MONASH University

Very preterm goal setting deficits and associated neural substrates at 13 years of age

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BA (Grad Dip)

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3D	Three dimensional
6PT	Six part test
ADHD	Attention deficit hyperactivity disorder
BADS-C	Behavioural Assessment of the Dysexecutive Syndrome for Children
BOLD	Blood oxygen level dependent
BRIEF	Behavior Rating Inventory of Executive Function
BW	Birth weight
CANTAB	Cambridge Neuropsychological Test Automated Battery
cBPW	Corrected biparietal width
cDGMA	Corrected deep gray matter area
CGM	Cortical gray matter
CSF	Cerebrospinal fluid
cTCD	corrected transcerebellar diameter
DGM	Deep gray matter
DKEFS	Delis-Kaplan Executive Function Systems
DMN	Default mode network
ECN	Executive control network
ECS	Executive control system
EDF	Executive dysfunction
EF	Executive function
ELBW	Extremely low birth weight
EP	Extremely preterm

EPI	Echo planar image
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FSIQ	Full scale intelligence quotient
FOV	Field of view
FT	Full-term
FWHM	Full width at half maximum
GA	Gestational age
ICA	Independent component analysis
ICV	Intracranial brain volume
IHD	Interhemispheric distance
IQ	Intelligence quotient
IVH	Intraventricular haemorrhage
JINS	Journal of the International Neuropsychological Society
KBIT-2	Kaufman Brief Intelligence Test Second Edition
LBW	Low birth weight
lFPN	Left frontoparietal network
MANTiS	Morphologically Adaptive Neonatal Tissue Segmentation
MCRI	Murdoch Children's Research Institute
MP-RAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MRI	Magnetic resonance imaging
NEC	Necrotising enterocolitis
PDA	Patent ductus arteriosus
PLIC	Posterior limb of internal capsule

PVL	Periventricular leukomalacia
RCH	Royal Children's Hospital
RCFT	Rey complex figure test
RCFT-OSS	Rey complex figure test organizational strategy score
RDS	Respiratory distress syndrome
rFPN	Right frontoparietal network
rs-fMRI	Resting state functional magnetic resonance imaging
RSN	Resting state network
TE	Echo time
TR	Repetition time
VIBeS	Victorian Infant Brain Study
VD	Ventricular diameter
VP	Very preterm
VLBW	Very low birth weight
WM	White matter
ZM	Zoo maps

Thesis overview

This thesis forms the major research component of the Doctorate of Clinical Neuropsychology program at Monash University, in Melbourne Australia, a four year combined clinical training and research program. This thesis was a collaborative study between the Monash Institute of Cognitive and Clinical Neurosciences, and the Murdoch Children's Research Institute (MCRI) based at the Royal Children's Hospital (RCH).

The current thesis was undertaken as part of the 13-year follow-up of the longitudinal Victorian Infant Brain Study cohort (VIBeS 13). This studies chief investigators included my supervisors Professor Peter Anderson and Associate Professor Deanne Thompson and their colleagues, Professor Terrie Inder, Professor Lex Doyle, Professor Jeffrey Neil, Doctor Katherine Lee, and Doctor Megan Spencer-Smith**.** At the time of commencing my dissertation, VIBeS 13 had an established set of study aims and objectives, as outlined in their National Health and Medical Research Committee awarded funding application, and ethics approved study protocol (RCH HREC:34100A). In collaboration with my supervisors, I developed a thesis topic and unique set of aims that complemented the larger study. I incorporated pre-existing study measures but also introduced additional measures specific to the aims of the current dissertation.

Under the guidance of my supervisors Dr Catherine Willmott, Professor Peter Anderson and Associate Professor Deanne Thompson, I was responsible for data collection and data entry. While Associate Professor Deanne Thompson and Jian Chen provided assistance and advice with regards to the magnetic resonance imaging (MRI), I completed the preprocessing and the analysis. I prepared each manuscript under the guidance of my supervisors, receiving additional input from VIBeS 13 collaborators. Dr Chiara Nosarti was invited to collaborate on the current dissertation given her research expertise in resting state functional neuroimaging.

In line with the Monash University guidelines, chapters are presented in a 'thesis by publication' format, in which parts of the thesis have been written as manuscripts and submitted for publication rather than the more traditional thesis format. As such, there is some repetition of introductory comments and methodologies across chapters.

The thesis starts with a comprehensive 'Introduction', which reviews current literature relevant to this dissertation topic, placing this study in the context of the broader literature, and finishes by outlining the thesis aims and hypotheses. Chapter two is comprised of a general methods section, which describes the breadth of measures incorporated into this dissertation, and their acquisition as part of the VIBeS 13 longitudinal cohort study. Chapters three, four, and five contain three prepared manuscripts and address the three major aims of the study, respectively. Regarding publication status; chapter three titled "Goal setting deficits at 13 years in very preterm born children" is published in the Journal of the International Neuropsychological Society (published April 2018). Chapter four titled "Neonatal brain abnormalities and brain volumes associated with goal setting outcomes in very preterm 13- year-olds" is currently under review at Brain Imaging and Behavior (submitted February 2018). Chapter five titled "Resting-state connectivity and goal setting outcomes of very preterm and full-term born children at 13 years of age" is an unpublished chapter in manuscript form. Finally, chapter six summarises thesis findings, followed by a general discussion of the contribution this work makes to the literature and clinical implications. It also outlines limitations, and provides recommendations for future research in this area.

