VPT (88%) and 36 (84%) full term children underwent MRI brain scans. The reasons children did not have imaging data at age 7 years were that they; failed the mock MRI (VPT, n = 18; term, n = 3), were too impaired (VPT n = 6), did not consent (VPT, n = 6, term, n = 1), were not in Melbourne (VPT, n = 3, term, n = 1), only came to one day of the protocol (VPT, n = 2, term, n = 1), child refused or was too scared (VPT, n = 2, term, n = 1). Of the 160 VPT and 36 term children with scans, 145 (91%) VPT and 34 (94%) term children had scans that were suitable for segmentation analysis after scans with movement artefact were excluded.

Neuropsychological assessment.

A psychologist, post-graduate psychology student, or research assistant conducted the neuropsychological assessments. Examiners underwent extensive training and were closely supervised. Assessments lasted approximately 4.5 hours and were split over two assessment days. Testing was conducted in a quiet room in the Royal Children's Hospital.

In order to maintain structure and consistency within assessments, tests were split into four blocks of approximately equal duration. This also allowed for adequate breaks for children. Test order within each block generally remained consistent. Referrals were made following assessments when appropriate; for example, a hearing test referral was made if a child fell equal to or below 1.25 SD on one or more of the language tasks.

Parent questionnaires.

A set of questionnaires was given to primary caregivers which focussed on themselves, the child, and their family. They were asked to complete the questionnaires while their child was seen for neuropsychological testing. Occasionally however, questionnaires were mailed to families prior to the assessment dates to complete and bring with them.

Materials and Measures

Approval for the study was obtained from the Human Research and Ethics Committee of the Royal Children's Hospital. Written consent from parents was obtained. Measures from the perinatal and 7 year follow-up were used for the purpose of this study. MRI measures will be discussed in the Neuroimaging section below.

Neonatal period.

Neonatal brain abnormality on MRI.

Neonatal abnormality was rated by a neonatal neurologist using a system described by (Kidokoro et al., 2013), which is an adaptation of a procedure applied previously (Inder, Wells, et al., 2003; Woodward et al., 2006). This scoring system rates the presence and severity of white matter abnormality (WM; cystic lesions, signal abnormality, myelination delay, callosal thinning, lateral ventricular volume, white matter volume), cortical grey matter abnormality (CGM; extracerebral space, signal abnormality, gyral maturation), deep grey matter abnormality (DGM; signal abnormality, deep grey matter volume) and

cerebellar abnormality (signal abnormality, cerebellar volume). A global abnormality score was also derived by the summing these four subscales (scores ranged from 0-40).

7 year follow-up.

Neuropsychological assessment.

Memory and learning were assessed at 7 years of age, corrected for prematurity, as part of a larger neuropsychological battery of standardised tests, including an estimate of IQ (Wechsler, 1999). The following memory tests were administered.

Working Memory Test Battery for Children (WMTB-C) (Pickering & Gathercole, 2001).

The WMTB-C is designed to assess working memory in both the verbal and visual domains in children aged between 5 and 15 years. Three subsets were administered. 1) Forward digit recall assesses immediate verbal memory. Participants are read a sequence of numbers and required to recall each sequence in original order. Number sequences increase from 1 digit to 9 digits, with 6 trials per sequence length. 2) Backward digit recall assesses verbal working memory. Similarly to forward digit recall, participants are required to repeat back a sequence of numbers to the examiner, but this time in the reverse order. 3) Block recall assesses immediate visual memory. Blocks on a three-dimensional board are tapped in a sequence by the examiner, and participants are required to tap them in the same sequence. Responses for each trial on all three subsets are scored 0 or 1, and a total score for each subtest reflects the number of trials completed correctly.

Subsets are scored using standard scores by age, with a mean of 100 and a standard deviation of 15. Measures were guided by the working-memory model proposed by (A. D. Baddeley & Hitch, 1974). Internal validity assessing whether test scores conform to the tripartite structure of the model is high, with a Goodness of Fit Index of .95.

California Verbal Learning Task – Children's Version (CVLT-C) (Delis, Kramer, Kaplan, & A., 1994).

The CVLT-C assesses verbal memory and learning. It is suitable for children aged 5 to 16 years and is designed within the context of an everyday memory task, using words on two hypothetical shopping lists (A and B). Participants are read a 15-item word list (list A), which they are asked to immediately recall. This procedure is repeated another 4 times, deriving a learning score. A second or distracter list (list B) is administered, and immediately followed by a short-delay free recall of List A. After approximately 20-minutes, long-delay free recall and recognition trials of List A are administered. Outcome measures include: immediate verbal memory (number of words recalled on trial 1 of list A), verbal learning (total number of words recalled across trials 1-5), and the number of words recalled after short and long delays.

Scaled scores (by age) for List A Trials 1-5 Total is a *T* score metric with a mean of 50 and a standard deviation of 10, with scaled scores ranging from 20 to 80. Scaled scores for the remaining indices are in *z* score metric with a mean of 0, standard deviation of 1, and a range of -5 to 5 with increments of 0.50. Internal reliability for this construct in 7 year olds is .85. Correlations between the CVLT-C List A Trials 1-5 raw score total, and the Wechsler Intelligence Scale for Children- Revised (WISC-R; Wechsler, 1974) Vocabulary standard score for children aged 5-8 years is .33. This indicates a mild relationship, suggesting the CVLT-C evaluates in large part, a cognitive domain different from verbal intelligence.

Dot Locations subtest from the Children's Memory Scale (CMS) (Cohen, 1997).

Dot Locations is an individually administered visual-spatial memory and learning assessment for children 5 to 16 years. Participants are presented with an array of 6 dots on a 3 x 3 grid and are required to learn their spatial location. This procedure is repeated another 2 times. Following these three learning trials, a single presentation and recall of a second (or distracter) dot array is conducted followed by a short-delay recall trial of the original dot array. A long-delay recall trial is administered approximately 20 minutes later.

Performance measures involve the first dot array only and include: immediate visual-spatial memory (trial 1), visual-spatial learning (total trials 1-3 of the first array), and visual-spatial memory after short and long delays.

Scaled scores for CMS subsets are by age, and have a mean of 10 and standard deviation of 3, with a range of 1 to 19. Internal reliability for Dot Locations at 7 years ranges from .57 to .76. Performance on the CMS was compared with intellectual functioning on the WISC-III in a sample of healthy controls. Correlations indicate construct validity for CMS indexes.

Social risk.

Social and environmental factors are important post-discharge in children born VPT. Those at moderate to high social risk show greater susceptibility to developmental problems (Larg, Graf, Kundu, Hunziker, & Molinari, 1990). A composite measure designed to assess social risk was used for the 2 year follow up (Roberts et al., 2008), and was again used at 7 years. The measure is comprised of six aspects of social status; 1) family structure (0 – two caregivers (nuclear); 1 – separated parents with dual custody, or cared by other intact family; 2 – single caregiver), 2) education of primary caregiver (0 – tertiary educated; 1 – 11-12 years of formal schooling; 2 – less than 11 years of formal schooling), 3) occupation of primary income earner (0 – skilled/professional; 1 – semiskilled; 2 – unskilled), 4) employment status of primary income earner (0 – English only; 1 – some English; 2 – no English), 5) language spoken at home (0 – English only; 1 – some English; 2 – no English), and 6) maternal age at birth (0 – older than 21 years; 1 – 18-21 years; 2 – younger than 18 years). Categorisation of families was either as lower social risk (social risk score of zero or one), or higher social risk (social risk score of two or more). The cut-off was based on composite social risk scales previously used in VPT infant follow-up studies (Hack, Breslau, Aram, & Weissman, 1992; Whitaker et al., 1996).

Imaging.

Hippocampal segmentation.

A single operator (C.O.) manually outlined the hippocampal formation in the coronal view. Of the 160 VPT and 36 full term children who underwent MRI brain scans, 145 VPT and 34 full term scans were suitable for analysis. Tracing always proceeded from the posterior to anterior sections in a sequential manner. Each slice of the hippocampal formation was traced from the superiomedial edge to the lateral edge, downwards to the inferior aspect and finally to the medial edge. In general, anatomical boundaries proposed by Watson et al. (1992) and (Pruessner et al., 2000) were followed, with reference to anatomical atlases by (Woolsey, Hanaway, & Gado, 2008). Whilst tracing occurred in the coronal view, reference was made to the sagittal and horizontal views in order to provide more reliable identification of structural boundaries.

The hippocampal formation can be subdivided into three sections: the hippocampal head, which is the anterior aspect, the hippocampal body, the medial part, and the hippocampal tail, which is the posterior aspect. Each of these aspects has distinct structural differences. The dentate gyrus, four CA regions, alveus and the fimbria were included within the HF measurement.

Boundaries of the hippocampal tail.

The most posterior slice of the hippocampal tail was defined as the slice where the crus of the fornix was clearly visible surrounding the hippocampus inferiomedially to the trigone of the lateral ventricle (TLV). Consistently, the lateral border was defined as the boundary between the white matter of the fimbria and the TLV. Medially, the border was where the quadrigeminal cistern met the hippocampal sulcus. Initially, an arbitrary border was used to help define the superior border of the hippocampal tail. This arbitrary border was a horizontal line from the superior border of the quadrigeminal cistern to the TLV. This was to help define and separate the hippocampal tail from the fasciolar gyrus, which sits above the hippocampal tail. Further anteriorly, the fimbria was used as the superior border.

The border between the hippocampus and the parahippocampal gyrus provided the inferior border (an upward slant medially). Although these procedures led to some exclusion of the medial and superior sections of the hippocampal tail at times, this method appeared to produce the most consistent approach for defining the hippocampal tail.

Boundaries of the hippocampal body.

The hippocampal body consists of several parts which fold into each other to create an S-shaped structure. The fimbria formed the superior border. The lateral border of the hippocampal body was defined by the inferior horn of the lateral ventricle, and the most visible inferiolateral grey matter was included. The medial border was where the subiculum joined with the hippocampal sulcus.

Boundaries of the hippocampal head.

The hippocampal head can be identified as the most anterior portion of the hippocampal formation. The first coronal slice is the appearance of the uncal recess in the superomedial portion of the hippocampus. This forms a distinct protuberance or "hook" which was used to identify the superomedial border. The inferior border was defined by the uncus, and the border between the entorhinal cortex and the hippocampus. The superior part of the hippocamapal grey matter becomes a combination of amygdala, hippocampus, and basal ganglia (putamen and globus pallidus) (Pruessner et al., 2000). When this occurred, the fimbria was used to separate the hippocampal formation from amygdala, evident as a line of white matter intermingling with cerebrospinal fluid (CSF). The lateral border was the border between the alveus and the temporal horn of the lateral ventricle. Further anterially, the medial edge was the most medial point of the temporal lobe. The last slice was identified as the most anterior slice where the temporal horn of the lateral ventricle was still seen laterally to the hippocampus.

Blinded repeat segmentations to assess intra-rata reliability were conducted 1 week apart. Intraclass correlation coefficients were 0.97 ($p<0.0005$) for the right and 0.96

($p<0.0005$) for the left hippocampal formations. Inter-rater reliability was 0.96 ($p<0.0005$) and 0.97 ($p<0.005$) for the right and left hippocampi respectively.

Statistical Analyses

All data were analysed using Stat 12 (StataCorp., 2011). Analyses for each study are provided in Chapters 6, 7 and 8.

Chapter 6: Paper 1

Neonatal Brain Abnormalities and Memory and Learning Outcomes at 7 Years in Children Born Very Preterm

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Abstract

Using prospective longitudinal data from 198 very preterm and 70 full term children, this study characterised the memory and learning abilities of very preterm children at 7 years of age in both verbal and visual domains. The relationship between the extent of brain abnormalities on neonatal magnetic resonance imaging (MRI) and memory and learning outcomes at 7 years of age in very preterm children was also investigated. Neonatal MRI scans were qualitatively assessed for global, white-matter, cortical grey-matter, deep grey-matter, and cerebellar abnormalities. Very preterm children performed less well on measures of immediate memory, working memory, long-term memory, and learning compared with term born controls. Neonatal brain abnormalities, and in particular deep grey matter abnormality, were associated with poorer memory and learning performance at 7 years in very preterm children. Findings support the importance of cerebral neonatal pathology for predicting later memory and learning function.

Key Words

Very preterm – VPT

Gestational age – GA

Neonatal brain abnormalities

Memory and learning

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Introduction

Very preterm (VPT; <32 completed weeks of gestational age [GA]) birth accounts for approximately 2% of births world-wide (World Health Organisation, 2012). While most VPT infants now survive, up to 60% of survivors will show later cognitive (Anderson & Doyle, 2003), motor (Williams, Lee & Anderson, 2009), academic (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever & Oosterlaan, 2009) and behavioural (Bhutta, Cleves, Casey, Cradock, & Anand, 2002) problems. One area that has not received much attention in VPT children is memory and learning. Given evidence suggesting impaired memory and learning in children born preterm compared with term born controls (Taylor, Klein, Minich & Hack, 2000; Rose, Feldman & Jankowski, 2005), and the high risk of brain pathology in this population (Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Woodard, Anderson, Austin, Howard, & Inder, 2006), further investigation of memory and learning outcomes and the association with brain pathology in preterm children is warranted especially within those born VPT.

Memory is a complex construct. Information initially enters a temporary storage system, or immediate memory. The capacity to manipulate and process this information while in temporary storage is referred to as working memory. Processes such as articulatory rehearsal (Baddeley, 1996) and attentional refreshment (Barrouillet & Camos, 2001) enable information to be transferred from temporary storage into the more durable long term memory. Long term memory can be broken down into subdivisions; explicit (declarative) and implicit (procedural) memory (Strauss, Sherman, & Spreen, 2006; Tulving, 1972). Explicit memory can be further subdivided into memory for specific events or experiences (episodic memory) and memory for facts (semantic memory) (Tulving, 1972). Immediate and working memory have both been associated with the prefrontal cortex (PFC), anterior cingulate, and parietal and occipital regions (Cabeza & Nyberg, 1997), whereas structures of the medial temporal lobe, including the hippocampus and related cortices (perirhinal, entorhinal and parahippocampal) have vital implications for the retention, storage and

retrieval of information (Moscovitch & Umilta, 1990; Nadel, Samsonovitch, Ryan, & Moscovitch, 2000).

Studies show that preterm children have difficulties with multiple components of memory. The majority of research has focused on immediate and/or working memory with preterm children exhibiting deficits in both visual (Isaacs et al., 2000; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Rose et al., 2009; Rose, Feldman, Jankowski & Van Rossem 2011; Woodward et al., 2005) and verbal (Böhm, Smedler, & Forssberg, 2004; Isaacs et al., 2000) modalities when compared to term controls. With regards to explicit memory, 12 month old preterm infants have shown deficits in the reproduction of action sequences (Rose et al., 2009), and children with very low birth weight (VLBW; <1500 g) have demonstrated reduced list learning, delayed recall, inaccurate recall (Taylor et al., 2000), and visual recall (Taylor, Minich, Klein, & Hack, 2004) compared with term controls. Additionally, poorer everyday memory (Isaacs et al., 2000) and recognition memory (Rose et al., 2005; Rose et al., 2009; Rose et al., 2011) have been reported in preterm cohorts.

Cognitive deficits, such as memory, in VPT children may be associated with neonatal brain injury and disrupted brain development (Ment, Hirtz, & Huppi, 2009). Historically, the major neuropathologies associated with VPT birth have been high-grade intraventricular haemorrhage (IVH) and cystic periventricular leukomalacia (PVL), both of which are easily detected on cranial ultrasound. These pathologies have been associated with moderate to severe cognitive and motor impairments (De Vries, Van Haastert, Rademaker, Koopman, & Groenendaal, 2004; Sherlock, Anderson & Doyle, 2005), but are now uncommon due to improved obstetric and neonatal care (observed in fewer than 10% of VPT survivors; Volpe, 2009). While most VPT infants avoid significant brain injury, magnetic resonance imaging (MRI) studies have revealed that the majority of VPT infants have diffuse white-matter abnormalities (Back, 2006; Boardman & Dyet, 2007; Inder et al., 2003), including enlarged lateral ventricles, white matter signal abnormalities and volume loss, thinning of the corpus callosum, and delayed myelination (Inder et al., 2003; Woodward et al., 2006). Grey matter

abnormalities, such as delayed gyration, increased subarachnoid space, and decreased cerebral grey matter volume, have also been detected in VPT infants (Inder, Huppi, Warfield, Kikinis, Zientara, et al., 1999; Woodard et al., 2006), and may be at least partly related to white matter abnormalities (Inder et al., 1999). Qualitative scoring systems for neonatal brain MRI (Inder et al., 2003; Miller et al., 2005; Woodward et al., 2006) suggest that approximately one fifth of VPT infants have moderate to severe white matter abnormalities and 50% have mild abnormalities (Inder et al., 2003; Miller et al., 2005).

Despite the recognition of brain abnormalities in VPT infants, few studies have examined the association between neonatal brain injury and later cognitive functioning in VPT children. Moderate-severe white matter abnormality has been reported to predict early cognitive delay, cerebral palsy and neurosensory deficits (Woodward et al., 2006), as well as executive functioning at preschool age (Woodward, Clark, Pritchard, Anderson, & Inder, 2011). At school age, mild and moderate-severe white matter abnormalities have been found to predict visual and verbal working memory deficits (Clark & Woodward, 2010) and motor impairment (Spittle, Cheong, Doyle, Roberts, Lee, et al., 2011). Similarly, grey matter abnormalities have been associated with early cognitive and motor delays (Woodward et al., 2006), and later impairments to visual working memory (Clark & Woodward, 2010).

In summary, although there is some evidence of memory deficits in VPT infants, a better understanding of memory and learning in VPT children is required, especially given the importance of these skills to academic progress and vocational success (Hornby & Woodward, 2009). Furthermore, it is unclear how memory and learning deficits reported in this population are related to neonatal brain abnormalities. As such, this study aims 1) to characterise memory and learning performance in both verbal and visual domains in 7 year old children born VPT compared with term controls, and 2) to evaluate the association between neonatal brain abnormalities and memory and learning functioning at 7 years of age in VPT children.

Materials and Methods

Participants.