Abstract

Children born very preterm (VP) demonstrate deficits in executive functions including inhibition, working memory and cognitive flexibility and goal setting (i.e., planning, organisation, strategic reasoning) in early childhood. The goal setting abilities of VP children during late childhood however, remain unclear. Goal setting abilities are likely to have developed markedly between early childhood and adolescence, given substantial development of the brain regions underpinning executive abilities during this period, It is especially important to understand the nature of VP goal setting skills during late childhood, since they are essential to the development of independent thinking and self-management skills that may assist children to succeed in new and increasingly complex environments, such as secondary school. The early risk factors of VP birth that are associated with goal setting skills in late childhood, as well as the neurological basis and functional connectivity networks underlying VP goal setting skills at this age are not yet elucidated.

The current studies aimed to investigate goal setting abilities of VP children during late childhood, and the neural substrates related to these skills, by 1) characterising goal setting skills of VP and children born full-term (FT) at 13 years of age, and related early risk factors within the VP group; 2) examining the relationship between neonatal magnetic resonance imaging brain abnormalities and volumes and goal setting abilities in VP children at 13 years; and 3) using resting state functional magnetic resonance imaging (rs-fMRI), to examine differences between VP and FT children in networks thought to be involved in goal setting, including left and right frontoparietal (lFPN, rFPN), executive control (ECN) and default mode (DMN) networks, and to examine network associations with goal setting skills at 13 years.

Participants included 177 VP and 61 FT control children aged 13 years from a prospective longitudinal study. Early risk factors involved sex, neonatal brain abnormalities, and medical

complications recorded during the neonatal period. Qualitative brain abnormality scores and quantitative brain volumes were derived from neonatal MRI brain scans conducted at term-equivalent age. Goal setting at 13 years was assessed using several cognitive measures of planning, organisation and strategic reasoning abilities. Resting state functional neuroimaging data was acquired at 13-years of age.

The VP group demonstrated a clear pattern of impairment and inefficiency across goal setting measures, consistent with parental report, compared with their FT peers. Within the VP group, moderate/severe brain abnormalities on neonatal MRI predicted adverse goal setting outcomes at 13.

In VP children, higher neonatal global brain, white matter, deep gray matter and cerebellum abnormality scores were associated with poorer goal setting scores at 13 years. There were positive associations between total brain volume, cerebellum, thalamic and cortical gray matter volumes and goal setting performance. Associations largely persisted after controlling for potential confounders.

Finally, VP children exhibited reduced functional connectivity compared with FT children within the rFPN, DMN and ECN, and particularly in frontal, temporal and occipital clusters, and within the lFPN, in frontal, temporal and insular clusters. VP children demonstrated greater functional connectivity than FT children in alternate frontal regions, including the frontal pole and pars triangularis. In both groups lFPN, rFPN, ECN and DMN connectivity was largely unrelated to goal setting performance.

This thesis highlights significant goal setting difficulties in VP children during late childhood, which are likely to have functional consequences academically, socially and vocationally. Additionally, goal setting difficulties at 13 years are associated with neonatal brain abnormalities and brain volumes, suggesting that neonatal MRI may help to identify VP children at risk for later executive dysfunction. Our study also supports the utility of rs-fMRI for understanding prematurity as a brain network

disorder, and contributes to the previously limited understanding of how neural connectivity relates to late childhood goal setting deficits in VP children.

General declaration

Monash University Declaration for thesis based or partially based on conjointly published or unpublished work.

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes an original paper accepted for publication in a peer-reviewed journal, an original paper under review in a peer-reviewed journal and an unpublished chapter in manuscript form. The core theme of the thesis is very preterm goal setting skills during late childhood and their neural substrates. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Monash Institute of Cognitive and Clinical Neurosciences (School of Psychological Sciences) under the supervision of Doctor Catherine Willmott, Professor Peter Anderson and Associate Professor Deanne Thompson.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers across multiple sites, and acknowledges input into team-based research.

In the case of chapters 3, 4 and 5, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status and Journal	Student; nature of contribution	Co-author(s); nature of contribution	Monash student co-author:	% of contribution
3	Goal setting deficits at 13	*Published* in Journal of the	Kristina Haebich;	-	-	65

	years in very preterm born children	International Neuropsychological Society	data collection, generation of research questions, literature review, data analysis, results, interpretation, manuscript			
				Catherine Willmott; generation of research questions, data analysis, input into manuscript	No	7.5
				Rachel Ellis; data collection, input into manuscript	No	5 collectively
				Alice Burnett; input into manuscript	No	
				Shannon Scratch; data collection, input into manuscript	No	
				Leona Pascoe, data collection, input into manuscript	Yes	
				Megan Spencer-Smith; input into manuscript	No	
				Jeanie Cheong; input into manuscript	No	
				Terrie Inder; input into manuscript	No	
				Lex Doyle; input into manuscript	No	
				Deanne Thompson; generation of research questions, data analysis, input into manuscript	No	10
				Peter Anderson;	No	12.5

				generation of research questions, data analysis, input into manuscript, interpretation		
4	Neonatal brain abnormalities and brain volumes associated with goal setting outcomes in very preterm 13- year-olds	*Under review* at Brain Imaging and Behavior	Kristina Haebich data collection, generation of research questions, literature review, data analysis, results, interpretation, manuscript	-	-	67.5
				Catherine Willmott; generation of research questions, data analysis, input into manuscript	No	7.5
				Shannon Scratch; data collection, input into manuscript	No	5 collectively
				Leona Pascoe; data collection, input into manuscript	Yes	
				Kate Lee; statistical consultation, input into manuscript	No	
				Megan Spencer-Smith; input into manuscript	No	
				Jeanie Cheong; input into manuscript	No	
				Terrie Inder; input into manuscript	No	

				Lex Doyle; input into manuscript	No	
				Deanne Thompson; generation of research questions, data analysis, input into manuscript	No	10
				Peter Anderson; generation of research questions, data analysis, input into manuscript	No	10
5	Resting-state connectivity and goal setting outcomes of very preterm and full-term born children at 13 years	Completed chapter	Kristina Haebich; data collection, generation of research questions, literature review, pre-processing, data analysis, results, interpretation, manuscript	-	-	65
				Deanne Thompson; generation of research questions, data analysis, input into manuscript	No	12.5
				Catherine Willmott; generation of research questions, data analysis, input into manuscript	No	7.5
				Chiara Nosarti; input into manuscript	No	2.5
				Jian Chen; neuroimaging preprocessing and analysis consultation, input into manuscript	No	
				Megan Spencer-	No	5 collectively

				Smith; input into manuscript		
				Terrie Inder; input into manuscript	No	
				Lex Doyle, input into manuscript	No	
				Peter Anderson; generation of research questions, data analysis, input into manuscript	No	7.5

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 2nd July 2018

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors

Main Supervisor signature: [redacted] **Date:** 2nd July 2018

Publications during enrolment

During my candidature, the following manuscripts were prepared and submitted from my doctoral data. I also presented doctoral research findings at an international conference in the final year of my candidature. These are outlined below:

Journal articles

Haebich, K. M., Willmott, C., Ellis, R., Burnett, A., Scratch, S., Pascoe, L., . . .Anderson, P. (2017). Goal setting deficits at 13 years in very preterm born children. Journal of the International Neuropsychological Society, *23*(4), 372-381, doi:10.1017/S1355617717001138

Haebich, K. M., Willmott, C., Scratch, S., Pascoe, L., Lee, K., Spencer-Smith, M., . . .Anderson, P. (2018). Neonatal brain abnormalities and brain volumes associated with goal setting outcomes in very preterm 13- year-olds. Brain Imaging and Behavior (under review).

Haebich, K. M., Thompson, D.K., Willmott, C., Nosarti, C., Chen, J., Spencer-Smith, M., et al. (2018). Resting-state connectivity and goal setting outcomes of very preterm and full-term born children at 13 years of age (complete chapter).

Conference presentations

Haebich, K. M., Willmott, C., Ellis, R., Burnett, A. C., Spencer-Smith, M., Cheong, J.L.Y., et al. (2017). Late childhood goal setting performance in very preterm born children. Paper presented at the International Neuropsychological Society, Cape Town, South Africa.

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On a more personal level, thank you to each of you for your patience, compassion, and understanding throughout my candidature. You have made this experience bearable during challenging times, and I am so grateful for your unfaltering belief in my ability. Together, you have helped me achieve an end result that is better than what I imagined myself to be capable of. Accordingly, thank you for helping me accomplish the greatest achievement in my life so far.

To my collaborators, Dr. Rachel Ellis, Dr. Alice Burnett, Dr. Shannon Scratch, Leona Pascoe, Dr. Megan Spencer-Smith, Associate Professor Jeanie Cheong, Professor Terrie Inder, Professor Lex Doyle, Dr. Kate Lee, Dr. Chiara Nosarti, and Jian Chen, I am very grateful for your guidance and assistance writing my thesis throughout my candidature. Your contributions have been invaluable.

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have never have been able to begin and complete this thesis without having you there to cheer me on. Thank you as well to other special family members, including my brother Jayson, and my beautiful Grandma Lorraine. Thank you to all my friends for enduring me, being patient when I neglected you, and for keeping a smile on my face. Special thanks to my best, most loyal and favourite friends, Alexandra, Lauren and Chloe.

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Chapter 1. Introduction

Chapter 1

The broad objective of this dissertation is to examine executive function in very preterm children at 13 years of age, with a specific focus on goal setting skills such as planning and organisational ability.

1.1. Premature birth

One in 10 Australian babies are born prematurely each year (Australian Institute of Health and Welfare, 2016). Infants are classified as preterm if born prior to 37 completed weeks' gestation, while those born less than 32 weeks' gestation are classified as very preterm (VP), and those born less than 28 completed weeks' gestation are classified as extremely preterm (EP; World Health Organization, 2013). Preterm infants often include those born at low (i.e., LBW; <2500 grams), very low (VLBW; <1500 grams) or extremely low birth weight (ELBW; <1000 grams; World Health Organization, 2013). Throughout this dissertation, 'preterm' refers to the general preterm population, including VP, EP, LBW, VLBW and ELBW, however the primary focus is VP literature.

A complex amalgamation of numerous gene-environment factors during pregnancy increase the risk of preterm birth (Behrman & Stith Butler, 2007). Poor nutrition during pregnancy as well as adverse environmental factors, including smoking, illicit drug use, and heavy alcohol consumption, increase the risk of preterm birth. Socioeconomic factors, including low income status and limited health care access, psychosocial factors such as elevated stress and experiencing stressful life events, as well as ethnicity are also related to preterm birth (Allen, 2008; Behrman & Stith Butler, 2007). Poor maternal health, medical conditions (e.g., preeclampsia), as well as assisted reproductive technology are also associated with preterm birth (Allen, 2008; Behrman & Stith Butler, 2007).