Participants were prospectively recruited into the Victorian Infant Brain Studies (VIBeS) cohort from the Royal Women's Hospital in Melbourne, Australia from July 2001 to December 2003. Eligible VPT infants were born <30 weeks' GA and/or <1250 g, without congenital abnormalities that would impair neurological function, and survived the neonatal period. In total, 227 VPT infants were recruited although two children died in early childhood and one was later excluded due to a late diagnosis of congenital infection known to affect developmental outcome, leaving 224 VPT infants. A control group of 77 term (37 to 42 weeks' GA) and normal birth weight (≥2500 g) children were also recruited; 46 were recruited during the neonatal period from the Royal Women's Hospital and the remaining 31 were recruited at 2 years of age from maternal-infant health centres. Previous follow-up assessments of VPT and control children have been performed at ages 2 and 5 years, corrected for prematurity (Roberts, Lim, Doyle, & Anderson 2011; Thompson, Wood, Doyle, Warfield, Lodygensky, et al., 2008; Treyvaud, Doyle, Lee, Roberts, Lim, et al., 2012). At the 5-year follow-up the VPT children exhibited poorer immediate/working memory compared to the term controls (Roberts et al., 2011). At the 7-year follow-up, 198 of the 224 VPT children (88% of infants) and 70 of the 77 control children (91%) were assessed.

Procedure and measures.

Approval for the study was obtained from the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital in Melbourne. Written informed consent was obtained from parents.

VPT infants had a brain MRI scan at term equivalent age, while the 46 term controls recruited in the neonatal period were scanned within 2 weeks of birth. T_1 (1.2 mm coronal slices; repetition time 35 msec; echo time 9 msec; flip angle 45°; field of view 210×158 mm; matrix 256×192) and T_2 weighted structural MR images (1.7-3.0 mm coronal slices; repetition time 4000 msec; echo time 60/160 msec; flip angle 90°; field of view 22×16 cm;

matrix 256×192, interpolated 512×512) were acquired with a 1.5 Tesla General Electric MRI scanner at Melbourne's Royal Children's Hospital. Infants were fed, settled and fitted with earmuffs before being scanned without sedation. Using T_1 and T_2 weighted scans, cerebral abnormality was rated by a neonatal neurologist using a system described by Kidokoro, Neil, & Inder, (2013), which is an adaptation of a procedure applied previously (Inder et al., 2003; Woodward et al., 2006). This scoring system rates the presence and severity of white matter abnormality (WM; cystic lesions, signal abnormality, myelination delay, callosal thinning, lateral ventricular volume, white matter volume), cortical grey matter abnormality (CGM; extracerebral space, signal abnormality, gyral maturation), deep grey matter abnormality (DGM; signal abnormality, deep grey matter volume) and cerebellar abnormality (signal abnormality, cerebellar volume) on a scale from 0 to 4. These four subscales are also summed to generate a global abnormality score (scores ranged from 0-40).

Memory and learning were assessed at 7 years of age, corrected for prematurity, as part of a larger neuropsychological battery of standardized tests, including a measure of intelligence (IQ; Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999). We selected standardized memory tests that are used widely both in clinical and research settings.

Working Memory Test Battery for Children (WMTB-C; Pickering & Gathercole, 2001).

Three subsets from the WMTB-C were administered. 1) Forward Digit Recall, which assesses immediate verbal memory. Participants are read a series of numbers and required to recall each sequence in original order. Number sequences increase from 1 digit to 9 digits, with 6 trials per sequence length. 2) Backward Digit Recall, which assesses verbal working memory. Participants are required to repeat sequences of numbers in the reverse order. 3) Block Recall, which assesses immediate visual-spatial memory. Blocks on a three-dimensional board are tapped in a sequence by the examiner, and participants are required to tap them in the same sequence. A total score for each subtest reflects the number of trials completed correctly.

California Verbal Learning Test – Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994).

The CVLT-C assesses verbal memory and learning. Participants are read a 15-item word list (list A), which they are asked to immediately recall. This procedure is repeated 5 times, deriving a learning score. A second or distracter list (list B) is administered, and immediately followed by a short-delay free recall of List A. After approximately 20-minutes, long-delay free recall and recognition trials of List A are administered. Outcome measures include: verbal working memory (number of words recalled on trial 1 of list A), verbal learning (total number of words recalled across trials 1-5), and number of words recalled after short and long delays.

Dot Locations subtest from the Children's Memory Scale (CMS; Cohen, 1997).

The Dot Locations subtest assesses visual-spatial memory and learning. Participants are presented with an array of 6 dots for 5 seconds on a 3 X 3 grid and are required to learn their spatial location. Next, participants are asked to place 6 plastic dots on a blank 3 X 3 grid in the same array as just seen. This procedure is repeated another 2 times. Following these 3 learning trials, a second (or distracter) dot array is presented followed by a short-delay recall trial of the original dot array. A long-delay recall trial is administered approximately 20 minutes later. Performance measures of interest in this study were visual learning (total trials 1-3 of the first array), and visual memory after short and long delays.

Social Risk.

There is a tendency for preterm cohorts to be of higher social risk than term-born cohorts, and higher social risk has been associated with an increased risk of developmental problems (Largo, Molinari, Kundu, Lipp, & Duc , 1990; Roberts, Howard, Spittle, Brown, Anderson, et al., 2008; Wang, McGlynn, Brook, Leonard, Piecuch, Hsueh et al., 2006). Preterm infants with moderate to high social risk are at increased risk of developmental problems (Hack, Breslau, Aram, Weissman, Klein, & Borawski-Clark, 1992) and are less likely to receive early intervention (Roberts et al., 2008). As part of the 7 year assessment,

parents completed a questionnaire to assess social risk based on family structure, language spoken at home, education of the primary caregiver, occupation and employment status of the primary income earner, and maternal age at birth (Roberts et al., 2008). Scores ranged from 0 – 12, with higher scores being reflective of greater social risk.

Statistical Analyses

Data were analysed using Stata 12 (StataCorp, 2011). Given the restricted age range of the children at follow-up, raw data were used. Scores were recorded as 'missing' if children were either too impaired to complete tasks, refused to complete tasks, or there was a problem with the assessment equipment (e.g. missing components of a task).

First, linear regression was used to examine differences between birth groups (VPT and term) on all outcome measures. Each model was fitted using generalised estimating equations (GEEs) with an exchangeable correlations structure and robust standard errors to allow for correlations between twins/triplets in the study, and included adjustment for age at testing. Subsequent analyses also controlled for social risk, and excluded children with a full-scale IQ<70 to determine the extent to which these factors explained the difference in performance between the groups. Impairment on each scale was classified as 1 standard deviation (SD) below the control group mean. Unadjusted logistic regression (fitted with GEEs) was used to compare the odds of impairment between the two groups on outcome measures.

Linear regression was also used to examine the relationship between the presence of brain abnormality (as continuous variables) at term and memory and learning outcomes at 7 years in the VPT group. The models were fitted using GEEs, and controlling for age at testing, social risk, and excluding children with IQ<70. Semi partial correlations (sr^2) were used to assess the percentage of variance accounted for by each independent predictor.

Results

Sample characteristics.

Table 1 shows the characteristics for the VPT and control groups. The gender ratio was similar between the VPT and term groups, although there was evidence of differences between groups for age at assessment (p=0.002) and social risk (p=0.001).

Table 1. Demographic and perinatal characteristics of the sample assessed at 7 years of age for the current study.

	Very Preterm sample *n* = 198	Term sample *n* = 70
GA (weeks), *M* (*SD*)	27.4 (1.9)	39.1 (1.3)
Age at assessment (years), *M (SD)*	7.5 (0.02)	7.6 (0.04)
Birth weight (*g*) , *M (SD)*	960 (222)	3323 (508)
Social risk, *M (SD)*	2.2 (1.8)	1.4 (1.4)
Small for gestational age, %	8.6	2.3
Male gender, %	52.3	48.6
Singleton, %	57.4	94.3
Antenatal corticosteroids, %	87.3	0
Postnatal corticosteroids, %	8.7	0
Bronchopulmonary dysplasia, %	33.1	0
Cystic periventricular leucomalacia, %	4.1	0
Intraventricular haemorhage grades 3/4%	3.5	0

GA = gestational age
M = mean
SD = standard deviation

Group differences on memory and learning outcomes at 7 years.

Table 2 shows that VPT children on average performed lower than term-born children on all measures of memory and learning, with the exception of CVLT-C trial 1 and long delay. While subsequent analysis adjusted for social risk and excluding children with IQ<70 resulted in some attenuation of results, evidence of group differences remained in the majority of outcomes.

Table 2. Associations between birth group and memory and learning outcomes at age 7 years

	VPT		Term		Adjusted for age only		Adjusted for age and social risk[a]		Adjusted for age, social risk, excluding children with IQ < 70[b]	
Outcome	N	M(SD)	N	M(SD)	*b*(95% CI)	*p*	*b*(95% CI)	*p*	*b*(95% CI)	*p*
Immediate Memory										
Digits Forward	191	25.70(4.67)	69	27.09(3.68)	-1.36(-2.51, -.22)	.02	-.60(-1.75, .55)	.31	-.42(-1.55, .72)	.47
Block Recall	186	20.63(4.74)	69	23.30(3.97)	-2.49(-3.71, -1.26)	<.01	-2.36(-3.60, -1.13)	<.01	-2.19(-3.42, -.96)	<.01
Working Memory										
Digits Backward	177	9.03(3.29)	68	10.97(3.50)	-1.96(-2.97,-.94)	<.01	-1.56(-2.54, -.60)	<.01	-1.60(-2.57, -.63)	<.01
CVLT-C Trial 1	187	5.28(2.00)	69	5.70(1.86)	-.43(-.97, .10)	.11	-.41(-.96, .14)	.14	-.38(-.92, .17)	.17
Memory/Learning										
CVLT-C										
Total Trials 1-5	187	37.31(10.04)	69	41.75(9.78)	-3.85(-6.73, -.97)	<.01	-2.97(-5.87, -.07)	.04	-2.80(-5.68, .07)	.06
Short Delay	187	6.76(3.04)	69	8.32(2.55)	-1.37(-2.11, -.62)	<.01	-1.11(-1.88, -.34)	<.01	-1.06(-1.83, -.29)	<.01
Long Delay	186	7.34(3.24)	69	8.16(2.90)	-.65(-1.49, .19)	.13	-.31(-1.15, .54)	.47	-.23(-1.07, .60)	.58
Dot Locations										
Total Trials 1-3	185	14.51(2.97)	69	15.93(2.08)	-1.27(-1.95, -.59)	<.01	-.96(-1.63, -.29)	<.01	-.97(-1.65, -.29)	<.01
Short Delay	186	4.90(1.31)	69	5.54(0.83)	-.64(-.94, -.34)	<.01	-.52(-.82, -.23)	<.01	-.53(-.82, -.23)	<.01
Long Delay	185	4.92(1.33)	69	5.48(0 .95)	-1.27(-1.95, -.59)	<.01	-.39(-.69, -.08)	.01	-.38(-.68, -.08)	.01

VPT = very preterm
CVLT-C = California Verbal Learning Test – Children's Version
b = coefficient for group from the linear regression model representing the difference in means between the VPT and term groups.
CI =confidence interval
M = mean
SD = standard deviation
[a] = 12 participants with missing data on social risk hence not included in the adjusted analysis.
[b] = 15 participants with missing data on social risk hence not included in the adjusted analysis.

Table 3 displays the proportion of children with impairment in the VPT and control groups for all outcome measures, and highlights that a higher proportion of the VPT group have impairments compared with the control group (i.e. performing more than one SD below the control group mean). There was evidence that the impairment rate was higher in the VPT group across all memory measures, with odds ratios ranging from 2.1 to 3.5.

Table 3. Frequency of children who performed in the impaired range (>1.0 standard deviation below the term group mean) on memory and learning outcome measures

	VPT Sample (n=198)%	Term Sample (n=70)%	Odds Ratio (95% CI)	*p*
Immediate Memory				
Digits Forward	27.8	10.1	3.20(1.39, 7.40)	<.01
Block Recall	39.3	18.4	2.91(1.47, 5.76)	<.01
Working Memory				
Digits Backwards	36.2	16.2	2.97(1.43, 6.16)	<.01
CVLT-C Trial 1	19.3	10.1	2.11(0.88, 5.11)	.09
Memory and Learning				
CVLT-C				
Short Delay	30.0	11.6	3.25(1.44, 7.35)	<.01
Long Delay	26.9	14.5	2.13(1.00, 4.51)	.05
Total Trials 1-5	28.3	10.1	3.49(1.48, 8.24)	<.01
Dot Locations				
Short Delay	31.2	13.04	3.12(1.45, 6.69)	<.01
Long Delay	40.8	15.2	2.31(1.07, 5.00)	.03
Total Trial 1-3	30.3	14.5	2.49(1.20, 5.13)	.01

Note. Some samples are less than the total sample due to missing data.
VPT = very preterm
CVLT-C = California Verbal Learning Test – Children's Version
CI = confidence interval

Neonatal brain pathology and memory and learning outcomes in children born VPT.

Figure 1 shows the presence of neonatal brain abnormalities as a predictor of memory and learning performances at 7 years in VPT children. The general trend is that increasing severity of neonatal brain abnormality is associated with reduced performance on memory and learning tasks in VPT children. Deep grey matter abnormality appeared to be the strongest predictor of memory functioning, associated with poorer scores for the majority of outcomes, although there were large overlaps in the 95% confidence intervals across the measures. Of the measures used, the CVLT-C total trials 1-5 was the most strongly predicted by neonatal brain abnormality. For the other outcomes, the association with brain abnormalities were generally weak, with the exception of deep grey matter abnormality. Sr^2 controlling for age at assessment, social risk, and excluding children with IQ<70, indicate that neonatal brain injury accounts for only a small amount of variance in the outcomes presented (1.93% to 8.36%).

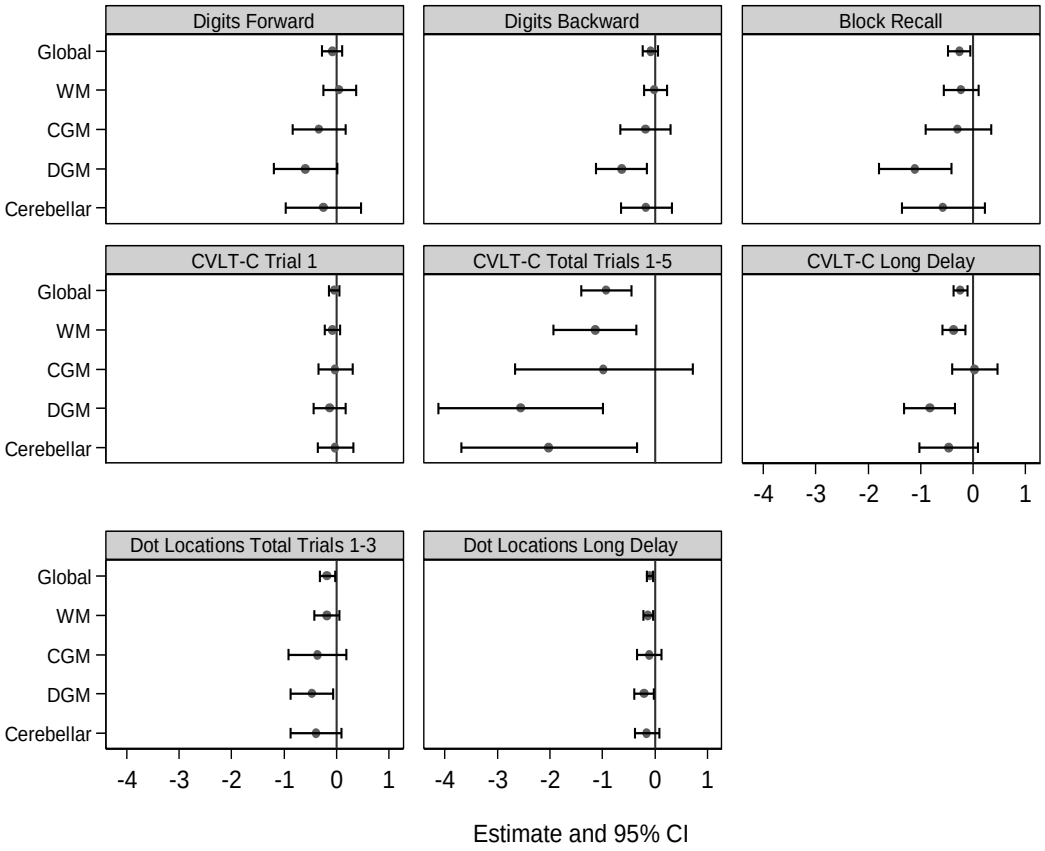

Figure 1. Association between brain injury at term and memory and learning at 7 years. The figure shows the linear regression coefficient and its 95% Confidence Interval (CI), which represents the change in memory and learning outcome per one unit change in brain abnormality score.

Discussion

In this prospective, longitudinal study, children born VPT performed consistently less well than term children across all measures of memory and learning in both the verbal and visual modalities at 7 years of age. Children born VPT had higher social risk than their term-born counterparts, and this contributed to poorer performance on a number of outcome measures. Given that VPT children with higher social risk are more susceptible to developmental difficulties and are less likely to receive early intervention than VPT children with low social risk (Roberts et al., 2008), we expected an attenuation of results on outcome

measures when social risk was controlled for. We also found evidence of an association between neonatal brain abnormalities and poorer memory and learning outcomes at 7 years in VPT children, especially with the presence of deep grey matter abnormality. Verbal learning appeared to be most vulnerable to neonatal brain pathology.

Understanding the mechanisms behind memory and learning deficits in VPT children improves the capacity to detect high-risk children at a young age. This is particularly important given the contribution of these skills to academic progress and success (Colom, Escorial, Shih, & Privado, 2007; Hornby & Woodward, 2009; Swanson, 1994), and has implications for enrolling children in early intervention programs that target memory enhancement. White matter abnormalities observed on neonatal MRI in VPT infants has been reported to be predictive of early developmental delay (Woodward et al. 2006), visual working memory at 6 years (Clark & Woodward, 2010), executive functioning at age 4 years (Woodward et al., 2011), motor impairment at age 5 (Spittle et al., 2011), and language functioning at age 7 years (Reidy, Morgan, Thompson, Inder, Doyle, 2013). The current study contributes to the literature by examining neonatal brain abnormalities more generally, not just white matter injury, and demonstrates that qualitative neonatal MRI is predictive of memory and learning at 7 years.