Prior to the 1970s, few EP infants survived the neonatal period due to the limited use of assisted ventilation, and many slightly more mature VP babies also died from respiratory distress caused by an absence of pulmonary surfactant (Saigal & Doyle, 2008). Since the 1980s, survival rates increased considerably in association with significant advances in neonatal intensive care and healthcare resources, including the introduction of surfactant to treat respiratory distress syndrome, widespread use of assisted ventilation, increasing and earlier use of antenatal corticosteroids, as well as changed attitudes towards intensive care treatment (i.e., active management of infants with gestations previously considered nonviable; Gultom, Doyle, Davis, Dharmalingam, & Bowman, 2008; Lopez et al., 2013; Lorenz, 2000, 2001; Roberts & Dalziel, 2006; Saigal & Doyle, 2008; Soll, 1998). Survival

rates have particularly improved for those infants of lowest gestational age and birthweight (Saigal & Doyle, 2008). In Australia, for example, the survival rate of preterm ELBW born infants increased from 25% in early 1980, to 73% in 1997 (Doyle & Victorian Infant Collaborative Study Group, 2004). More recently, survival rates of infants born in Australia and New Zealand between 2007 and 2013 have been estimated at 64% for EP infants born at 24 weeks' gestation, and 94% for VP infants born at 28 weeks' gestation (Helenius, Sjors, Shah et al., 2017).

Very preterm birth is associated with considerable cost to society and families. Compared with only 10% of infants born full-term (FT; ≥ 37 to ≤ 41 weeks' gestation), approximately 72% of preterm born infants require intensive care admission for medical treatment at birth (Australian Institute of Health and Welfare, 2016), imposing a substantial cost upon the health care system. Reduced labour market productivity may also occur if parents of preterm infants require additional leave from employment (Gennaro, 1996; Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). Parents of VP infants may experience significant emotional distress during the neonatal period (Ionio et al., 2016). Negative consequences often persist following hospital discharge, including reduced employment hours, financial strain, emotional distress, social isolation and relationship strain (Kusters, van der Pal, van Steenbrugge, den Ouden, & Kollee, 2013). Ongoing medical follow-up and early intervention services are often necessary for VP survivors following hospital discharge, and allied health services and special education may be required throughout childhood, and early adulthood (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007; Kusters et al., 2013; Stevenson, McCabe, Pharoah, & Cooke, 1996).

1.2. Complications of VP birth

Adverse medical complications of preterm birth increase with decreasing gestational age (GA) and/or birth weight, and are associated with high rates of morbidity and mortality (Stoll et al., 2015). The major morbidities commonly experienced by VP infants that occur due to organ immaturity, infection and inflammation will be outlined in the following section, touching on the adverse neurodevelopmental consequences associated with these complications.

1.2.1. Patent ductus arteriosus

Patent ductus arteriosus (PDA) is a life threatening complication associated with preterm birth, affecting approximately a third of VP infants (D. Evans, 2003; Kluckow & Evans, 2000). In PDA, the blood vessel connecting the main pulmonary artery and the aorta, named the ductus arteriosus, fails to close after birth. While the ductus arteriosus of FT infants typically closes within 3 days following birth, the ductus arteriosus of VP infants is underdeveloped at the time of birth and may remain open (D. Evans, 2003). It is critical that the ductus arteriosus closes after birth to allow blood to circulate from the heart to the lungs for oxygenation. Infants with PDA often require ventilators to support their breathing, and may require surgical, medicinal and catheter-based interventions to help close the ductus arteriosus. Closure of the ductus arteriosus is critical to prevent excess blood flow throughout the arteries of the heart and lungs, and subsequently, lowered blood perfusion to critical bodily organs as well as respiratory distress. Lowered blood perfusion to the brain can cause hypoxic brain injuries, such as intraventricular haemorrhaging and periventricular brain injury (Benitz, 2015). Further, decreased blood flow to the intestines and kidneys increases the likelihood that a VP infant will develop necrotising enterocolitis and/or renal failure (Hamrick & Hansmann, 2010). Respiratory distress caused by increased blood flow can cause haemorrhagic pulmonary edema, poor lung compliance (i.e., difficulties expanding and contracting relative to changes in pressure), respiratory illness and chronic lung disease (Dzialowski & Greyner, 2008; Nemri, 2014). Patent ductus arteriosus is associated with negative neurodevelopmental outcomes, in particular, surgical intervention for PDA has been associated with the development of cerebral palsy, intellectual disability, vision and hearing impairments, as well as poorer general intellectual functioning (Chorne, Leonard, Piecuch, & Clyman, 2007; R W Cooke, 2005).

1.2.2. Respiratory illness

Given that fetal lungs develop rapidly until 40 weeks gestation, particularly during the second and third trimester, VP infants are born with immature lungs and often require prolonged periods of assisted ventilation or oxygen therapy in order to survive the neonatal period (Jobe & Bancalari, 2001; Moss, 2006; Shepherd & Nelin, 2017). Immature lungs also render VP infants vulnerable for respiratory complications, which increase in incidence rate with decreasing GA and or birth weight (BW; Darlow, Cust, & Donoghue, 2003; Doyle et al., 2006; Gilbert, Nesbitt, & Danielsen, 2003; Shepherd & Nelin, 2017).

Respiratory distress syndrome (RDS) is a common complication for VP infants, in which the lungs are deficient of a lipid and protein comprised fluid named surfactant, which prevents the air sacs from deflating (Moss, 2006). Symptoms of RDS may include tachypnea, chest retraction, apnea and cyanosis (Moss, 2006). Respiratory distress syndrome is treated with surfactant replacement therapy, and to keep the lungs inflated, oxygen therapy and ventilation is provided. While such treatments are essential for enabling affected infants to survive, their administration can be associated with adverse consequences. For example, prolonged oxygen therapy can cause bronchopulmonary dysplasia (BPD) a chronic respiratory disease in which the lung's air sacs are injured. Bronchopulmonary dysplasia renders infants vulnerable to further serious medical complications, including infections (e.g., sepsis, necrotising enterocolitis), which may necessitate the administration of potentially harmful medications (e.g., postnatal corticosteroids; Anderson & Doyle, 2006; Fuller, Guthrie, & Alvord, 1983; Garg, Kurzner, Bautista, & Keens, 1988; Hack & Fanaroff, 2000; Skidmore, Rivers, & Hack, 1990). Bronchopulmonary dysplasia is also associated with an increased risk for hypoxia and brain injury, as well as generally poorer brain development (P. J. Anderson & Doyle, 2006, 2008; Fuller et al., 1983; Garg et al., 1988; Wood et al., 2005).

Respiratory complications experienced by VP infants are associated with later physical and neurodevelopmental difficulties. Physiologically, persistent structural pulmonary abnormalities render VP infants vulnerable to lowered airway flow, reactivity and diffusion capacity, as well as high rates of respiratory diseases (e.g., asthma; (Gross, Iannuzzi, Kveselis, & Anbar, 1998; Moss, 2006; Pelkonen, Hakulinen, & Turpeinen, 1997). Regarding neurodevelopment, neurosensory impairments (e.g., motor disorders, cerebral palsy), poorer language development, academic underachievement, and cognitive impairments (e.g., poor visuospatial perception, attention, memory, and new learning abilities) are linked with RDS and BPD in VP infants (P. J. Anderson & Doyle, 2006; Hintz et al., 2007; Patrianakos-Hoobler et al., 2010).

1.2.3. Infection

Sepsis is a severe and potentially life threatening bacterial infection commonly experienced by VP infants. Early onset sepsis is contracted by preterm infants from their mothers, from maternal fever or uterus/placenta tissue infections in utero, from the birth canal or maternal bleeding during childbirth, or in association with a difficult delivery (Anderson-Berry, Bellig, & Ohning, 2015). Late onset sepsis is

contracted postpartum in the neonatal environment, acquired from bacteria colonised on medical objects (e.g., endotracheal tubes, ventilators) or people, with longer neonatal intensive care unit stays increasing the risk for sepsis infection (Anderson-Berry et al., 2015). Immature immune systems of VLBW/EP infants make them more vulnerable to contracting infections like sepsis (D. Kaufman & Fairchild, 2004; Stoll et al., 2002). Sepsis incidence rates have significantly increased in recent decades in association with increased survival rates of low GA/BW infants (Alshaikh, Yusuf, & Sauve, 2013; Anderson-Berry et al., 2015). Sepsis is linked with serious medical complications such as meningitis and pneumonia (Muhe et al., 1999), as well as brain white matter abnormalities due to increased pro-inflammatory cytokines, blood–brain barrier permeability, and hypotension along with impaired cerebral blood flow auto-regulation (Graham, Holcroft, Rai, Donohue, & Allen, 2004; D. K Shah et al., 2008; Silveira, Procianoy, Dill, & da Costa, 2008; Volpe, 2008b). Sepsis is associated with adverse neurodevelopmental outcomes for VP/VLBW children, including neurosensory, motor and general cognitive impairment (Alshaikh et al., 2013; Hentges et al., 2014; D. K Shah et al., 2008).

Necrotising enterocolitis (NEC) is a gastrointestinal complication commonly experienced by VP neonates whereby sections of bowel tissue incur infection and inflammation-induced necrosis due to reduced oxygen. Necrotising enterocolitis can lead to systemic inflammation of bodily organs, including the brain (Martin et al., 2010; D. K Shah et al., 2008). Medical and/or surgical intervention is required to treat NEC (P. W. Lin & Stoll, 2006). Very preterm/EP/ELBW infants with NEC who have undergone surgical intervention often also have identified white matter brain abnormalities, and are therefore are at greatest risk for poorer neurodevelopmental outcomes, including cerebral palsy, motor impairments, academic underachievement and cognitive deficits such as attention, visual perceptual, and general intellectual functioning difficulties (P. J. Anderson et al., 2011; Johnson, Wolke, Hennessy, & Marlow, 2011; Martin et al., 2010; C. M. Rees, Pierro, & Eaton, 2007; Roze et al., 2011; Schulzke, Deshpande, & Patole, 2007; D. K Shah et al., 2008). Incidence rates of NEC increase in association with decreasing GA/BW (Holman, Stoll, Clarke, & Glass, 1997; M. I. Rowe, Reblock, Kurkchubasche, & Healey, 1994; Schulzke et al., 2007).

1.3. Premature birth and the brain

Neonatal brain injury and altered brain development are common consequences of premature birth. Mechanisms of preterm brain development are best understood in the context of typical brain

development. The following section will begin with a brief overview of early brain development, thereafter discussing mechanisms of brain injury associated with VP birth.