Although it is unclear whether the memory and learning impairments identified in this VPT sample reflect developmental delay or deficit at this stage of development, findings are consistent with other studies reporting memory outcomes in children and adolescents born VPT (Böhm et al., 2004; Clark & Woodward, 2010; Taylor et al., 2000; Taylor et al., 2004; Taylor et al., 2011; Woodard et al., 2005). VPT children in the current study have previously been reported to have working memory deficits compared to their term born peers at 5 years of age (Roberts et al., 2011). In the current study, immediate and working memory in VPT children were characterised by deficits in the initial acquisition of visual information as well as the manipulation of verbal material when compared with term controls. Relative to term controls, the efficacy of the learning process for visual formation

was reduced, and there was a trend for a higher risk of impaired verbal learning in the VPT population. A discrepancy between the groups in recall after short and long delays was also present: recall following a short delay was reduced for both verbal and visual material in the VPT group, but only reduced for recall of visual information after a long delay. Overall, recalling of visual information appears to be more impaired in VPT children than verbal information. This may be due to the use of different memory networks for these modalities, suggesting a higher vulnerability of visual networks to neonatal brain injury in VPT birth.

Consideration of memory models may provide insight into the processes underlying memory and learning impairments experienced by VPT children. An issue of long-standing debate has been whether immediate/working memory and long term memory systems are separate entities, or whether they act independently but are linked in parallel (Baddeley, 1997; Hebb, 1949). Most recent evidence supports the latter view (Baddeley 2000; Baddeley, 2003; Hodges, 2007) because patients with immediate phonological impairments have also been found to display specific deficits in long term phonological learning (Baddelely, Papagno, & Vallar, 1998). Consistently, verbal memory and learning skills in our VPT group was characterised by impaired immediate/working memory and short delay recall, with relatively preserved long delay recall. This pattern of impairment may reflect a primary impairment of immediate and/or working memory. In contrast, visual memory and learning impairments in the VPT cohort were more generalised, suggesting more extensive deficits to underlying networks.

An important finding in the current study was that across each memory outcome approximately 30% of VPT children performed at least 1 SD below the control group mean. Odds ratios showed that the VPT group had approximately 3 times greater odds of impairment than the full-term sample. This highlights the high frequency of memory impairments in VPT children, which is a significant concern given that memory is a core cognitive skill that underlies other cognitive domains (Swanson, 2008). Memory and learning deficits have also been associated with academic success such as mathematical and

grammatical abilities (Bull, Espy, & Wiebe, 2008; Sansavini et al., 2006). Based on our findings, we would strongly advocate that a detailed assessment of memory and learning is incorporated into the surveillance programs of VPT children in early school or preschool age.

Increased global abnormality score (the sum of pathology in cerebral white matter, cortical grey matter, deep grey matter and cerebellum) was associated with poorer memory outcomes in the VPT group, particularly immediate visual memory, learning in visual and verbal modalities, and ultimately the consolidation of visual and verbal material in long term memory. This finding highlights the potential impact that neonatal brain abnormalities observed on MRI associated with VPT birth can have on later memory and learning. Deep grey matter abnormality, which in this case refers to the basal ganglia and thalamus, was the strongest predictor of memory and learning performance. The basal ganglia play an important role in memory and learning, with simultaneous activation of its structures and the medial temporal lobe systems during learning tasks (Packard & Knowlton, 2002; Seger, 2006). Similarly, lesions to the thalamus can result in amnesia, supporting its vital role in memory (Aggleton & Brown, 1999; Moscovitch, Rosenbaum, Gilboa, Addis, Westmacott, 2005), and bilateral lesions have been associated with memory impairments to verbal and non-verbal material (Cipolotti, Husain, Crinion, Bird, Khan, et al., 2008). Recent findings suggest that both basal ganglia and thalamic activations are present during verbal immediate/working memory (Moore, Li, Tyner, Hu, & Crosson, 2013). As such, deep grey matter abnormalities may compromise a number of structures that have a role in memory and learning.

White matter, cerebral grey matter and cerebellum abnormalities were only weakly associated with poorer performance on memory measures at age 7 years, and the relationships often failed to reach statistical significance. Total number of words recalled on the CVLT-C appeared to be most strongly associated with MRI defined neonatal brain abnormality, and was associated with all scales with the exception of cortical grey matter.

These findings suggest that extensive networks throughout the brain may subserve more complex tasks, such as verbal learning, in VPT children.

One of the strengths of the current study was the use of measures which assess multiple components of memory and learning. This contrasts much of the previous literature that has tended to have a narrow focus. Although this has helped improve our understanding of the memory and learning difficulties many VPT children endure, methodological issues remain to be addressed. First, there were unequal sample sizes, with more children in the VPT group than in the term group, and second, the two birth groups were not entirely matched with respect to socioeconomic status – the VPT group having greater social risk than the term group.

Findings from the current study extend our understanding of memory and learning impairments in VPT children, and substantiate the predictive value of the neuropathological processes that underlie these difficulties. This information is important for VPT children and their parents in order to understand the child's potential and limitations, and to make appropriate educational and vocational choices. It also aids educators in developing interventions to minimise the impact of memory and learning impairments on academic achievement, and helps us understand the biological mechanisms behind these impairments. Further research examining ways to reduce the rate of cerebral abnormalities in VPT infants is essential for improving their long-term outcome.

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Chapter 7: Paper 2

Hippocampal Volume and Memory and Learning Outcomes at 7 Years in Children Born Very Preterm

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Abstract

Using magnetic resonance imaging, this study compared hippocampal volume between 145 very preterm children and 34 children born full term at 7 years of age. The relationship between hippocampal volume and memory and learning impairments at 7 years was also investigated. Manual hippocampal segmentation and subsequent 3D volumetric analysis revealed reduced hippocampal volumes in very preterm children compared with term peers. However, this relationship did not remain after correcting for whole brain volume and neonatal brain abnormality. Contrary to expectations, hippocampal volume in the very preterm cohort was not related to memory and learning outcomes. Further research investigating the effects of very preterm birth on more extensive networks in the brain that support memory and learning in middle childhood is needed.

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Key words and abbreviations

Very preterm – VPT

Gestational age – GA

Neonatal

Hippocampal Formation

Segmentation

Memory and Learning

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Introduction

Over the past 20 years there has been a steady rise in preterm birth worldwide (World Health Organization, 2012). In 2010, an estimated 14.9 million babies were born preterm (<37 weeks' gestational age), and approximately 20% of these are born very preterm (VPT), defined as birth prior to 32 weeks' gestational age (GA; Goldenberg, Culhane, Iams, & Romero, 2008). Many VPT children experience later cognitive (Anderson & Doyle, 2003), academic (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever & Oosterlaan, 2009) and behavioral (Bhutta, Cleves, Casey, Cradock, & Anand, 2002) problems, and up to 60% will show diffuse and focal structural brain injury (Ment, Hirtz, & Huppi, 2009; Inder, Anderson, Spencer, Wells, & Volpe, 2003). In addition to high rates of brain injury, brain growth has been reported to be delayed in VPT infants and children (Thompson et al., 2008; Taylor et al., 2011). In particular, hippocampal volume has been found to be significantly reduced in VPT children compared with their term born counterparts (Gimenez et al., 2008; Thompson et al., 2008; Nosarti et al., 2002). The hippocampi have a well-established role in memory and learning (Moscovitch & Umilta, 1990; Nadel, Samsonovich, Ryan & Moscovitvh, 2000), and children born VPT often show impairments in these domains (Omizzolo et al., 2013; Rose, Feldman, & Jankowski, 2005; Taylor, Klein, Minich, & Hack, 2000; Woodward, Edgin, Thompson, & Inder 2005). This raises the question whether there may be a relationship between reduced hippocampal volume and memory and learning impairments.

The hippocampal formations comprise a group of several related brain areas within the left and right medial temporal lobes, including the dentate gyrus, hippocampus, subiculum, presubiculum, parasubiculum and entorhinal cortex (Amaral & Lavenex, 2007). They are known to be particularly vulnerable to many of the stressors and medical complications associated with VPT birth, including infection, hypoxia-ischemia, poor nutrition, hypoglycemia, hypothyroidism, and stress hormones (Gadian et al., 2000; Isaacs et al., 2000; Sizonenko et al., 2006; Khwaja & Volpe, 2008). These complications can result in reductions in gray matter volumes (Inder, Warfield, Wang, Huppi & Volpe, 2005; Volpe,

2009), including pyramidal cell death, a slowing of neural migration (Rees, Breen, Loeliger, McCrabb & Harding, 1999) and neuronal injury (Volpe, 2001) to the hippocampi.

In vivo measurement and volumetric analyses of the brain utilizing magnetic reasonance imaging (MRI) have become key components of neuroimaging research (Konrad et al., 2009). Manual segmentation and automated measures, such as voxel-based morphometry, have been used to investigate the hippocampal formation. However, manual segmentation is still considered the gold standard (Konrad et al., 2009), as voxel-based morphometry has been reported to produce significantly larger estimates of volume (Cherbuin, Anstey, Réglade-Meslin, & Sachdev, 2009). Most studies within the VPT literature have utilized manual segmentation, and have reported reduced hippocampal volume in VPT infants (Lodygensky et al., 2008; Thompson et al., 2008), children (Isaacs et al., 2000; Lodygensky et al., 2005), and adolescents (Abernethy, Palaniappan, & Cooke, 2002; Nosarti et al., 2002). Although fewer studies have employed voxel-based morphometry, reduced hippocampal volumes in adolescents (Gimenez et al., 2008) and young adults (Lawrence et al., 2010) born VPT have also been noted using this methodology.

Positron emission tomography (PET) studies indicate that the medial-temporal lobe, particularly the hippocampi, and the prefrontal cortex are vital for learning and long-term memory function (Cabeza & Nyberg, 1997). Memory is a complex system, involving the initial registration of information into immediate memory, followed by the manipulation of this information in working memory. Material is then transferred to long-term memory using processes such as articulatory rehearsal (Baddeley, 1996) and attentional refreshment (Barrouillet & Camos, 2001), where it is stored for later retrieval. Impairments to memory and learning have been reported in VPT infants as young as twelve months of age on a paradigm involving the reproduction of action sequences and recognition of pictures (Rose et al., 2005). Deficits to immediate/working memory in older VPT cohorts (Böhm, Smedler, & Forssberg, 2004; Vicari, Caravale, Carlesimo, Casadei, & Allemand 2004; Sansavini et al.,

2006) and verbal list learning in very low birth-weight children (Taylor, et al., 2000) have also been reported.

A number of studies have investigated hippocampal volume and its relationship to general intellectual abilities and neurodevelopmental outcomes in preterm populations. Reduced hippocampal volumes in VPT neonates have been associated with poorer performance on the Mental Development and Psychomotor Development Indices of the Bayley Scale of Infant Development (BSID-II) at 2 years' corrected age (Thompson et al., 2008). In VPT children at 8 years of age, reduced hippocampal volumes have been associated with poorer full scale IQ (Lodygensky et al., 2005; Peterson et al., 2000). Moreover, left hippocampal volume reduction at 15-16 years of age has been associated with low IQ in adolescents born with very low birth weight (VLBW; <1250 g) (Abernethy et al., 2002). Isaacs and colleagues (2004) also reported a relationship between reduced hippocampal volumes and poorer Performance IQ in a cohort of adolescents born VPT and/or VLBW. In contrast, Abernethy and colleagues (2004) found little evidence for a relationship between hippocampal volumes in VPT children at 7 years and full scale IQ.

Fewer studies have specifically examined the relationship between hippocampal volume and memory and learning in those born VPT, with published reports having a narrow focus. This is surprising given evidence for the important role of the hippocampi in memory and learning (Moscovitch & Umilta, 1990; Cabeza & Nyberg, 1997; Nadel et al., 2000). While the hippocampi have typically been related to episodic long-term memory function, evidence suggests that they may also play a significant role in immediate/working memory (Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Piekema, Kessels, Mars, Petersson, & Fernandez, 2006). In the VPT population, Beauchamp et al. (2008) found that reduced neonatal hippocampal volumes were associated with poorer visual working memory on a delayed alternation task in VPT 2 year olds. Reduced hippocampal volumes in adolescents aged 13 years who were born VPT/VLBW has been associated with poorer everyday memory (Isaacs et al., 2000; 2003), and left hippocampal volume reduction in

those born VPT has been reported to correlate with reduced verbal recognition memory and learning performances at age 10-18 years (Giménez et al., 2004).

In summary, research investigating the association between hippocampal volume and multiple components of memory and learning in a large, representative and contemporary VPT cohort is needed. This is especially important given the significance of these skills for academic progress and success (Bull, Epsy, & Wiebe, 2008; Hornby & Woodward, 2009; Sansavini et al., 2006), highlighting the need for early detection and intervention. Using this framework, we recently reported that VPT children performed more poorly on measures of memory and learning in both verbal and visual domains compared with term controls at 7 years of age, with approximately 30% of the VPT group performing at least 1 SD below the control group mean (Omizzolo et al., 2013). Using children from the same cohort of VPT and term children, this study aims: 1) to compare hippocampal formation volume between VPT and term controls at age 7 years, and 2) to evaluate the association between hippocampal volume and memory and learning functioning in VPT children at 7 years.

Methods

Participants.

Participants were part of the Victorian Infant Brain Studies (VIBeS) cohort, a prospective, longitudinal study examining brain abnormality and development in VPT children. Recruitment occurred from July 2001 to December 2003 at the Royal Women's Hospital in Melbourne, Australia; 224 VPT infants with either a GA of <30 weeks or a birth weight of <1250 g were recruited. Infants with severe congenital abnormalities that would impair neurological function were excluded. A concurrent control group of 46 children born full term (37 to 42 weeks' GA) and of normal birth weight (≥2500 g) was also recruited from the Royal Women's Hospital. An MRI brain scan was conducted on all infants without sedation, and at term equivalent age for VPT subjects. Follow-up assessment occurred at ages 2, 5 and 7 years (corrected for prematurity). At the latest follow up at 7 years of age,

198 VPT (88%) and 43 (93%) term children had a neuropsychological assessment, and 160 VPT (81%) and 36 (84%) term children had a MRI brain scan. The main reasons children did not have imaging data at age 7 years were that they were too anxious or unsettled (VPT, n = 18; term, n = 3), did not consent (VPT, n = 6, term, n = 1) or were too impaired (VPT n = 6). Neuropsychological assessments and MRI brain scans were completed over two days. Of the 160 VPT and 36 term children with scans, 145 (91%) VPT and 34 (94%) term children had scans that were suitable for analysis after scans with movement artefact were excluded.

Procedure and measures.

This study was approved by the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital. Parents gave written informed consent for their child to participate. MRI scanning took place at the Children's MRI Centre at Melbourne's Royal Children's Hospital with a 3 Telsa Trio Siemens MRI machine (Siemens, Erlangen, Germany). Prior to the MRI scan, each child underwent a mock MRI scanning session that was aimed to familiarise the child with the scanning procedure. Scans were conducted without sedation or anesthesia, and both T_1 (0.85mm sagittal slices, flip angle = 9°, repetition time = 1900ms, echo time = 2.27ms, field of view = 210 x 210mm, matrix= 256 x 256) and T_2 weighted (0.90mm sagittal slices, repetition time = 3200ms, echo time = 447ms, field of view = 240 x 215mm, matrix = 256 x 230) structural images were acquired.

Hippocampal segmentation.

A single operator (C.O.) manually outlined left and right hippocampal formations in the coronal view of the T_1 scan using ITK-SNAP 2.2.0 (see Figure 1), and was blinded to all perinatal data (including to which birth group the images belonged). Tracing always proceeded from the posterior to anterior sections in a sequential manner (i.e. beginning at the hippocampal tail, and followed by the hippocampal body and head). Each slice of the hippocampal formation was traced from the superiomedial edge to the lateral edge, downwards to the inferior aspect, and finally to the medial edge. In general, anatomical boundaries proposed by Watson and colleagues (1992) and Pruessner and colleagues

(2000) were followed, with reference to anatomical atlases by Woolsey, Hanaway and Gado, (2003). While tracing occurred in the coronal view, reference was made to the sagittal and horizontal views in order to provide more reliable identification of structural boundaries. The dentate gyrus, four cornu ammonis regions, alveus and the fimbria were included within the hippocampal formation measurement.

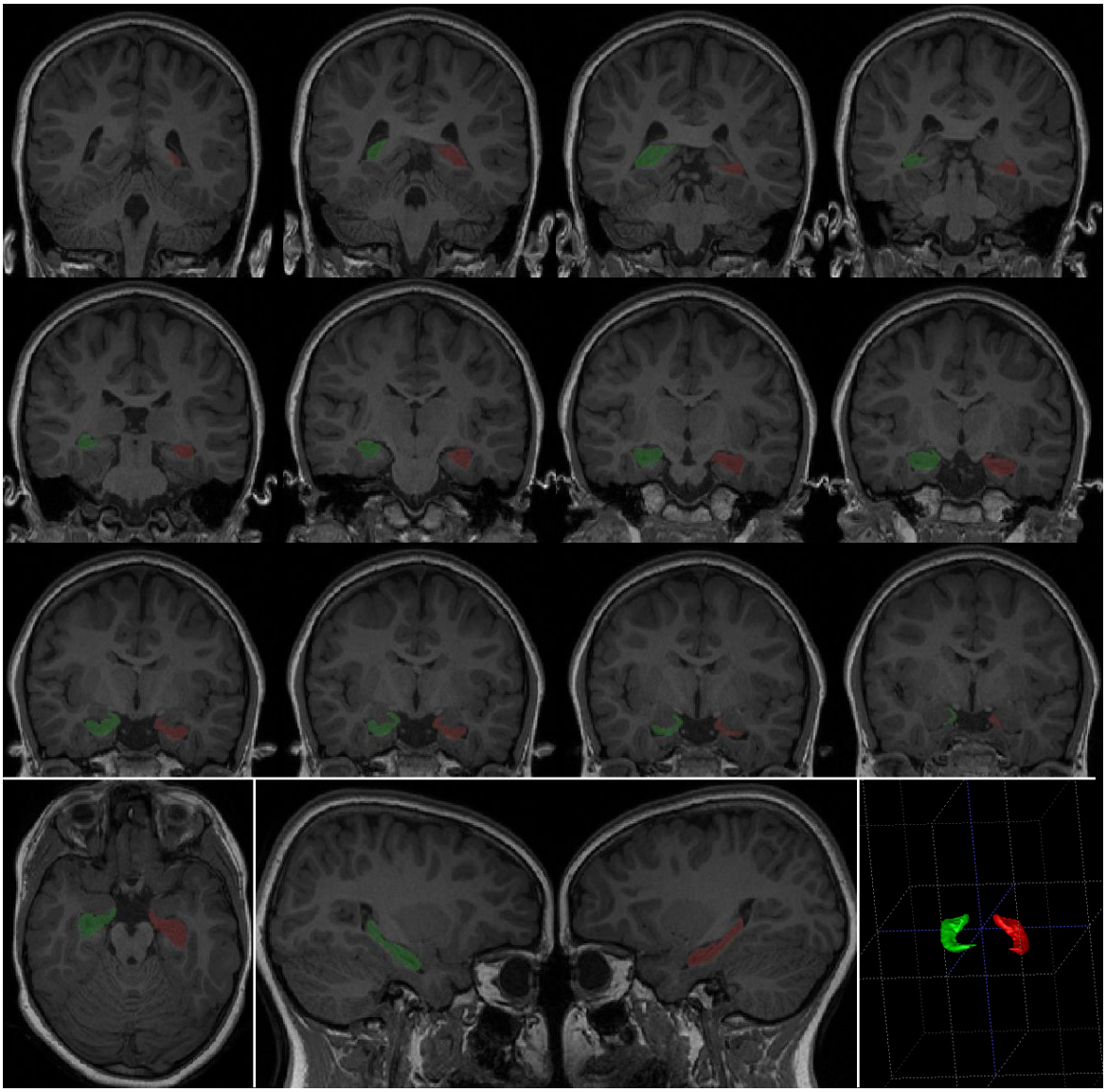


Figure 1. T1 image showing left (green) and right (red) hippocampal boundaries as traced on (a) the coronal plane from anterior to posterior, (b) the axial plane, (c) the sagittal plane, and (d) the 3-dimensional representation.