1.3.1. Typical brain development

The complex structural and cellular changes necessary for fetal brain development commence during the third embryonic week of life (Ortinau & Neil, 2014). From embryonic day 25, symmetric neuronal proliferation and migration begins from the ventricular zone (Ortinau & Neil, 2014). Cell division transitions to an asymmetric process from day 33, marking the beginning of neurogenesis which involves the generation of neurons and glial cells from neural stem cells (Noctor, Flint, Weissman, Dammerman, & Kriegstein, 2001). Shortly after neurogenesis commences, the subventricular zone and germinal matrix are formed, although their development continues into the third trimester of pregnancy (Ortinau & Neil, 2014). At approximately 10 weeks gestation, the subventricular zone preplate is split by migrating neural cells to form the cortical plate above, and the subplate below (Ortinau & Neil, 2014; Volpe, 2008a). After neuronal migration is completed between 20 to 24 weeks gestation, the processes of cortical organisation commence, involving axon and dendrite development, apoptosis (i.e., programmed cell death) and synaptogenesis (Ortinau & Neil, 2014; Rakic, 1985). By approximately 22 weeks gestation, oligodendrocyte progenitor cells are present, leading to the formation of pre-oligodendrocytes (Ortinau & Neil, 2014). Pre-oligodendrocyte development peaks between 23 to 32 weeks gestation (Ortinau & Neil, 2014; Rivkin et al., 1995). Cortical organisation continues throughout the second and third trimester, involving the development of neural networks, formation of the cerebral cortex, proliferation of radial glial cells (i.e., astrocytes, oligodendrocytes and microglia), and a fourfold increase in cortical brain volumes (Ortinau & Neil, 2014). Between 24 to 40 weeks gestation, pre-oligodendrocytes are the dominant cell comprising cerebral white matter (Gopagondanahalli et al., 2016). From 29 weeks gestation, white matter volumes increase approximately fivefold and gray matter demonstrates a threefold increase (Huppi et al., 1998). Rapid development in cortical surface area, sulci and gyri development are also seen from 27 weeks, secondarily followed by an increase in the complexity of regionally specific cortical folding (see Figure 1.1.; Huppi et al., 1998). While mature oligodendrocytes capable of myelinating neural axons (i.e., generating a protective sheath around axons) are present from mid-gestation, they only become abundant after full term gestation is reached, and developing rapidly into the second year of

life (Gopagondanahalli et al., 2016; Kinney & Back, 1998; Ortinau & Neil, 2014).

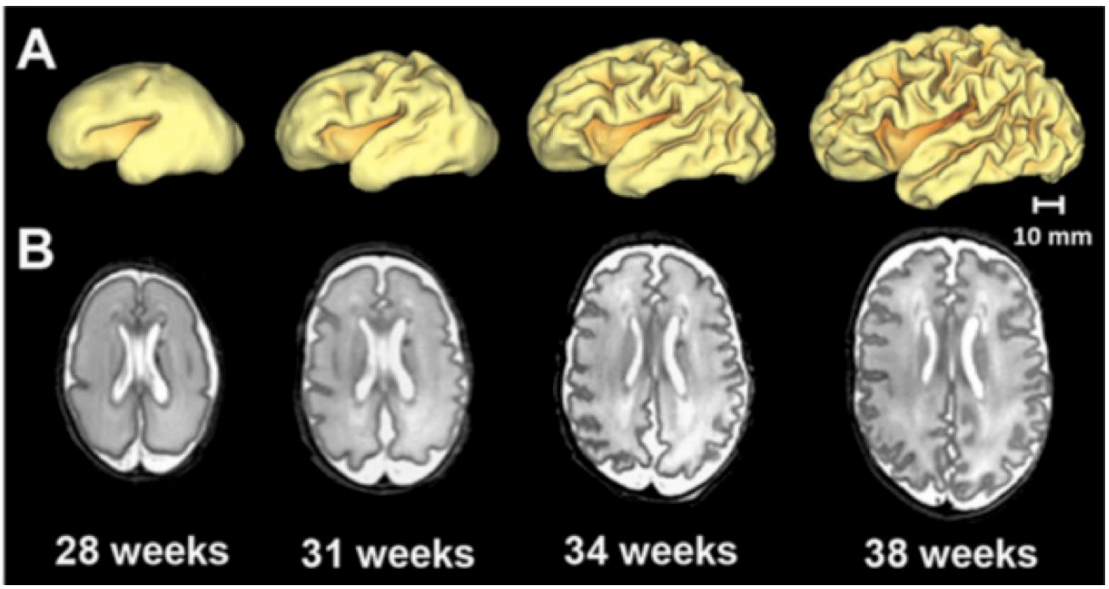

Figure 1.1. Early brain development at 28, 31, 34, and 38 weeks post-menstrual age demonstrated by A) 3-dimensional surfaces of gryal and sulcal formation generated from T_2-weighted images of premature infants and B) axial T_2 images illustrating regionally-specific cortical folding occurring in the premature brain secondary to sulcation and gyration throughout early development. Images were obtained from the magnetic resonance imaging brain scan of a single preterm infant. Note. Figure adapted from (Smyser, Kidokoro, & Inder, 2012).

Full term gestation is optimal for the pre-programmed processes of typical fetal brain development to take place. Mechanisms of premature birth serve to disrupt typical brain development however, rendering the brain vulnerable to injury or insult. A combination of primary and subsequent secondary maturational disturbances contribute to brain injury in premature infants, such as disrupted proliferative zone and white matter development leading to hypomyelination and impaired cortical developmental (Volpe, 2009a). The following section will review key mechanisms and types of brain injury experienced by preterm infants.