Boundaries of the hippocampal tail.

The most posterior slice of the hippocampal tail (HT) was defined as the slice where the crus of the fornix was clearly visible surrounding the hippocampus inferiomedially to the trigone of the lateral ventricle (TLV). Consistently, the lateral border was defined as the boundary between the white matter of the fimbria and the TLV. Medially, the border was where the quadrigeminal cistern met the hippocampal sulcus. Initially, an arbitrary border was used to help define the superior border of the HT. This arbitrary border was a horizontal line from the superior border of the quadrigeminal cistern to the TLV. This was to help define and separate the HT from the fasciolar gyrus, which sits above the HT. Further anteriorly, the fimbria was used as the superior border. The border between the hippocampus and the parahippocampal gyrus provided the inferior border (an upward slant medially). Although these procedures led to some exclusion of the medial and superior sections of the HT, this method appeared to produce the most consistent approach for defining the HT.

Boundaries of the hippocampal body.

The fimbria formed the superior border of the hippocampal body (HB). The lateral border of the HB was defined by the inferior horn of the lateral ventricle, and the most visible inferiolateral grey matter was included. The medial border was where the subiculum joined with the hippocampal sulcus.

Boundaries of the hippocampal head.

The hippocampal head (HH) can be identified as the most anterior portion of the hippocampal formation. The first coronal slice of the HH was defined when the uncal recess appeared in the superomedial portion of the hippocampus. This formed a distinct protuberance or “hook” which was used to identify the superomedial border. The inferior border was defined by the uncus, and the border between the entorhinal cortex and the hippocampus. When the grey matter at the superior part of the hippocampal formation became interspersed with amygdala, hippocampus, and basal ganglia (putamen and globus

pallidus; Pruessner et al., 2000), the fimbria was used to separate the hippocampal formation from amygdala, evident as a line of white matter intermingling with CSF. The lateral border was the border between the alveus and the temporal horn of the lateral ventricle. Further anterior, the medial edge was the most medial point of the temporal lobe. The last slice was identified as the most anterior slice where the temporal horn of the lateral ventricle was still seen laterally to the hippocampus.

Repeat segmentations to assess intra-rater reliability were conducted 1 week apart on 10 subjects. Intra-class correlation coefficients were 0.97 ($p<0.01$) for the right and 0.96 ($p<0.01$) for the left hippocampal formations. Inter-rater reliability was carried out by an experienced operator (D.K.T) on 10 subjects. Intra-class correlation coefficients were 0.96 ($p<0.01$) for the right hippocampus and 0.97 ($p<0.01$) for the left hippocampus.

Neuropsychological assessment.

Children underwent extensive neuropsychological assessment as part of the 7 year follow-up. Selected measures from the test battery were used to assess IQ as well as memory and learning within the verbal and visual modalities and are outlined below.

Wechsler Abbreviation Scale of Intelligence (WASI; Wechsler, 1999).

IQ was estimated using the 4-subset version of the WASI.

Working Memory Test Battery for Children (WMTB-C; Pickering & Gathercole, 2001).

Three subsets from the WMTB-C were administered. Forward Digit Recall was used to assess immediate verbal memory and involved each child being read a sequence of numbers which they were required to recall in the same order. Number sequences began at 1 digit and increased to 9 digits (or until ceiling was reached), with 6 trials per sequence. Digits were read at a rate of 1 per second. Backward Digit Recall measured verbal working memory and had a similar process, although children were required to repeat sequences in the reverse order. Block Recall assessed immediate visual memory. The examiner tapped an

array of three-dimensional blocks in a sequence (also at a rate of one per second), and participants were required to tap them in the same sequence. Responses on all tasks were scored 0 or 1 for each trial, and a total score reflected the number of trials completed correctly.

California Verbal Learning Test – Children's Version (CVLT-C; Delis, Kramer, Kaplan & Ober, 1994).

The CVLT-C (Delis et al., 1994) was used to measure verbal memory and learning. Children were read a 15-item word list (List A) and asked to immediately recall the list. This was repeated another 4 times, which in total derived a learning score. Next, a second or distracter list (List B, also of 15 words) was administered, which children were also required to immediately recall, followed by a short-delay recall of List A. After a 20 to 30 minute delay, long-delay recall and recognition trials of List A were administered. Outcome measures were immediate verbal memory (number of words recalled on trial 1 of list A), verbal learning (total number of words recalled across trials 1-5), and memory after short and long delays.

Dot locations subset from the Children's Memory Scale (Cohen, 1997).

Dot locations was used to assess visual memory and learning. Children were presented with an array of 6 dots on a 3x3 grid and required to immediately recall their spatial location. This procedure was repeated two more times, and was followed by a second (or distractor) dot array. A short-delay recall of the original dot array was then administered, which was followed by a long-delay recall 20 to 30 minutes later. Outcome measures included immediate visual memory (trial 1), visual learning (total trials 1-3), and visual memory after short and long delays.

Neonatal brain abnormality score.

A neonatal neurologist rated cerebral abnormality on T_1 and T_2 structural scans using a system described by Kidokoro, Neil, & Inder (2013), which is an adaptation of a procedure applied previously (Inder et al., 2003; Woodward, Anderson, Austin, Howard, &

Inder, 2006). This scoring system rates presence and severity of white matter abnormality (cystic lesions, signal abnormality, myelination delay, callosal thinning, lateral ventricular volume, white matter volume), cortical grey matter abnormality (extracerebral space, signal abnormality, gyral maturation), deep grey matter abnormality (signal abnormality, deep grey matter volume) and cerebellar abnormality (signal abnormality, cerebellar volume) on a scale from 0 to 4. These four subscales are summed to produce a global neonatal brain abnormality score (scores ranged from 0 to 40).

Social risk.

Social risk was defined as a high score on a parent questionnaire based on family structure, language spoken at home, education of primary caregiver, occupation and employment status of primary income earner, and maternal age at birth (overall score 0-12; Roberts et al., 2008).

Statistical Analyses

Data were analyzed using Stata 12 (StataCorp, 2011). Raw scores were used to report test results, and scores were recorded as "missing" when children were too impaired to complete tasks. Linear regression was used to examine differences between birth groups (VPT and term) in left and right hippocampal volumes (measured in cubic centimetres; cc), with separate models applied to each hemisphere. Each model was fitted using generalized estimating equations (GEEs) with an exchangeable correlations structure and robust standard errors to allow for correlations between twins/triplets in the study. Subsequent analyses controlled for gender, intracranial volume (ICV), and neonatal brain abnormality score.

Linear regression was also used to determine the relationships between left and right hippocampal volumes and memory and learning outcomes in the VPT cohort. Again, models were fitted with GEEs and robust standard errors. Secondary analyses adjusted for the effects of gender, ICV, and neonatal brain abnormality score.

Results

Sample characteristics.

Sample characteristics of the VPT and term cohorts are outlined in Table 1. ICV was smaller on average in the VPT group (6.3% reduction compared with term born peers, p<.01). Groups also differed on neonatal brain abnormality score (p<0.01), IQ (p<0.01), the percentage of singletons (p<0.01) and social risk (p<0.01). In contrast, there was little difference in gender, handedness, and age at assessment between the VPT and term groups.

Table 1. Demographic and perinatal characteristics of the sample assessed at 7 years of age for the current study.

	Very Preterm sample *n** = 145	Term sample *n** = 34
GA (weeks), *M* (*SD*)	27.5(1.9)	38.9(1.3)
Age at assessment (years), *M (SD)*	7.5(0.2)	7.5(0.2)
Birth Weight (*g*)	972(222)	3277(508)
IQ, *M (SD)*	98.8(13.1)	109.8(12.3)
Social risk, *M (SD)*	2.1(1.7)	1.2(1.6)
Intracranial volume, *M(SD)*	1325(118)	1414(99)
Neonatal brain abnormality score, *M(SD),*	5.6(3.4)	1.8(1.5)
Non right-handers, %	30.9	21.7
Small for gestational age, %	9.0	2.9
Male gender, %	49.7	50.0
Singleton, %	53.1	94.1
Antenatal corticosteroids, %	87.6	0
Postnatal corticosteroids, %	4.9	0
Bronchopulmonary dysplasia, %	29.7	0
Cystic periventricular leukomalacia, %	3.5	0
Intraventricular hemorrhage grades 3/4%	3.5	0

*Some sample sizes are less than the total sample due to missing data (social risk [very preterm = 139, term = 33]. Intracranial volume [very preterm = 144], and postnatal corticosteroids [very preterm = 144].
M = mean
SD = standard deviation
GA = gestational age
IQ = general intellectual functioning

Table 2 displays the mean group differences for the VPT and term control groups on the memory and learning measures, and illustrates the generalized memory deficits of this VPT group.

Table 2. Mean group differences on memory and learning outcomes at age 7 years

	Adjusted for age		Adjusted for age, social risk, excluding children with IQ<70	
Outcome	Mean group difference (95%CI)	p	Mean group difference (95%CI)	p
Immediate Memory				
Digits Forward	-1.26(-2.84, .31)	.11	-.57(-2.13, .98)	.47
Block Recall	-2.86(-4.44, -1.28)	< .01	-2.87(-4.40, -1.34)	< .01
Working Memory				
Digits Backward	-2.21(-3.47, -.96)	< .01	-1.98(-3.23, -.72)	< .01
CVLT-C Trial 1	-.34(-1.10, .42)	.39	-.31(-1.09, .47)	.44
Memory/Learning				
CVLT-C				
Total Trials 1-5	-3.25(-7.55, 1.05)	.14	-2.57(-6.94, 1.79)	.25
Short Delay	-1.25(-2.19, -.31)	< .01	-1.05(-2.03, -.08)	.03
Long Delay	-.87(-1.94, .21)	.11	-.59(-1.66, .49)	.28
Dot Locations				
Total Trials 1-3	-1.49(-2.29, -.69)	< .01	-1.11(-1.92, -.30)	< .01
Short Delay	-.80(-1.08, -.52)	< .01	-.74(-1.03, -.44)	< .01
Long Delay	-.56(-.91, -.22)	< .01	-.49(-.84, -.14)	< .01

Note: lower scores reflect poorer performance in the VPT group. N ranges from 179-164 depending on the outcome.
VPT = very preterm
CVLT-C = California Verbal Learning Test – Children's Version
CI =confidence interval

Hippocampal volume analysis.

Table 3 shows that VPT children had reduced right ($p<0.01$) and left ($p<0.01$) hippocampal volumes compared with term controls. The VPT group displayed a reduction of 5.9% to the right hippocampus, and 6.8% to the left hippocampus relative to mean hemispheric volume in the term controls. However, the evidence for these differences reduced for the right and left hippocampi when gender, ICV, and neonatal brain abnormality were added to the model (see Table 3). The proportion of variance (R^2) accounted by birth group (i.e. VPT and term) was 4.8% for right hippocampal volume and 7.2% for left

hippocampal volume. R^2 increased to 10.3% for the right hippocampus and 14.1% for the left hippocampus when gender was added to the model, 23.1% (right hippocampus) and 25.4% (left hippocampus) when ICV was added, and 25.4% (right hippocampus) and 26.8% (left hippocampus) when neonatal brain abnormality was added. Of interest, there was little evidence that the association between group and hippocampal volume differed between genders (interaction; left hippocampal volume p=0.81, right hippocampal volume p=0.89).

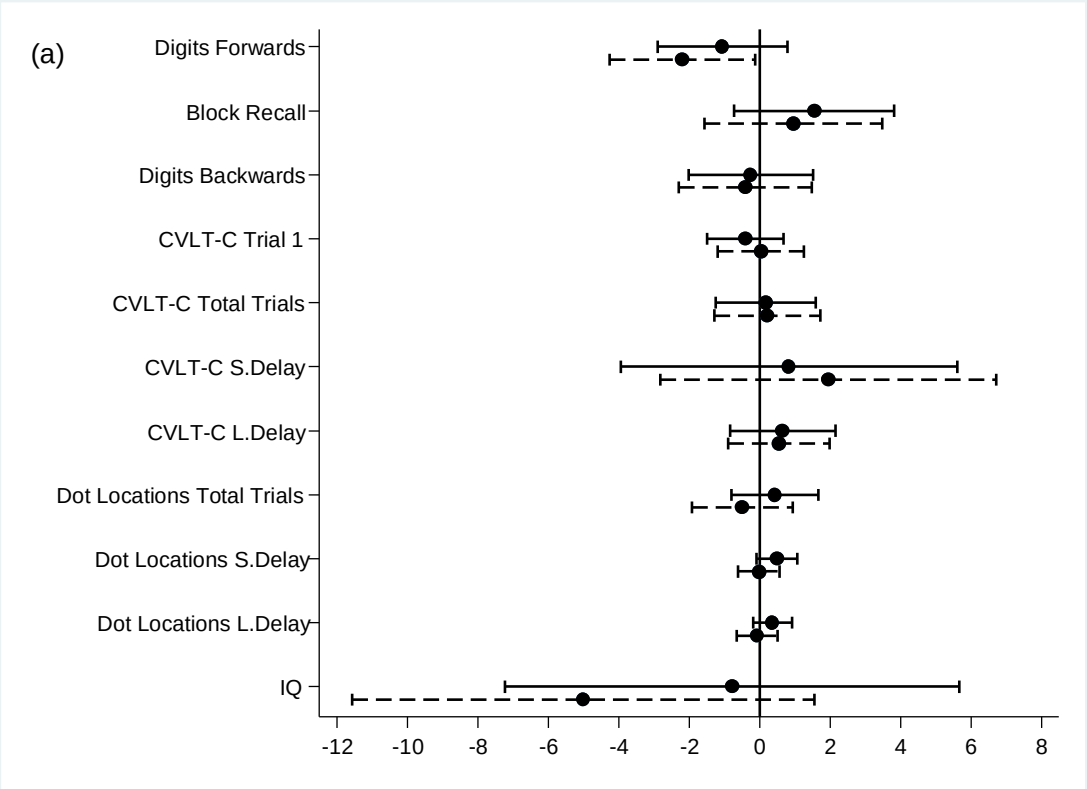
Table 3. Associations between birth group and hippocampal volume at 7 years

			Unadjusted *n* = 179		Adjusted for gender, ICV, neonatal brain abnormality *n* = 177	
Volume (cc)	VPT *M(SD)*	Term *M(SD)*	*b*(95%CI)	*p*	*b*(95% CI)	*p*
Right	3.19(0.36)	3.39(0.31)	-0.19(-0.31, -0.07)	<0.01	-0.001(-0.13, 0.13)	0.98
Left	3.30(0.35)	3.54(0.32)	-0.24(-0.36, -0.11)	<0.01	-0.07(-0.20, 0.05)	0.26

VPT = very preterm
ICV = intracranial volume
M = mean
SD = standard deviation
CI = confidence interval
b = coefficient for group from the linear regression model representing the difference in means between the VPT and term groups

Hippocampal volume as a predictor of memory and learning outcomes in children born VPT.

Figure 2 displays the relationship between left (a) and right (b) hippocampal volumes and performance on memory and learning outcomes in the VPT group. Unadjusted and analyses adjusted for gender, ICV and neonatal brain abnormality score showed that neither left or right hippocampal volumes were associated with performance on our memory or learning outcomes. Right and left hippocampal volumes did not predict IQ in the VPT group in unadjusted or adjusted (i.e., gender, ICV and neonatal brain abnormality score) models (see Figure 2).



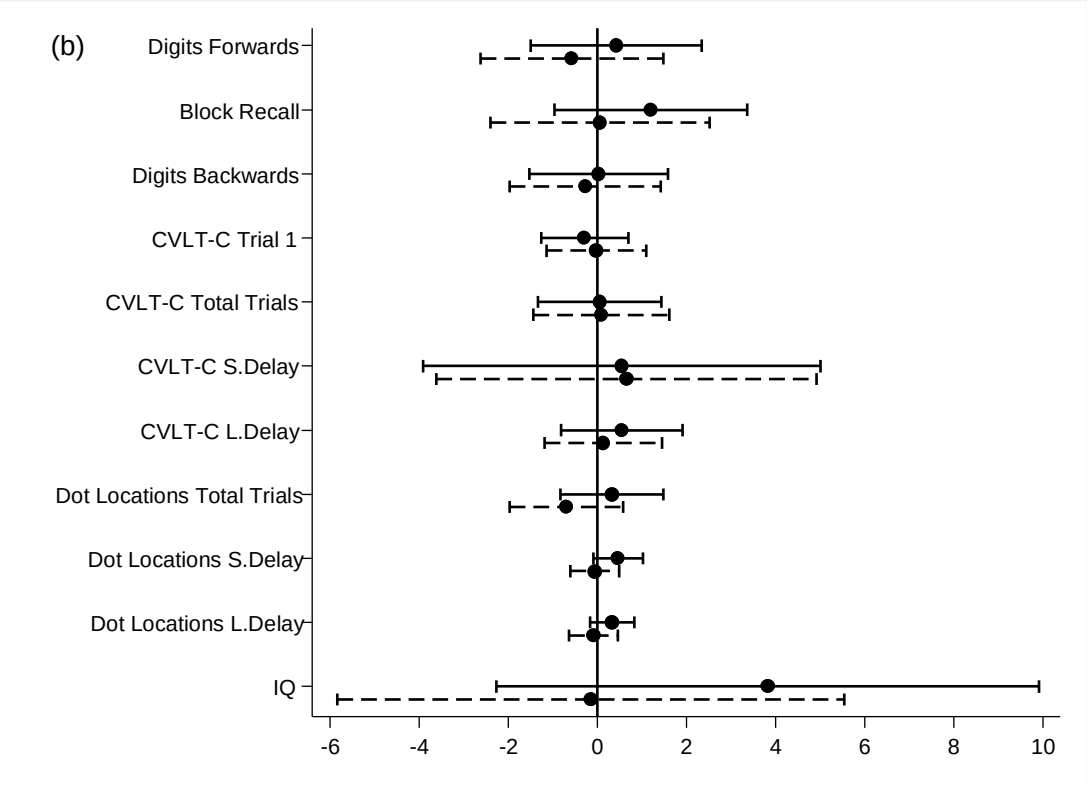


Figure 2. Regression coefficients and 95% confidence intervals for the association between hippocampal volume and memory and IQ measures at 7 years of age in the VPT children for (a) the left hippocampus, and (b) the right hippocampus. Estimates represent the difference in outcome are per cc change in hippocampal volume from an unadjusted analysis (dotted lines) and an analysis adjusted for gender, ICV and neonatal brain abnormality (solid lines).

Discussion

This prospective, longitudinal study investigated hippocampal volume, and memory and learning outcomes in 7 year old children born VPT. Children born VPT had smaller hippocampi compared with their term peers, but not after adjusting for gender, ICV and neonatal brain abnormality. Contrary to expectation, we found little evidence of a relationship between hippocampal volume and memory or learning outcomes within the VPT group.

Previous research has reported hippocampal volume reductions in VPT and/or VLBW cohorts when compared to term born peers in the neonatal period as well as later childhood (Gimenez et al., 2004; Isaacs et al., 2000; Isaacs et al., 2003; Nosarti et al., 2002; Peterson et al., 2000; Thompson et al., 2008). Whilst some of these studies report that hippocampal volume reductions in these children persist after adjusting for overall brain size (Isaacs et al., 2003; Gimenez et al., 2004; Nosarti et al., 2002; Peterson et al., 2000), others do not (Isaacs et al., 2000; Thompson et al., 2008). Like previous studies, our unadjusted analyses showed reduced hippocampal volumes in the VPT group, however subsequent analyses indicated that these differences were largely related to overall smaller brain size (in the case of the right hippocampus) and neonatal brain injury (in the case of the left hippocampus). For example, hippocampal volume reductions in the VPT cohort (right = 5.8%, left = 6.8%) were similar in magnitude to whole brain volume reduction (ICV = 6.3%).

Although the hippocampi resemble adult morphology at approximately 5 years of age (Insausti, Cebada-Sanchez, & Marcos, 2010), they continue to grow with further organisation, dendritic branching, and myelination into adolescence (Insausti, et al., 2010). Given this study examined hippocampal volumes in VPT children at 7 years of age, the full effects of VPT birth on normal hippocampal growth may not be apparent until later in development. In support of this argument, studies examining hippocampal volumes in older children and adolescents born VPT show larger hippocampal reductions in comparison to whole brain volume (Gimenez et al., 2004; Isaacs et al., 2003; Nosarti et al., 2002; Peterson

et al., 2000). For example, Nosarti and colleagues (2002) reported a 6.0% decrease in whole brain volume in a group of VPT 15 year olds compared with term controls, but found a 15.6% and 12.1% decrease in the right and left hippocampi respectively. Furthermore, Gimenez and colleagues (2004) reported a whole brain volume reduction of approximately 8% in their cohort of VPT children and adolescents aged 10-18 years compared with term controls, but found a 16.7% and 15.5% reduction in left and right hippocampal volumes respectively.

A number of methodological factors may help explain the differences in hippocampal volumes between our study and the aforementioned studies. Nosarti et al., (2002) recruited their VPT cohort during the late 1970s and early 1980s, whereas our cohort was recruited in the early 2000s. The substantial advances in perinatal care that have occurred over the past two decades, and particularly in the 1990s (Horbar et al., 2002), might have protective effects on the hippocampi. Further, Gimenez and colleagues (2004) utilized voxel-based morphometry for hippocampal analysis, whereas our study utilized manual segmentation, which is arguably a more precise and reliable estimate (Cherbuin et al., 2009).

Previous studies have shown that reduced neonatal hippocampal volume is associated with a number of intellectual and neurodevelopmental outcomes in VPT children and adolescents. For example, neonatal hippocampal volume reductions have been linked to developmental and motor delays at 2 years of age (Thompson et al., 2008), and reduced hippocampal volumes at 8 years of age has been associated with poorer full scale IQ (Lodygensky et al., 2005; Peterson et al., 2000). In this study we found no evidence for an association between hippocampi volume and IQ. Possible explanations for this discrepancy include the younger age of children in the current study, varying measures of IQ used across studies, and differences in segmentation protocols for hippocampal formations between studies.

Additionally, previous research has linked reduced hippocampal volumes during adolescent years to everyday memory impairment (Isaacs et al. 2000; 2003), and verbal

learning and recognition memory impairment (Giménez et al., 2004) in VPT cohorts. Although VPT children in our study have been found to perform poorer than term controls in IQ and memory measures (Omizzolo et al., 2013), we were unable to associate memory functioning or IQ with hippocampal volumes measured at 7 years. Thus, our findings suggest that the effects of VPT birth on memory and learning at age 7 years are not confined to hippocampal volumes alone.

The VPT brain is not a typically developing brain. A recent account of functional localization suggests that when a task is sufficiently difficult, and therefore exceeds the resources of a particular brain area, other areas will be recruited to assist with the excess workload (Just, & Varma, 2007). When the development of a particular brain structure is altered during VPT birth, such as the hippocampi, resources in this area may be reduced and additional regions recruited (Lawrence et al., 2010). This theoretical account may explain why hippocampal volume itself was insufficient to explain memory and learning deficits in our VPT cohort, and suggests the involvement of more complex networks and neural systems.

The hippocampal formations have extensive connections across multiple brain regions (Rolls, 2000; Thierry, Gioanni, Degenetais, & Glowinski, 2000). Studies investigating neural networks underlying memory and learning highlight the important role of the prefrontal and parietal cortices (Cabeza & Nyberg, 1997), and show hippocampal-prefrontal interactions (Hasselmo, & Sarter, 2011). For example, the right anterior hippocampus and the right dorsolateral prefrontal cortex have been implicated with successful verbal memory processing in adults (Johnson, Saykin, Flashman, McAllister, & Sparling, 2001). Furthermore, prefrontal regions have been associated with general cognitive ability and memory in VPT children (Woodward et al., 2005). Early damage to the hippocampi associated with VPT birth, such as neonatal brain injury and the effects of corticosteroids, may secondarily influence memory and learning abilities by disrupting the underlying neural and functional circuitry of these areas.

The current study has a number of strengths. First, measures that assess multiple components of memory and learning were utilized to investigate the relationship with hippocampal volume in childhood. This contrasts previous literature that reports a limited number of neuropsychological measures. Second, each child participated in a mock MRI scan which exposed them to the scanning environment to ensure best quality images. Finally, our study was the first to have neonatal brain imaging in a VPT cohort, and therefore, allowed us to control for the effect of early neonatal brain abnormalities on later outcome.

While the current study provides insight into the integrity of the hippocampal formations following VPT birth, one methodological limitation remains to be addressed. Although manual tracing is considered the gold standard in measuring hippocampal volume (Konrad et al., 2009), it is prone to human error, especially when defining the boundaries of the hippocampal and entorhinal regions and the borders between the hippocampus and amygdala (Konrad et al., 2009). Furthermore, there are a large number of different anatomical protocols for delineating the hippocampal formation, which provide a possible source of variance and inconsistency in findings between studies and conditions (Geuze, Vermetten, & Bremner, 2005; Konrad et al., 2009; Van Leemput et al., 2009). In the current study, however, there was excellent intra-observer and inter-observer agreement in measurement of hippocampal volumes.

In conclusion, findings from this study demonstrate that hippocampal volume alone does not give sufficient insight into the role that this vital region plays in memory and learning in children born VPT at 7 years of age. Future research might examine whether particular regions of the hippocampus are more affected by VPT birth, and whether specific regions are more strongly associated with memory and learning outcomes. Research investigating the neural substrates and networks which foster memory and learning in this population are also needed, ideally using techniques such as tractography. Establishing the functional consequences of altered hippocampal development will help us understand and

identify at-risk children early in their development.

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Chapter 8: Paper 3

Longitudinal growth and morphology of the hippocampus through childhood: Impact of prematurity and implications for memory and learning

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Abstract

The effects of prematurity on hippocampal development through early childhood are largely unknown. The aims of this study were to 1) compare the shape of the very preterm (VPT) hippocampus to that of full-term (FT) children at 7 years of age, and determine if hippocampal shape is associated with memory and learning impairment in VPT children, 2) compare change in shape and volume of the hippocampi from term-equivalent to 7 years of age between VPT and FT children, and determine if development of the hippocampi over time predicts memory and learning impairment in VPT children. T_1 and T_2 magnetic resonance images were acquired at both term equivalent and 7 years of age in 125 VPT and 25 FT children. Hippocampi were manually segmented and shape was characterized by boundary point distribution models at both time-points. Memory and learning outcomes were measured at 7 years of age. The VPT group demonstrated less hippocampal infolding than the FT group at 7 years. Hippocampal growth between infancy and 7 years was less in the VPT compared with the FT group, but the change in shape was similar between groups. There was little evidence that the measures of hippocampal development were related to memory and learning impairments in the VPT group. This study suggests that the developmental trajectory of the human hippocampus is altered in VPT children, but this does not predict memory and learning impairment. Further research is required to elucidate the mechanisms for memory and learning difficulties in VPT children.

Key words: very preterm children, hippocampal size and shape, development, magnetic resonance imaging, neurodevelopmental outcome

Abbreviations:

CMS	Children's Memory Scale
CVLT	California Verbal Learning Test
FT	full-term
GA	gestational age
ANCOVA	analysis of covariance
MRI	magnetic resonance imaging
SHARM-PDM	spherical harmonics-point distribution model
VPT	very preterm
WMTB-C	Working Memory Test Battery for Children

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Introduction

The human hippocampal formation undergoes rapid growth and morphological development in the perinatal months, including cytoarchitectural differentiation and infolding of the dentate gyrus and cornu ammonis regions into the medial temporal lobe (Steven E Arnold & John Q Trojanowski, 1996; Kier et al., 1997; Okada et al., 2003; Seress, 2001). One may expect this mesial temporal lobe structure to be particularly susceptible to the effects of very preterm birth (VPT; <32 completed weeks of gestational age [GA]) given the degree of hippocampal development in the perinatal period. Infection, hypoxic-ischemia, lung disease, and stress (Gadian et al., 2000; E. B. Isaacs et al., 2000; Khwaja & Volpe, 2008) are a number of complications associated with VPT birth that have been reported to be associated with hippocampal pathology (Rees et al., 1999; Volpe, 2000). Previous studies have reported reduced hippocampal volume in VPT infants (D. K. Thompson et al., 2008) and adolescents (Gimenez et al., 2008; Nosarti et al., 2002) and altered hippocampal shape in VPT infants (Deanne K. Thompson et al., 2013) compared with their FT peers. Although cross-sectional evidence demonstrates compromized hippocampal development as a result of prematurity, there is currently no longitudinal information on hippocampal development in VPT children.

Several cross-sectional studies have described hippocampal growth through childhood. In a post-mortem study, hippocampal volume increases were reported between one and two years of age (Kretschmann et al., 1986). Volumetric magnetic resonance imaging (MRI) studies have demonstrated maximum hippocampal growth to occur between one and two months of age, with continued rapid growth up to two years of age (Knickmeyer et al., 2008; Utsunomiya et al., 1999) and slowed growth up to 14 years (Utsunomiya et al., 1999). Uematsu et al. (2012) reported nonlinear age-related hippocampal volume changes between 1 month to 25 years, again with most growth occurring during the first few years of life and peaking at 9-11 years of age. The structural development of the hippocampus may parallel functional development.

Functionally, the hippocampal formation is vitally involved with memory and learning (R. Cabeza & L. Nyberg, 2000; Nadel et al., 2000). Memory involves the initial registration of information into a temporary storage system, referred to as immediate memory, and the capacity to process this information while in temporary storage is referred to as working memory (A. D. Baddeley & Hitch, 1974). Processes such as articulatory rehearsal (A. Baddeley, 1996) and attentional refreshment (Barrouillet & Camos, 2001) are used to transfer this material into long-term memory, where it is stored for later retrieval. VPT children often show memory and learning impairments (E. B. Isaacs et al., 2000; E. B. Isaacs et al., 2003; C. Omizzolo et al., 2013; Rose et al., 2005; Woodward et al., 2005), and reduced hippocampal volume has been associated with compromized working memory in VPT children at 2 years of age (Beauchamp et al., 2008) and poorer everyday memory in VPT adolescents (E. B. Isaacs et al., 2000; E. B. Isaacs et al., 2003). Left hippocampal volume reduction has also been correlated with reduced verbal recognition memory and learning in preterm teenagers (Gimenéz et al., 2004). While we have previously reported that hippocampal shape in VPT infants is not associated with memory and learning performance at 7 years of age (Deanne K. Thompson et al., 2013), it remains unknown whether hippocampal shape at 7 years, or the change in shape or volume between infancy and 7 year of age relates to memory and learning.

This study aims to: 1) compare the shape of the hippocampus between VPT and full-term (FT) children at 7 years of age, and determine if hippocampal shape of VPT children is associated with memory and learning impairment at age 7 years, and 2) compare change in (a) shape and (b) volume of the hippocampi from term-equivalent to 7 years of age between VPT and FT children, and determine if change in the shape or volume of the hippocampus are associated with memory and learning impairment at 7 years in VPT children.

Materials and Methods

Participants.

Participants were prospectively recruited at birth from the Royal Women's Hospital in Melbourne, Australia from July 2001 to December 2003 as part of the Victorian Infant Brain Studies cohort. The VPT group consisted of 227 infants with either a GA of <30 weeks or a birth weight of <1250 g. Subjects with congenital abnormalities that would impair neurological function were excluded. A concurrent control group was also recruited from the Royal Women's Hospital, and consisted of 46 FT (37 to 42 weeks' GA) and normal birth weight (≥2500 g) infants. All infants underwent an MRI brain scan at term equivalent age (40 weeks +/- 2 weeks). A total of 184 VPT and 32 FT infant scans (79% of the original sample) were suitable for hippocampal analysis. Of the remaining subjects, some were unable to be scanned within the term equivalent age range (38-42 weeks' GA; *n*=14), and some were excluded due to imaging artefact (*n*=43).

At 7 years corrected age, all participants underwent a brain MRI and neuropsychological assessment, with follow-up rates (from the original sample) of 88% for the VPT group (*n*=198) and 93% for the FT group (*n*=43). Of these, 145 VPT and 34 FT children had MRI and outcome data at 7 years; the remainder were unable to be scanned (n=45), or scans were excluded due to image artefacts (*n*=17). A total of 125 VPT and 25 FT children had MR images able to be analysed at both time points (term-equivalent and 7 years), which is the sample used in the current study.

This research complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and the Human Research Ethics Committee of the Royal Women's Hospital and the Royal Children's Hospital granted approval for the study. Written informed consent was obtained from parents.

Imaging.

Infant scanning (gestational age range 38-42 weeks) took place at the Royal Children's Hospital, Melbourne. T_2/ proton density weighted MR images (1.7-3.0 mm coronal slices; repetition time 4000 msec; echo time 60/160 msec; flip angle 90°; field of view 22 ×16 cm; matrix 256×192, interpolated 512×512) were acquired with a 1.5 Tesla General Electric MRI scanner.

MRI scanning was repeated at 7 years of age at the Royal Children's Hospital, Melbourne. Prior to the scan, children underwent a mock MRI scanning session to familiarize each child with the scanning environment and procedure. Scans were conducted without sedation, and T_1 weighted (0.85mm sagittal slices, flip angle = 9°, repetition time = 1900ms, echo time = 2.27ms, field of view = 210 x 210mm, matrix= 256 x 256) structural images were obtained using a 3Tesla Trio Siemens MRI machine (Siemens, Erlangen, Germany).

Hippocampal segmentation.

Hippocampal segmentation was conducted on MRI scans at both term equivalent age and at 7 years of age. Hippocampal formations in the term equivalent data were manually outlined by a single operator (D.K.T) in the coronal view on the combined raw T_2- and proton density–weighted image volumes (obtained by volume addition) to increase contrast for optimal visualization of hippocampal boundaries (Deanne K Thompson et al., 2012; D. K. Thompson et al., 2008). Infant hippocampal segmentation was performed with the 3Dslicer 2.5 software (http://slicer.org/), with reference to anatomical atlases (Duvernoy, 2005; Mai, Assheuer, & Paxinos, 1997). The tracing scheme has been previously described in detail (Deanne K Thompson et al., 2012; D. K. Thompson et al., 2008). Hippocampal volumes were delineated a second time on 15 randomly chosen images for reliability analysis. Intraclass correlation coefficients were 0.97 for the right and 0.96 for the left hippocampus.

At 7 years, the hippocampi were manually delineated by operator C.O. The structure was manually outlined in the coronal view of the T_1 scan using ITK-SNAP 2.2.0 (see Figure

1). Again, anatomical boundaries generally followed those proposed by Watson et al. (1992) and Pruessner et al. (2000), with reference to an anatomical atlas (Woolsey et al., 2008). While tracing occurred in the coronal view, reference was made to the sagittal and axial views in order to provide more reliable identification of structural boundaries. The dentate gyrus, four cornu ammonis regions, alveus and the fimbria were included within the hippocampal formation measurement. Boundary definition has been previously described in detail (C. Omizzolo et al., in press). Repeat segmentations to assess intra-rater reliability were conducted on 10 subjects. Intra-class correlation coefficients were 0.97 for the right and 0.96 for the left hippocampal formations.