1.3.2. Mechanisms of preterm brain injury

Hypoxic-ischaemia is considered one of the leading causes of brain injury in preterm infants

(Volpe, 2009a). The immature brain development of a preterm infant renders it susceptible to hypoxic-ischaemic brain injury. A preterm infant's cerebrovascular network is fragile given an underdeveloped distal arterial network and reduced capacity to auto-regulate cerebral blood flow, resulting in a limited capacity to sustain effective blood flow in compensation for hypoxic-ischaemic events (Gopagondanahalli et al., 2016; Volpe, 2009a). Immature brain development at the cellular level also contributes to preterm infant susceptibility for hypoxic-ischaemia. At the time of preterm birth, the brain's white matter is predominantly comprised of pre-oligodendrocytes, and the neurons of the subplate are reaching peak mass and development (Gopagondanahalli et al., 2016). Subplate neurons are key to the development of axons, the cortex, deep nuclear structures including the thalamus and basal ganglia (Gopagondanahalli et al., 2016). Subplate neurons and pre-oligodendrocytes are particularly vulnerable to hypoxic-ischaemia with pre-oligodendrocytes primarily affected and resulting in white matter injury, and axonal de-afferentiation occurring secondarily, leading to injury to the brain's deep gray matter (Rees & Inder, 2005). Intrauterine infections, neonatal or fetal infections and ischemia-induced inflammation may also contribute to the pathology of preterm brain injury by inciting excess production of pro-inflammatory cytokines (i.e., immune cell signalling molecules; Ahya & Suryawanshi, 2017). Systemic upregulation of pro-inflammatory cytokines contributes to injury to developing brain cells such as the pre-oligodendrocytes, resulting in white matter injury (Deng, Pleasure, & Pleasure, 2008; Folkerth, 2005; S. Rees & Inder, 2005).

Periventricular leukomalacia (PVL) is the major form of hypoxic-ischaemic brain injury affecting preterm infants (Volpe, 2001). In PVL, the pre-oligodendrocytes of the cerebral white matter and subplates neurons beneath the neocortex experience either cystic or diffuse neuropathological injury largely in response to insufficient blood and oxygen supply. Cystic PVL is characterised by focal lesions within the periventricular white matter which evolve into fluid filled cysts (Volpe, 2008a). These cysts are macroscopic in size, and easily identified on cranial ultrasound (Sankar & Mundkur, 2005). While the neurodevelopmental consequences of cystic PVL are severe, with 60% to 100% of infants developing cerebral palsy, incidence rates are low with approximately 3% of VLBW infants affected (Sankar & Mundkur, 2005; Volpe, 2008a). In comparison, diffuse PVL is documented in approximately 75% of EP/VP infants, using T_2-weighted MRI scans to identify the high signal intensity (i.e., cellular density) that signifies diffuse white matter injury (Sankar & Mundkur, 2005; Volpe, 2008a). Diffuse PVL is characterised by acute pre-oligodendrocyte loss, accompanied by astrogliosis and

microgliosis, which results in a reduction in myelin producing oligodendrocytes and consequently, decreased white matter in the regions surrounding the ventricle (Selip et al., 2012; Volpe, 2008a). Neurodevelopmental consequences associated with diffuse PVL are less severe than those of cystic PVL, including mild deficits in motor and visual abilities, as well as working memory deficits (Resic et al., 2008; Volpe, 2003; Zubiaurre-Elorza et al., 2012).

Intraventricular haemorrhage (IVH) is another brain injury commonly affecting preterm infants, occurring in up to 20% of VP infants (Sarkar, Bhagat, Dechert, Schumacher, & Donn, 2009). Intraventricular haemorrhage typically results from bleeding in the germinal matrix, positioned adjacent to the lateral ventricles, a brain region comprised of immature neuron and glia precursor cells which is rich in blood vessels (Mukerji, Shah, & Shah, 2015). The germinal matrix of preterm infants is underdeveloped and fragile, and thus highly vulnerable to hypoxic-ischaemia and fluctuations in cerebral flow (Ballabh, 2010). Complications associated with preterm birth increase an infant's risk for developing an IVH, including an immature respiratory system, which increases the risk of hypoxic-ischaemia, and fluctuating arterial blood flow, which contributes to excessive cerebral blood flow and venous pressure (McCrea & Ment, 2008). Intraventricular haemorrhages are graded according to severity, with bleeds confined to the germinal matrix or lateral ventricles are referred to grade 1 and 2 IVH, while grades 3 and 4 are related to ventricular dilation and WM infarction respectively. Grade 3 and 4 IVH is associated with poorer neurodevelopment, including cerebral palsy and intellectual disability (Ballabh, 2010).

1.3.3. Preterm neonatal brain injury

Magnetic resonance imaging (MRI) techniques have enabled the detailed examination of brain pathology in the preterm born population during the neonatal period. Reductions in brain volumes as well as brain abnormalities are commonly documented in the cortex and deep nuclear structures of preterm neonates, revealing the extent of brain pathologies incurred (Inder, Warfield, Wang, Huppi, & Volpe, 2005).

Volumetric MRI has enabled the quantitative measurement of infant brain structures, in order to characterise the impaired brain growth of preterm infants at term-equivalent age. Very preterm infants demonstrate volume reductions in white and gray matter structures that are indicative of poorer brain

development than FT infants (Keunen et al., 2016). Brain regions found to be particularly vulnerable include the cortical gray matter, cerebral white matter, hippocampus, as well as subcortical structures, including the basal ganglia and thalami, corpus callosum and cerebellum (Keunen et al., 2012; Thompson, Inder, et al., 2012; Thompson et al., 2008; Volpe, 2009a). Decreased brain volumes are accompanied by increased cerebrospinal fluid volumes (Keunen et al., 2012). White matter injury, IVH, intrauterine growth restriction, corticosteroids, respiratory illness and decreasing GA are associated with decreased brain volumes in preterm samples (Keunen et al., 2012), however reduced brain volumes are also documented in the absence of severe medical complications (Inder et al., 2005; Limperopoulos et al., 2005; Mewes et al., 2006; Thompson et al., 2007).