Due to the longitudinal nature of this study, all 7 year hippocampal segmentations were reviewed and edited by D.K.T to match boundary definitions used at term equivalent. This required deleting several slices of the hippocampal tail in 7 year segmentations when they extended posterior to the point where the crus of the fornix fused with the pulvinar nucleus. This was necessary because this section of the tail was not included in infant segmentations, as it was not able to be consistently delineated. Inter-rater reliability was carried out between operators D.K.T and C.O. on 10 subjects, and intra-class correlation coefficients were 0.96 for the right and 0.97 for the left hippocampus.

Hippocampal shape analysis.

Morphological analysis of the delineated neonatal hippocampal formations was conducted using the spherical harmonics-point distribution model (SPHARM-PDM) (Shi et al., 2007; Styner, Gerig, Lieberman, Jones, & Weinberger, 2003). This model characterizes both global and local shape (Gerig, Styner, Jones, Weinberger, & Lieberman, 2001; Styner et al., 2006). This technique has been previously described in detail (Deanne K. Thompson et al., 2013). In brief, both infant and 7 year hippocampal masks were resampled to isotropic resolution and minimally smoothed. Boundaries were converted to triangular surface meshes (Lorensen & Cline, 1987) which were deformed to spheres (Brechbühler, Gerig, & Kübler, 1995), thereby creating spherical parameterizations. Smoothed PDM shape

representations of segmentation boundaries were subsequently registered by Procrustes alignment (Styner et al., 2006).

For the longitudinal morphometric analysis, the 7 year hippocampal surfaces were aligned to the infant surfaces by Procrustes alignment, including a scaling component in order for the 7 year-old hippocampi to match the infant hippocampi. Vectors and magnitudes of the difference between infant and 7 year surfaces were created by subtracting the infant meshes from the 7 year hippocampal meshes.

Neonatal brain abnormality score.

At term-equivalent age, data was collected on brain abnormality. Cerebral abnormality was scored by a neonatal neurologist on infant T_1 and T_2 structural scans using a previously described system (Kidokoro et al., 2013). Presence and severity of white matter abnormality (cystic lesions, signal abnormality, myelination delay, callosal thinning, lateral ventricular volume, white matter volume), cortical grey matter abnormality (extracerebral space, signal abnormality, gyral maturation), deep grey matter abnormality (signal abnormality, deep grey matter volume), and cerebellar abnormality (signal abnormality, cerebellar volume) was rated and combined to give an overall abnormality score from 0-17.

Neuropsychological assessment.

At 7 years of age, corrected for prematurity, tests from widely used memory and learning test batteries were administered. Three subsets from the Working Memory Test Battery for Children (WMTB-C) (Pickering & Gathercole, 2001) were administered to assess immediate and working memory: 1) Forward Digit Recall which assesses verbal immediate memory; 2) Backward Digit Recall which assesses verbal working memory; and 3) Block Recall which assesses spatial immediate memory. A total score for each subtest reflects the number of trials completed correctly.

The California Verbal Learning Test (CVLT) – Children's Version (Delis et al., 1994) was used to assess verbal memory and learning, and involves the presentation of a list of 15 words over 5 trials. Variables of interest included verbal learning (total number of words recalled over 5 trials) and long delay recall. The Dot Locations test from the Children's Memory Scale (CMS) (Cohen, 1997) was used to assess visual-spatial memory and learning, and involves learning the spatial location of dots over 3 trials. Variables of interest were visual-spatial learning (total number of correct locations recalled over 3 trials) and long delay recall.

Due to the restricted age range of the children (6.6 to 8.1 years), raw rather than standardized data were used for analyses. Scores were reported as 'missing' when children were too impaired to complete tasks, refused to participate in tasks, or there was a problem with the testing equipment (e.g. missing components of a task). Impairment was defined as performance <1 standard deviation (SD) below the FT group mean for all memory and learning tasks.

Statistical Analyses

For groupwise morphometric comparisons at 7 years of age, group-specific PDMs were generated. For each vertex, the signed distance from the mean surface for each PDM was evaluated for evidence of differences (defined as $p<0.05$, Bonferroni corrected), indicating areas of local expansion or contraction. Univariate Hotelling T^2 statistical testing was used on the corresponding boundary points across all subjects, with permutation testing to correct for multiple comparisons. Intracranial volume was included in the analyses as a scaling factor, to correct for the effect of head size. The analysis was repeated including neonatal brain abnormality score as a covariate. The association between hippocampal shape at 7 years and memory and learning outcomes was assessed by comparing hippocampal shape at 7 years between VPT children with and without memory and learning impairments using univariate Hotelling T^2 tests. This analysis was repeated

covarying for neonatal brain abnormality score using multivariate analysis of covariance (ANCOVA).

In order to determine longitudinal morphometric change in the hippocampus between term-equivalent and 7 years of age, t-tests were used to determine whether the signed distances were different from zero for each vertex separately for the VPT and FT groups. To compare the morphological change over time between VPT and FT children, ANCOVA was carried out on the morphometric change from term to age 7 years. The association between change in hippocampal shape and memory and learning outcomes was assessed by comparing the change in hippocampus shape from term to 7 years between impaired and non-impaired VPT children using ANCOVA. This analysis was repeated covarying for neonatal brain abnormality score using multivariate ANCOVA. All morphometric analyses were corrected for multiple comparisons using Bonferroni correction.

The change in hippocampal volume from birth to 7 years in the VPT and FT groups was compared using Stata 12. A single mixed regression model was fitted to the left and right hippocampi measurements at term and 7 years, including time as a covariate and using a random effect to allow for the correlations between observations within an individual. Group differences (VPT vs. FT) in change in hippocampal volume was assessed by allowing the effect of time to vary by group (group-by-time interaction), and allowing the effect of time and group to vary by hemisphere (3-way interaction). Secondary analyses adjusted for change in intracranial volume and neonatal brain abnormality score. Finally, the association between change in hippocampal volume and memory and learning impairment at age 7 years in the VPT group was assessed using separate logistic regression models for each hippocampal volume (left and right) and outcome combination. Secondary analyses adjusted for change in intracranial volume and neonatal brain abnormality score.

Results

Sample characteristics.

Characteristics of the VPT and FT cohorts are described in Table I. As expected GA at birth ($p < 0.001$) and birth weight ($p < 0.001$) were lower in the VPT subjects, while brain abnormality score ($p <0.001$), and the incidence of multiple births ($p < 0.001$), bronchopulmonary dysplasia ($p = 0.002$), and antenatal corticosteroids ($p < 0.001$) were higher in VPT subjects compared with FT subjects. The VPT sample had higher rates of memory and learning impairment compared with the FT group at 7 years of age, with strong evidence of group differences for the verbal working memory ($p = 0.002$) and immediate spatial memory ($p = 0.004$) domains.

Table I

Perinatal and 7 year characteristics of the very preterm and full-term cohorts

	Very Preterm *n* = 125	Full-term *n* = 25
Perinatal characteristics		
GA (weeks), *M* (*SD*)	27.5 (1.9)	38.7 (1.3)
Birth weight (g), M (SD)	968 (2245)	3255 (517)
Small for gestational age, n (%)	13 (10)	1 (4)
Singleton, n (%)	68 (54)	24 (96)
Intracranial volume (cc), *M (SD)*	447.3 (72.7)	456.3 (54.6)
Neonatal brain abnormality score, *M (SD)*	5.3 (3.1)	1.5 (1.3)
Male sex, n (%)	62 (50)	14 (56)
Antenatal corticosteroids, n (%)	108 (86)	0 (0)
Postnatal corticosteroids[a], n (%)	7 (6)	0 (0)
Bronchopulmonary dysplasia, n (%)	37 (30)	0 (0)
Cystic periventricular leukomalacia, n (%)	5 (4)	0 (0)
Intraventricular haemorhage grades 3/4, n (%)	5 (4)	0 (0)
7 year characteristics		
Age at assessment (years), *M (SD)*	7.5 (0.2)	7.6 (0.2)
Intracranial volume (cc), M (SD)	1332.6 (119.7)	1435.3 (125.7)
Impaired verbal immediate memory[a], n (%)	29 (23)	2 (8)
Impaired verbal working memory[b], n (%)	60 (48)	4 (16)
Impaired spatial immediate memory[c], n (%)	52 (42)	3 (12)
Impaired verbal learning, n (%)	24 (19)	5 (20)
Impaired verbal long delay recall[a], n (%)	32 (26)	3 (12)
Impaired spatial learning[a], n (%)	50 (40)	6 (24)
Impaired spatial long delay recall, n (%)	31 (25)	3 (12)

GA= Gestational Age, M= Mean, SD= Standard Deviation. Impairment defined as <1 SD from mean of full-term children. M = mean, SD = standard deviation. [a] Missing 1 subject, [b] Missing 9 subjects, [c] Missing 3 subjects, [d] Missing 2 subjects

Hippocampal shape at 7 years of age.

At 7 years of age VPT children's hippocampi were more outwardly displaced (greater expansion) in the anterior-posterior direction and less inwardly displaced (more contracted) along the medial border (Fig 1a) than FT children. There were several scattered regions where there was strong statistical evidence for groupwise shape differences, particularly for the right side, which mainly corresponded to areas of expansion in the VPT children (Fig 1b). The pattern of shape differentiation was explained by greater infolding, or 'curling up' of the FT hippocampus, while the VPT hippocampus remained straighter (Fig 1c). Most regions where there was statistical evidence of expansion in the VPT hippocampus remained after adjusting for neonatal brain abnormality score (Fig 1d).

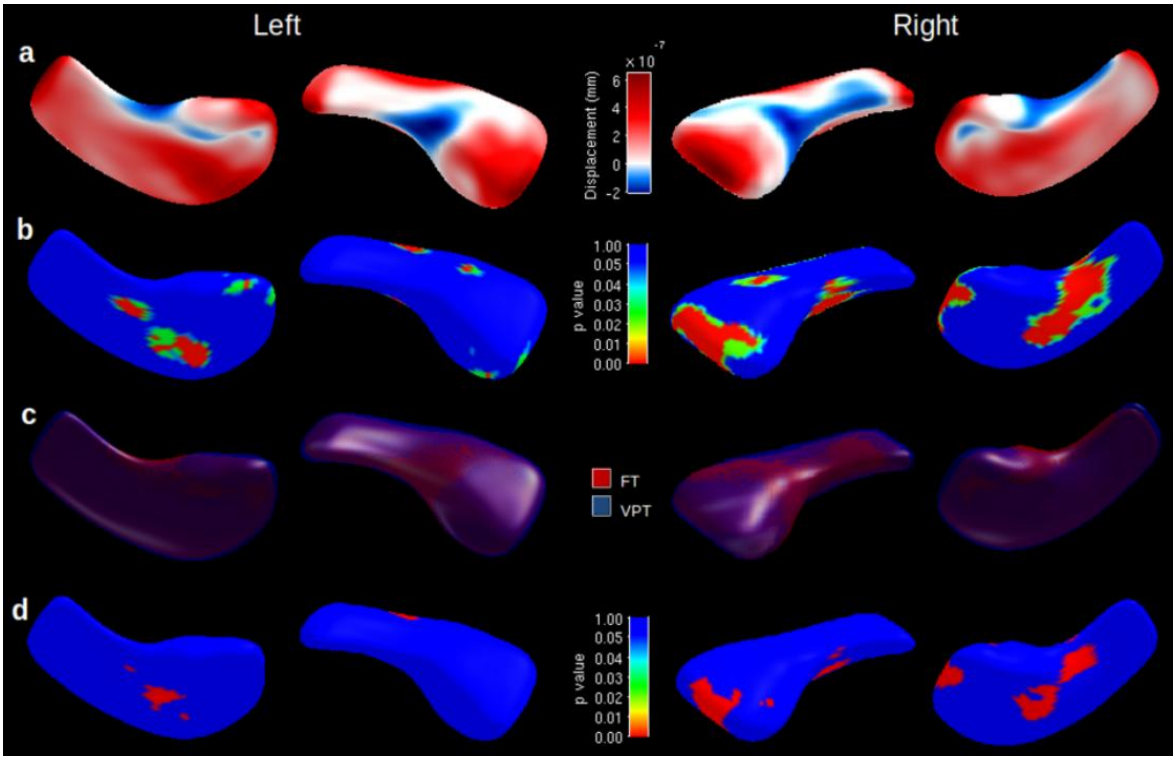

Figure 1. Shape differences for very preterm (VPT) vs. full-term (FT) children at 7 years, displayed for the right and left hippocampi. (a) Displacement map with areas of positive expansion (red) or negative contraction (blue) of the VPT hippocampal surface from the mean surface, overlaid on mean of all hippocampi. (b) Statistical p-value map of shape difference after permutation testing overlaid on mean of all hippocampi. (c) Mean overlay of VPT (blue) and FT (red) hippocampi. (d) Bonferroni corrected statistical maps of shape differences for VPT vs. FT children's hippocampi after correcting for brain abnormality score.

There was little evidence of an association between hippocampal shape and impairment on memory and learning measures in VPT 7-year-olds.

Longitudinal hippocampal shape.

Between infancy and 7 years of age, the morphological change in the hippocampus was similar for VPT and FT children. In general, both VPT and FT children's hippocampi 'curled up' more by 7 years of age. There were several areas of expansion from infancy to 7 years into the inner medial border of the hippocampus, and a corresponding contraction along the lateral border in both groups (Fig 2a). There was evidence of lateral contraction between time points in all major zones, as well as zones of medial expansion in the VPT population (Fig 2b). The overlay of the 7 year hippocampus onto the infant hippocampus further demonstrated hippocampal infolding between time-points for both groups (Fig 2c). There were some regions where the medial expansion and lateral contraction between time-points appeared greater in VPT children (Fig 2d). There were only small portions of the hippocampi where there was statistical evidence that the longitudinal shape change differed between VPT and FT children. These regions mainly corresponded to greater medial expansion and lateral contraction of the VPT hippocampal surface, particularly for the right side (Fig 2e), and remained after adjusting for total MRI score (Fig 2f). There was little evidence that change in hippocampal shape between infancy and 7 years in VPT children was associated with impairment on memory and learning measures.

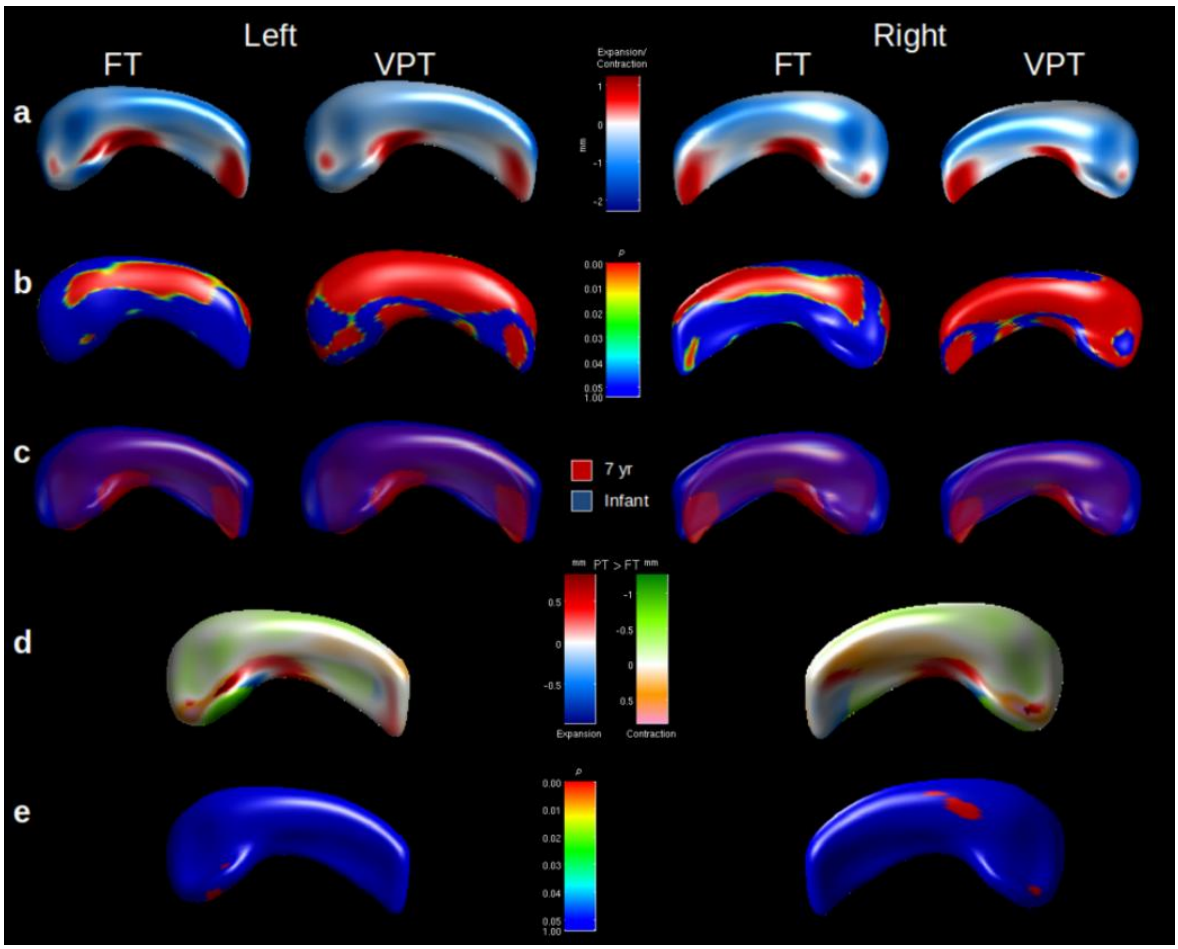

Figure 2. Shape differences between infancy and 7 years for full-term (FT) and very preterm (VPT) children. (a) Displacement map with areas of expansion (red) and contraction (blue), overlaid on mean of all hippocampi. (b) Statistical p-value map of shape difference between time-points, after Bonferroni correction. (c) Mean overlay of infant (blue) and 7 year (red) hippocampi, where the 7 year surface is scaled to match the infant surface. (d) Displacement map with areas of expansion (red) or contraction (green) greater in VPT children, or expansion (blue) or contraction (orange) greater in FT children, between term and 7 years (red). (e) Statistical p-value map demonstrating the evidence for differences in longitudinal shape change between FT and VPT children, after Bonferroni correction.

Longitudinal hippocampal volume.

The average change in hippocampal volume from the neonatal period to 7 years of age was smaller for VPT children than for FT children (Table II, interaction: -0.22, 95% CI -0.29 to -0.14, $p < 0.001$). This difference remained following adjustment for change in

intracranial volume and neonatal brain abnormality score (interaction: -0.14, 95% CI -0.21 to -0.07, $p < 0.001$). Overall the change in volume was greater for the right hippocampus compared with the left hippocampus (main effect $p = 0.001$), however there was little evidence that the effect of group varied by hemisphere (interaction $p = 0.82$).

Table II

*Left and right hippocampal volume (cc) at term and 7 years, and change in volume from term- to 7 years for very preterm and term children**

Hippocampal volume, mean (95% CI)	Very preterm		Full-term	
	Right	Left	Right	Left
Neonatal	1.14 (1.10)	1.12 (1.08, 1.17)	1.21 (1.11, 1.31)	1.18 (1.08, 1.28)
7-year	2.85 (2.80, 2.89)	2.74 (2.70, 2.77)	3.15 (3.05, 3.25)	3.00 (2.90, 3.10)
Change	1.71 (1.67, 1.75)	1.62 (1.58, 1.66)	1.97 (1.88, 2.06)	1.82 (1.73, 1.91)

* Results from a single model including measurements from the left and right hemisphere at both time points, allowing the effect of time and hemisphere to be different in the two groups, and allowing for a 3 way interaction between group, hemisphere and time

In the VPT group, there was little evidence for a relationship between change in hippocampal volumes between infancy and 7 years and memory and learning impairment, on both unadjusted analyses (Fig 3) or analyses adjusted for intracranial volume and neonatal brain abnormality analyses (data not shown).

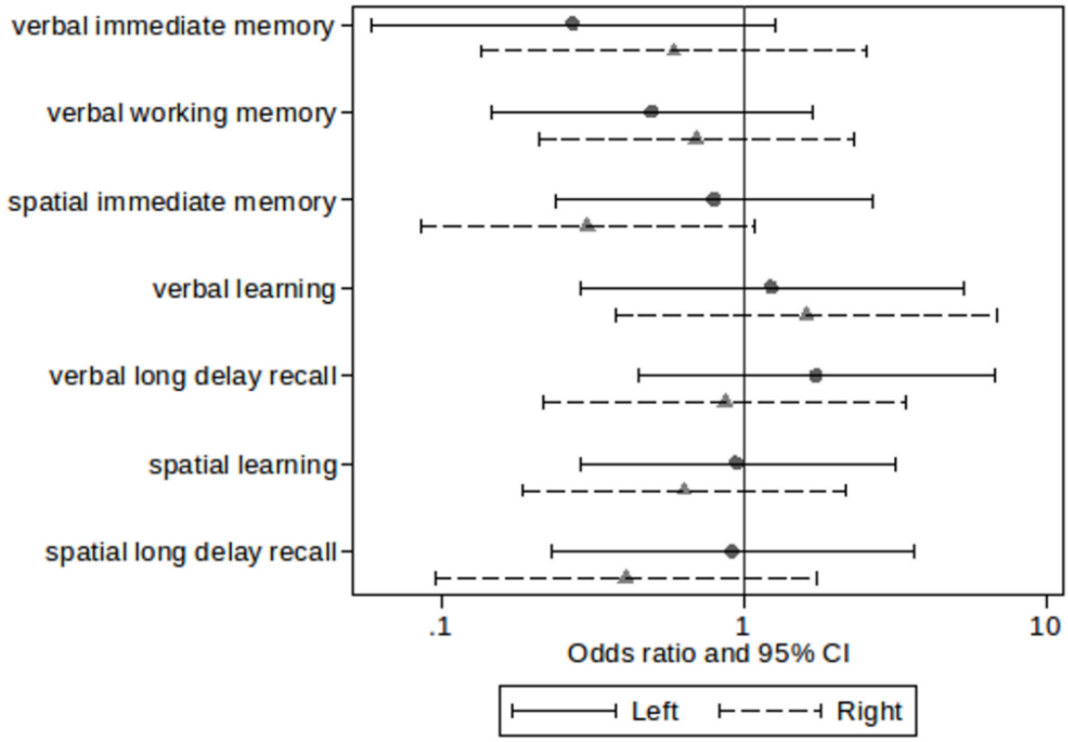

Figure 3. Association between change in hippocampal volume and memory and learning impairment at age 7 years (binary outcomes). Results are the odds ratios and 95% confidence intervals (CI) for an impairment per unit difference in the change in hippocampal volume from separate unadjusted logistic regression models.

Discussion

Despite VPT hippocampi showing more immature shape at 7 years than FT hippocampi (less infolded), the morphological change over time was similar between groups, indicating that shape differences present in infancy (Deanne K. Thompson et al., 2013) persisted but the trajectory was relatively typical thereafter in VPT children. Volumetrically, FT children's hippocampi grew more between infancy and 7 years of age than VPT children, with more growth in the right than the left hippocampus for both groups. There was little evidence that hippocampal shape at age 7 or either volumetric or morphological changes from term to 7 years were associated with memory and learning impairments in the VPT group at 7 years.

At 7 years, VPT hippocampi were less infolded than those of FT children. We have previously shown that this cohort of VPT subjects displayed straighter hippocampi at term-equivalent age (Deanne K. Thompson et al., 2013). This suggests that the alterations in hippocampal shape that occurred in the perinatal period persist into childhood, and therefore hippocampal development did not catch up. Altered hippocampal shape in the VPT child may result from exposures and injury shortly after birth, a period in which the hippocampus undergoes rapid synaptic, dendritic, and oligodendroglial development (Insausti et al., 2010), and is actively establishing cortical-hippocampal connections (Hevner & Kinney, 1996). The VPT infant hippocampus is vulnerable to a range of complications following birth which may alter the normal progression of these developmental processes such as neuronal or white matter damage (Ramenghi et al., 2007), which may result in alterations of hippocampal shape (Qiu et al., 2010).

Shape changes in the hippocampus from term to 7 years were similar for the VPT and FT children with both showing more infolding at 7 years. Considering shape alterations are present at term equivalent age in VPT infants (Deanne K. Thompson et al., 2013), the period within the neonatal intensive care unit is likely the period of greatest vulnerability for the hippocampus. It should be noted that this study is the first to show that further hippocampal infolding occurs during childhood, even in healthy full-term populations. Previously, hippocampal inversion was thought to be complete by around 25 weeks of gestation (Bajic et al., 2010).

Hippocampal growth is compromized in the neonatal period following very preterm birth (D. K. Thompson et al., 2008). Findings from the current study showed that hippocampal growth between term-corrected and 7 years of age was slower in VPT children, even after taking into account change in overall brain size. This indicates that the hippocampus continues to be specifically vulnerable in VPT children well after infancy, and into childhood. A major hippocampal growth spurt occurs between infancy and 2 years of age (Utsunomiya et al., 1999), which may be altered in those born VPT. This may explain

why, in the same cohort, we found a 3.4% lower hippocampal volume in VPT compared with FT subjects in infancy (D. K. Thompson et al., 2008), which had increased to a 6.3% difference by 7 years of age (C. Omizzolo et al., in press). Furthermore, others have reported even larger differences of around 15% between VPT adolescents and FT controls (Gimenéz et al., 2004; Nosarti et al., 2002). Together these results suggest that the VPT hippocampal volumes do not catch up with those of term-born peers, and indeed the gap may widen.

Altered hippocampal growth in VPT children is likely due to the susceptibility of the hippocampus to complications associated with VPT birth (Gadian et al., 2000; Khwaja & Volpe, 2008), in particular white matter injury and the subsequent associated neurological sequelae (Volpe, 2009). However, the slower growth of the hippocampi in VPT children appears to be independent of brain injury, as VPT children still had a slower hippocampal growth rate after adjusting for the neonatal brain abnormality score. Disturbingly, the full impact of prematurity on hippocampal growth may not be apparent until around 9-11 years of age, when hippocampal growth peaks (Uematsu et al., 2012). On the other hand, our results suggest that there may be a window of time early in development where it may be possible to intervene in order to improve hippocampal growth in VPT populations.

Though hippocampal asymmetry develops in utero (Deanne K Thompson et al., 2009), we confirmed that asymmetrical development of the hippocampi continues into childhood. The greater growth of the right compared with the left hippocampus during childhood seen in the study is consistent with previous research reporting rightward asymmetry in children (Giedd et al., 1996; Pfluger et al., 1999; Utsunomiya et al., 1999) and adults (Uematsu et al., 2012; Watson et al., 1992). Given there was little evidence of group by hemisphere interactions, it would appear that VPT children showed similar growth in each hemisphere during childhood as FT children, despite the fact that they have altered hippocampal asymmetry in infancy (Deanne K Thompson et al., 2009).

Within VPT children, there was little evidence that hippocampal shape at age 7 years, or hippocampal growth from term to 7 years (volumetric or morphological change)

were associated with memory and learning impairment at 7 years of age. We were surprised that our hippocampal growth measures were not related to functional impairments in these domains, especially considering we have shown positive associations between infant hippocampal volume and memory functioning at 7 years (Deanne K. Thompson et al., 2013). However the current results are consistent with our previous findings that hippocampal volume at 7 years is not related to memory and learning performance (C. Omizzolo et al., in press). In contrast, previous research in populations with memory and learning difficulties has demonstrated an association between hippocampal volume and performance on the CVLT (Riggins et al., 2012; Willoughby, Sheard, Nash, & Rovet, 2008). It could be that the measures of memory and learning employed in this study were not sensitive to subtle volumetric and morphological changes in the VPT hippocampus. An alternative explanation is that memory and learning impairment in the VPT group reflects pathology in other components of the neural memory network, which includes but is not limited to prefrontal and parietal regions (Roberto Cabeza & Lars Nyberg, 2000), as well as the thalamus and basal ganglia (C. Omizzolo et al., 2013).

It is commonly accepted that development of memory and learning functions continue to mature well after 7 years of age (Gathercole, 1998; Gathercole et al., 2004), and given that the hippocampus continues to mature into adolescence (Insausti et al., 2010), the full effects of impaired hippocampal growth and development on memory and learning function may not be apparent until later in development. Although no previous study has examined the relationship between longitudinal hippocampal development and memory and learning in VPT cohorts, a few studies have linked reduced hippocampal volume to everyday memory impairment (E. B. Isaacs et al., 2000; E. B. Isaacs et al., 2003) and verbal learning and recognition memory impairment (Gimenéz et al., 2004) during adolescence.

Despite the fact that the current study assessed multiple components of memory and learning in both visual and verbal modalities, it is possible that altered hippocampal development in this VPT group would have be related to performance on other memory and

learning measures such as those assessing paired associative learning and everyday memory functioning. Another limitation to this study is that manual segmentation is prone to human error, and there are many different protocols for hippocampal segmentation reported in the literature. The current study employed a common method of hippocampal segmentation based on the protocol put forward by Watson and colleagues (Watson et al., 1992), and both intra- and inter-rater reliability were high. Furthermore, the morphological analysis assumes perfect registration of all hippocampi into a common reference space. As this is not always possible, the accuracy of our results may be affected by alignment error. All alignments were qualitatively assessed for accuracy to minimize this risk.

In conclusion, hippocampal shape is less mature in VPT children at 7 years of age than in FT children, which corresponds with similar morphological differences observed at term equivalent age. The findings from the current study provide unique insight into the developmental trajectory of the human hippocampus from the neonatal period to 7 years of age in children born VPT and at term. These findings are the first to show that the hippocampus undergoes further infolding between infancy and 7 years of age in both VPT and FT children. We also show that the VPT hippocampus does not undergo typical volumetric development throughout childhood, with delayed growth between infancy and 7 years. The relationship between delayed hippocampal growth as a result of VPT birth and cognitive deficits still remains unclear. Further research is required to examine this association later in development, ideally during adolescence. Future studies may wish to examine whether early intervention can close the gap between VPT and FT hippocampal development, which will likely improve later cognitive functioning.

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Chapter 9: General Discussion

Summary of Results

This thesis aimed to investigate the effect of VPT birth on memory and learning abilities at 7 years of age. In particular, it examined the association between neonatal brain injury and hippocampal development with memory and learning functioning in VPT 7 year-olds.

This thesis was divided into three studies, reported as three individual papers. Paper 1 found that VPT children performed consistently less well than term born peers across all measures of memory and learning in both the verbal and visual-spatial modalities at 7 years of age. Neonatal brain abnormality, especially deep grey-matter abnormality, was associated with poorer memory and learning in the VPT children. Additionally, the VPT group had higher social risk than the term controls, which contributed to their poorer performance on a number of outcome measures. Findings from this study demonstrate that VPT birth has a detrimental and enduring effect on memory and learning functioning, and substantiate the predictive value of neuroimaging techniques.

Paper 2 demonstrated that VPT children had reduced hippocampal volumes at age 7 compared with term born children, although this difference did not persist after adjustment for gender, ICV and neonatal brain abnormality. Contrary to expectations, there was little evidence to support a brain-behaviour relationship between hippocampal volume and memory or learning outcomes within the VPT group. Paper 3 showed that hippocampi grew more between infancy and 7 years of age in typically developing controls compared with VPT children, with more growth in the right than left hippocampus for both birth groups. However, volumetric change between infancy to 7 years of age was not related to memory or learning functioning in the VPT children at age 7. While hippocampal volume differences were not associated with memory and learning performance, this does not mean that the hippocampus is not important for these functions. Alternatively, is possible that

morphological (shape) differences or deficiencies in hippocampal track projections are related to poor functioning. Thus, further investigation of the association between delayed hippocampal growth and memory and learning abilities in VPT children is an important area for future research.

Implications of VPT Birth for Memory and Learning

Recent research supports the argument that immediate/working memory and long term memory systems are distinct yet related constructs (Unsworth, 2010). A. D. Baddeley (2007) suggests that the episodic buffer is important for the interaction between immediate/working memory and long term memory systems. This theory suggests that impairment to one component of the memory and learning system may have a compounding effect. Therefore, it is appropriate to examine memory and learning using a broad conceptual framework, particularly when attempting to understand these abilities in populations with compromised brain development, such as VPT children.

Consistent with this argument, the current study incorporated a battery of tests that assessed immediate memory, working memory, long term memory and learning. This approach contrasts with much of the previous research investigating memory and learning abilities in VPT children which has tended to focus on a specific component of the memory system. As discussed in Paper 1, the pattern of memory impairment in the verbal modality (i.e., impaired immediate/working memory and short delay recall, and relatively preserved long delay recall) may reflect a primary impairment of immediate and/or working memory abilities in the VPT group. In contrast, greater generalisation of impairments to visual-spatial abilities may indicate more extensive deficits to underlying networks. These findings support the premise that impairment to an early stage of the memory process may affect subsequent stages, emphasising the hierarchical nature of the system.

The finding that VPT children showed greater impairment to visual-spatial memory and learning abilities is consistent with previous research demonstrating impaired visual-

spatial immediate memory (C. S. H. Aarnoudse-Moens et al., 2012; Curtis et al., 2002; E. B. Isaacs et al., 2000; Luciana et al., 1999; Rose et al., 2009; Rose et al., 2011; S. Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004; Woodward et al., 2005), working memory (C. S. H. Aarnoudse-Moens et al., 2012; Beauchamp et al., 2008; Cossu et al., 1999; Jongbloed-Pereboom et al., 2012; Kagan, 1981; Ni et al., 2011; S. Vicari et al., 2004; Woodward et al., 2005), and learning and long term memory (I. S. Baron et al., 2012; Rose et al., 2009) in preterm and/or VLBW cohorts. In contrast, studies investigating these abilities in the verbal domain show mixed findings (C. S. H. Aarnoudse-Moens et al., 2012; Fraello et al., 2011; E. B. Isaacs et al., 2003; Ni et al., 2011; Rose et al., 2009; Taylor et al., 2004).

Developmental differences between verbal and visual-spatial memory and learning networks have been reported in healthy children. Studies agree that while both networks demonstrate a parallel increase in capacity with age, there is an advantage of approximately 1.5 items in immediate verbal memory when compared to immediate spatial memory from 4 years of age until adulthood (Gathercole, 1998; Nichelli, Bulgheroni, & Riva, 2001). Furthermore, the phonological loop is thought to resemble its adult-like organisation from age 7 years (Gathercole & Hitch, 1993), whereas the visual-spatial sketchpad shows further development up until 11 years of age (Miles et al., 1996; Wilson et al., 1987). Developmental changes in the recruitment of brain regions during visual-spatial working memory tasks has also been reported in older children (Crone et al., 2006; Káldy & Sigala, 2004). Given that VPT children in the current study were assessed at 7 years, memory and learning impairments may reflect fundamental changes to the networks which underlie these abilities, especially within the visual-spatial modality.

Despite a small and somewhat conflicting body of research investigating the development of long term memory, implicit memory appears to undergo limited development from approximately 3 years of age, whereas explicit memory is thought to improve consistently into adolescence (Murphy et al., 2003). Changes at a neural level have also supported this finding (Ofen et al., 2007; Thomas et al., 2004). This is encouraging, and

suggests that there may be a window of opportunity in which early intervention may take advantage of neural plasticity to help reduce the long-term memory impairments in VPT populations.

Memory and learning impairments experienced by VPT children may have implications for cognitive functioning more generally. Memory is a core cognitive skill that underlies many other cognitive processes. For instance, working memory has been found to underlie age-related changes to both fluid and crystallized intelligence (Swanson, 2008), having consequences for academic development. A link between phonological loop capacity and vocabulary in healthy children has also been reported, suggesting that immediate/working memory may support long term language acquisition (A. Baddeley et al., 1998). Additionally, Bull et al. (2008) found that visual-spatial immediate/working memory in healthy preschool children predicted their mathematical abilities during primary school, and verbal immediate/working memory predicted later mathematical and reading abilities.

Within the preterm literature, Sansavini et al. (2007) found strong relationships between reduced phonological immediate/working memory and grammatical difficulties in children aged 3.5 years. Given the frequency of memory and learning impairments in our VPT group, this raises concerns for educational progress and subsequent academic achievement. Thus, a detailed assessment of memory and learning abilities as part of surveillance programs of VPT children is needed in the early school or preschool years.

At this stage, it remains unclear whether memory and learning impairments in our VPT group represent a developmental delay or deficit. Previous research supports both possibilities. With regards to developmental delay, Tideman (2000) found that group differences between 4 year-old preterm and control children on a number of cognitive measures, including immediate memory, were not present at 9 or 19 years of age. Further, Ritter, Nelle, Perrig, Steinlin, and Everts (2012) demonstrated that VPT/VLBW children at age 8 performed more poorly than age-matched controls on a working memory task,

whereas VPT/VLWB children at 12 years of age performed similarly to age-matched controls on the same measure (Ritter et al., 2012). In terms of developmental deficits, long term memory impairment in preterm children at 12 months of age has been found to persist until early childhood (36 months of age) (Rose, Feldman, & Jankowski, 2005), and children born <750 g have persistently performed more poorly than controls on verbal list learning between 7 and 14 years of age (Taylor et al., 2004). Our VPT group was found to have impaired verbal working memory at 5-years of age (Roberts et al., 2011), with the current study demonstrating that this continues until 7 years of age. Given that memory and learning capacity continues to mature well after 7 years of age, examination of abilities during pre-adolescence is merited to further understand the ongoing nature of the impairments.

The Impact of VPT Birth on the Brain

The VPT brain is at high risk of early and widespread brain injury. As a result, the contribution of the hippocampus may be reduced and additional regions recruited to assist with memory and learning development (Lawrence et al., 2010). A novel aspect of the current study was the ability to investigate the impact of early brain injury on memory and learning abilities in 7 year-old VPT children. The neonatal brain abnormality scores allowed for a greater understanding of the neuropathology underlying the memory and learning difficulties identified in VPT children.

Normal maturation of the cerebral cortex is not a simple linear process (see Figure 9). Rather, it is a dynamic series of events that follows an orderly, non-linear pattern of overlapping stages of development, with developmental peaks occurring in different regions at various times (V. Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2001; Nitin Gogtay et al., 2004). Therefore, neuronal development is tightly defined with respect to timing, and any disruption may divert both the expected course and ultimate outcome. Additionally, the effects of disruptions may be qualitatively different depending on the developmental stage of each neuronal process (V. Anderson et al., 2001).

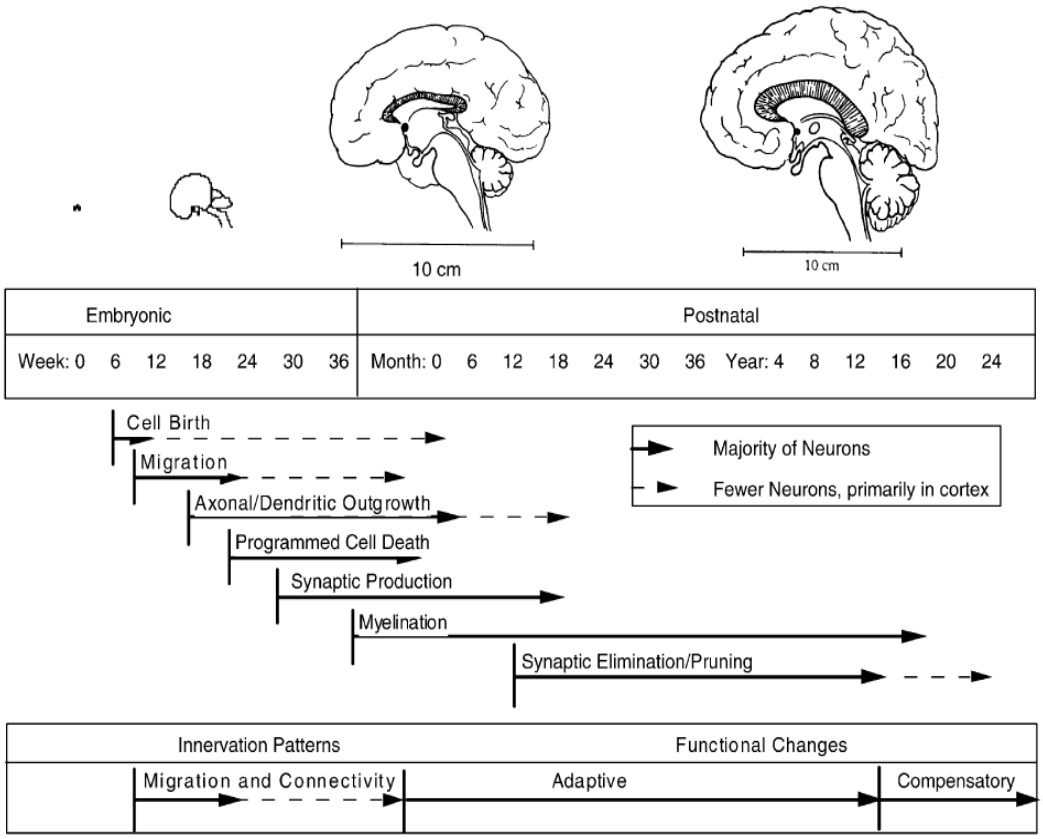

Figure 8. Neuroanatomical growth from the embryonic stage to adulthood, and the periods of vulnerability (bottom). Insults that occur early in life will be assimilated into innervation patters, whereas those that occur later will cause functional changes that are more adaptive (V. Anderson et al., 2008).

Figure 9 indicates that significant neuronal processes occur at the time when VPT infants are born (i.e. before 32 weeks' GA). All brain structures are shown to expand in the third trimester, with volume expansion driven by maturational processes of axon extension, dendrite elaboration, synaptogenesis, glial proliferation and maturation. Brain injuries associated with VPT birth may have the potential to influence the entire course of skill development by disrupting the onset and/or order of acquisition and the rate of acquisition. Indeed, the current study demonstrated that repercussions of neonatal brain injury in VPT children on memory and learning development continued until 7 years of age.

In this study, neonatal brain abnormality which affected the DGM (i.e. the basal ganglia and thalamus) was most predicative of memory and learning impairments in VPT children. Consistently, research has implicated both the basal ganglia and thalamus with memory functioning (Aggleton & Brown, 1999; Cipolotti et al., 2008; Moore, Li, Tyner, Hu, & Crosson, 2012; Moscovitch et al., 2005). Both structures have also been found to be particularly sensitive to hypoxic ischemic brain injury - a common complication associated with VPT birth (F. Cowan et al., 2003). As such, early damage to these areas appears to interrupt the course of memory and learning skill development in VPT children.

Using diffusion-weighted imaging, Schneider et al. (2007) examined apparent diffusion coefficient (ADC) values to investigate normal brain maturation in healthy neonates in utero from 23 to 37 weeks' GA. ADC values have been found to correlate with progressive brain maturation. The basal ganglia demonstrated a rise in maturation (i.e. ADC values) with a peak at 30 weeks' GA followed by a linear negative correlation of ADC values with GA. The maturation of the thalamus occurred earlier, with ADC values showing a strong linear negative correlation with GA. Given the rapid development of these structures during the third trimester they are probably highly vulnerable to neurological insult when VPT birth occurs, which likely alters ongoing development and the cognitive functions they subserve.

Consistently, there is evidence that DGM structures experience disrupted maturation in preterm cohorts. Whilst the typical growth pattern of thalamic and later basal ganglia structures has been reported in VPT infants (Nossin-Manor et al., 2012), striking volume reductions to these structures have been found at TEA in preterm children when compared to term born controls (Boardman et al., 2006). Findings from the current study contribute to the literature by documenting the functional changes associated with disrupted DGM development due to VPT birth (i.e. impaired memory and learning).

Injury to DGM structures may reflect the global nature of impaired brain development in VPT children. Impaired white matter tract development has been found to

result in a disconnection between the thalamus/basal ganglia and developing CGM, which is thought to affect the integrity of DGM structures (Boardman et al., 2006; Nossin-Manor et al., 2012; Srinivasan et al., 2007). Although WM injury was weakly associated with memory and learning performance in our VPT group, it may have secondarily impacted the integrity of DGM structures. Taken together, these findings draw attention to the atypical development of DGM structures, and highlight the implications for theories behind memory and learning impairment in VPT children.

Previous research has found associations between reduced hippocampal volume and impaired performance on memory and learning tasks in VPT cohorts (Gimenéz et al., 2004). However, findings from the current study show little support for this relationship at 7 years of age in children born VPT. Understanding the association between hippocampal volume and memory and learning in typical development may provide further insight into this relationship.

The 'developmental perspective' of the hippocampal volume-memory relationship suggests that improvement in memory performance after 3 years of age will be accompanied by decreasing hippocampal volumes (when expressed as a proportion of increasing total brain volume) (Van Petten, 2004). Consistently, a negative relationship between hippocampal volume and memory (i.e. smaller is better) has been reported in a number of studies examining healthy children, adolescents and young adults (Chantôme et al., 1999; Foster et al., 1999; Mackay et al., 1998; Sowell, Delis, Stiles, & Jernigan, 2001; Yurcelun-Todd, Killgore, & Cintron, 2003). According to this view, the lack of evidence supporting the relationship between hippocampal volume and memory and learning outcomes in our VPT group may suggest typical development.

Examination of anterior and posterior segments of the hippocampi separately may also yield important insights into the relationship between hippocampal volume and memory and learning functioning in VPT children. This suggestion is in light of findings that demonstrate different patterns of development in posterior (increases over time) and

anterior (loss over time) (N. Gogtay et al., 2006) portions of the hippocampus. Furthermore, there is evidence that the relationship between memory and volume in the anterior/posterior segments of the hippocampus differ in healthy development (Poppenk & Moscovitch, 2011). Whether these findings are reflected in hippocampal volumes of VPT children remains unknown at this stage.

Volumetric measures do not provide insight into the organisational processes that occur during neural development. As discussed in Chapter 3, memory formation is largely dependent on the afferent/efferent relationships between the medial temporal lobe and the neocortex. It is possible that changes in the make-up or ratio of hippocampal/neocortex neurons may disrupt the ability of the hippocampus to support memory and learning functioning in VPT children. Examination of other components in the neural network which underlies memory and learning may provide further insight into these abilities in VPT children, such as the entorhinal cortex, parahippocamapal and perirhinal cortices, and association areas. Additionally, morphological differences and the integrity of hippocampal tracts may be associated with less efficient memory and learning in VPT children.

Clinical Implications

As mentioned in Paper 1, there are a higher proportion of preterm families from social disadvantaged backgrounds in comparison to term born controls. Preterm children with moderate to high social risk have an increased risk of developmental problems (Hack et al., 1992) and are less likely to receive early intervention (Wang et al., 2006). Consistently, elevated social risk in the VPT group contributed to the memory and learning difficulties exhibited by these children.

There is often a long period of time between parents identifying or becoming worried about their children's development, addressing these concerns with health care workers, and then being referred to intervention services (Roberts et al., 2008). Roberts et al. (2008) found that almost 50% of VPT children with moderate to severe disabilities and

72% of VPT children with mild disabilities were not receiving services at 2 years of age. This period of delay may be related to the degree of social risk; families with higher levels of education and income may be better able to identify cognitive delays in their children, approach services, afford private therapy while waiting for public services, or recruit resources via alternative pathways. Increased education for parents of VPT children and greater access to social services would have secondary advantages for the cognitive outcomes of VPT children.

Qualitative assessment of MRI brain scans using the neonatal brain abnormality scoring tool helped to predict memory and learning impairments in the VPT group at age 7. It was found that VPT infants with neonatal brain abnormalities are at greatest risk for later problems and therefore, should be closely monitored so that they can be enrolled in targeted early intervention programs as soon as difficulties begin to emerge. For example, recent evidence suggests that working memory can be trained in children. Løhaugen et al. (2011) found that ELWB and term control adolescents who completed 5 weeks of a computerised working memory training program (CogMed RM) improved on tasks measuring immediate/working memory, long term memory and learning. A more recent study by the same group demonstrated that VLBW pre-schoolers improved on working memory tasks following 5 weeks of completing CogMed JM (Grunewaldt, Løhaugen, Austeng, Brubakk, & Skranes, 2013). Memory training before starting school may prevent or reduce the impact of memory or learning difficulties on educational achievement.

Although CogMed is the most well-known memory training program, other commercially available working memory programs include Jungle Memory, which is based on three different working memory tasks, and Cognifit, which is based on verbal, visual, and cross-modal working memory tasks. Each of these programs argues to benefit children with poor grades at school by improving working memory difficulties. However, the development and evaluation of memory training programs is still in the early stages, and conclusions on the effectiveness of these programs from recent narrative reviews (Klingberg, 2010;

Morrison & Chein, 2011; Shipstead, Redick, & Engie, 2010) and meta-analyses (Melby-Lervåg & Hulme, 2013) are highly variable.

As previously mentioned, difficulties with memory and learning in VPT children can have detrimental consequences for academic progress and success, such as mathematical skills, reading and vocabulary. Indeed, Roberts et al. (2011) found that 44% of VPT children at 5 years had vulnerabilities in more than 1 domain of school readiness in comparison to 16% of term controls. Importantly, there is a tendency for vulnerabilities in school readiness skills at a young age to become more pronounced over time. Surveillance programs which incorporate a detailed assessment of memory and learning abilities may be built into yearly management programs for VPT children at school to help reduce further morbidity.

Each of the above points has important implications for long-term outcomes of children born VPT. Addressing these challenges alongside the continued medical developments directed towards protecting the neonatal brain will likely improve the quality of life for VPT children and reduce morbidity associated with memory and learning difficulties.

Strengths and Limitations of the Current Study

One of the major strengths of the current study was the longitudinal nature of the design, which allows for in depth analysis of the predictors of later outcomes and of individual change across development. This cohort is one of a limited number of large, prospective cohorts of VPT children in the world, with neuroimaging data and extensive cognitive, behavioural, and environmental data of children and their families at multiple time points. Additionally, follow-up rates were high at each time point, with 88% of the VPT group and 91% of the term group being assessed most recently at 7 years of age.

With regards to the sample however, the main limitation relates to unequal group sizes. It is possible that this reduced power in the analyses and ultimately, impacted the

nature of the findings. Groups also differed on socio-economic status which resulted in an attenuation of some results, although social risk was adjusted for statistically to identify group differences independent of this factor.

Cognitive functioning was assessed using standardised measures that are used widely in both clinical and research settings, and that have strong reliability and validity. Cognitive domains, including memory and learning, were selected for investigation because of their known susceptibility to impairment in VPT cohorts. Measures of memory and learning were chosen to assess multiple components of function in order to obtain a comprehensive profile of these skills in VPT children.

A limitation however, was that our assessment of memory and learning lacked measures of everyday memory, paired associate learning, and visual-spatial working memory. Given the particular vulnerability of visual-spatial memory and learning abilities in the VPT group, it is also questionable whether the measures within this modality were more sensitive to impairment than the measures of verbal memory and learning. As a whole, it is possible that our outcomes measures were not sensitive to hippocampal integrity given that we found little evidence for a relationship between hippocampal volume and memory and learning in the VPT group.

Another limitation regarding the assessment of memory and learning was that tasks in the verbal and visual-spatial modalities were not entirely comparable. First, the CVLT-C involves the use of 15 items, whereas Dot Locations only involves 6 items. Second, the method of item presentation differs between the two tasks; words in the CVLT-C are presented at a rate of 1 per second, but all dots are presented at once in Dot Locations. Third, there are 5 learning trials in the CVLT-C and only 3 in Dot Locations. The use of comparable measures across modalities would have allowed for a more comparable understanding of these functions.

A novel aspect of this study was the neonatal MRI brain scans and qualitative assessment of neonatal brain abnormality in VPT children. Although several MRI evaluation

scales have been developed to define the severity of brain injury at TEA (Inder, Wells, et al., 2003; Miller et al., 2005; Sie et al., 2005), they often only address WM and CGM abnormality and therefore, underestimate the full extent of neonatal brain abnormalities in this population. In contrast, our assessment of neonatal brain abnormality incorporated measures of global, DGM and cerebellar injury in addition to WM and CGM abnormality, and is more objective in defining both brain injury and impaired growth. This provided unique evidence for the consequences of early brain injury associated with VPT birth on later memory and learning functioning. Moreover, adjustment for neonatal brain injury enabled the investigation of both group differences in hippocampal volume, and the association between hippocampal volume and memory abilities over and above the effect of brain pathology at TEA.

With regards to brain imaging at 7 years, volumetric data for the hippocampal formation was acquired using manual segmentation on high quality MRI scans. Manual segmentation is considered the gold standard technique for volumetric hippocampal analysis, and an in-depth description of segmentation boundaries and tracing was provided. Although manual segmentation is considered the preferred technique when measuring hippocampal volume, it is more prone to human error and discrepancy between boundary definitions than automated techniques. Nevertheless, high inter-rater reliability within the current study suggests that volumetric protocols at TEA and 7 years of age were consistent and therefore, reliably represented hippocampal growth over time in the VPT group. Moreover, this project was the first to examine the developmental trajectory of hippocampal volumes in VPT children.

Overall, findings from the current study are based on scientific and theoretical conceptualisations of memory, learning and brain function, and can be generalised to the wider VPT population.

Areas of Future Research

Future research should continue to examine memory and learning abilities in VPT children given that development of these skills continues throughout childhood into adolescence. Within the current research group, this would be an important area for inclusion in the planned 12 year follow-up to establish whether VPT children catch-up to their peers or fall further behind. It will also be important to assess the secondary impact of memory and learning difficulties on other cognitive and educational skills, and the efficacy of early intervention such as memory training programs.

Further investigation into the neural systems which subserve memory and learning in VPT children is needed to provide greater insight into the nature of the impairments. Based on findings from this study, the integrity of the thalamus and basal ganglia (injury and growth) would seem key areas of future examination. Even though the relationship between hippocampal volume and memory and learning abilities was weak in this study, it would be equally important to examine the neuronal relationships and networks which support the role of the hippocampal formation in memory and learning (such as the extended medial temporal lobe and cortical regions) using techniques such as tractography.

Another important area for future investigation is whether the relationship between memory and volume in the anterior/posterior segments of the hippocampus differs in VPT. Finally, continued examination of hippocampal developmental trajectory will be important to determine whether these structures remain proportionately smaller in relation to whole brain volume.

Conclusions

The current study provides a valuable contribution to the literature on the memory and learning abilities of children born VPT. A significant proportion of VPT children experience memory and learning impairments at 7 years of age, which is associated with early brain injury. Conducting routine assessments of neonatal MRI brains scans, and

implementing early memory and learning intervention will assist the long-term academic and vocational success for these children. Continued follow-up of memory and learning abilities and the brain networks which subserve these abilities will further improve our understanding of the VPT brain.

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