Premature birth also results in a range of brain abnormalities observable during the neonatal period. Using MRI brain abnormality rating scales, the range and severity of VP/VLBW brain abnormalities have been identified, including punctate lesions, loss of white matter, enlarged lateral ventricles (ventriculomegaly), thinned/smaller corpus callosum, delayed myelination and cortical folding, as well as increased subarachnoid space (see Figure 1.2.; Anderson, Laurent, Woodward, & Inder, 2006; Anderson, Cheong, & Thompson, 2015; Counsell & Boardman, 2005; Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Thompson et al., 2014). MRI reporting scales enable the extent and range of brain injuries experienced by VP infants to be evaluated. Kidokoro, Neil, and Inder (2013) developed one such scale, which measures white matter, cortical gray matter, deep gray matter, cerebellum and global brain abnormalities across scales (for a detailed description, please refer to section 2.6.2. and Table 2.3 of Chapter 2; Kidokoro, Neil, & Inder, 2013). Understanding the nature of brain injuries evident during the neonatal period may help to better understand poor neurodevelopmental outcomes documented in VP populations (Kidokoro et al., 2013).

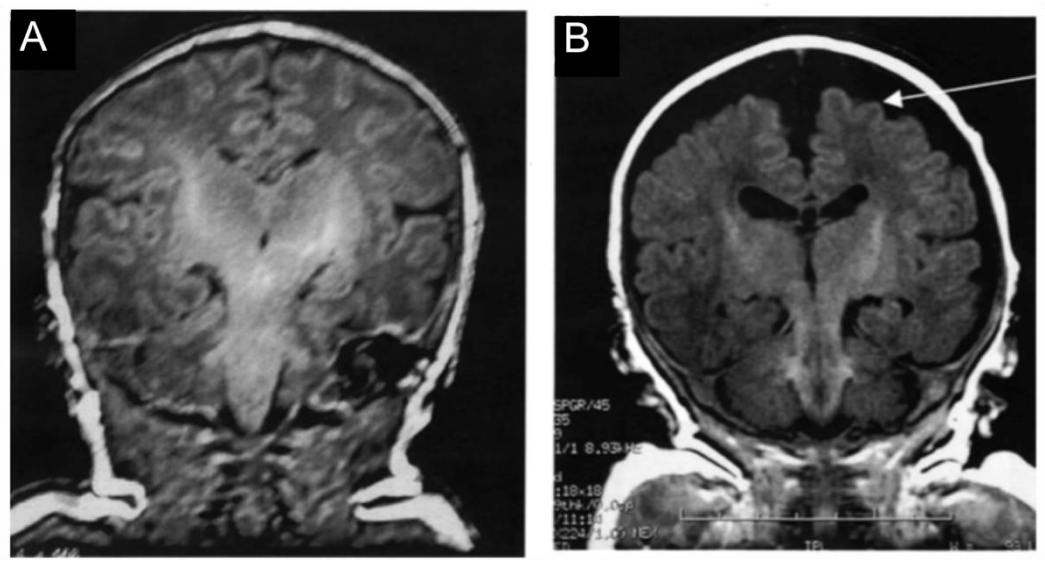

Figure 1.2. Comparison of magnetic resonance images both obtained at term equivalent of A) an infant born at 30 weeks gestation and B) an infant born at 23 weeks' gestational age with evidence of moderate ventriculomegaly with markedly enlarged subarachnoid spaces (arrow), diffuse white matter loss and immature gyration. Note. Figure adapted from (Inder et al., 2003).

1.4. Neurodevelopmental outcomes of preterm birth

As a consequence of significant adversity experienced by VP infants during early development, neurodevelopmental difficulties are prevalent in this population. The following section will outline the common neurodevelopmental sequelae associated with VP birth.

1.4.1. Neurodevelopmental sequelae

Advances in neonatal care have failed to reduce rates of neurodevelopmental impairments in VP children. Due to the increased likelihood that even the sickest and smallest infants will now survive the neonatal period, a greater proportion of preterm children are vulnerable to adverse outcomes. In a large Victorian geographic cohort, approximately 71% of 8-year-old EP children (<28 weeks' gestation) exhibited at least one mild to severe neurodevelopment impairment, with 50% exhibiting multiple deficits (Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013). Motor and vision impairments, behavioural and social-emotional difficulties, reduced intellectual functioning, and

primary cognitive deficits are the most common neurodevelopmental difficulties reported in follow-up of VP infants throughout childhood.

Motor and vision impairments are a widely documented consequence of VP birth. Motor impairments associated with VP birth commonly include fine motor, gross motor and visuomotor integration difficulties, evident during infancy and persisting throughout childhood (Brown, Doyle, Bear, & Inder, 2006; de Kieviet, Piek, Aarnoudse-Moens, & Oosterlaan, 2009; Moreira, Magalhaes, & Alves, 2014). Impairment may be mild to moderate (e.g., poor balance and manual dexterity, motor incoordination), to severe in nature (i.e., cerebral palsy; Spittle & Orton, 2014). The severity of motor impairments experienced by VP children increases in association with perinatal risk factors, including NEC, PVL and decreasing GA/BW (Himpens, Broeck, Oostra, Calders, & Vanhaesebrouck, 2008; Moreira et al., 2014; A. J. Spittle & Orton, 2014).

Retinopathy of prematurity (i.e., retinal vascular disease) or PVL are typically associated with vision impairments in VP children, involving reduced visual acuity or peripheral vision, strabismus, and myopia (Leung, Thompson, Black, Dai, & Alsweiler, 2017). Vision impairments can impede the development of brain regions supporting visual processing, possibly resulting in poor global motion perception, visuoperceptual and visuomotor integration skills (Leung et al., 2017). Motor and vision impairments may negatively impact a VP child's activity participation levels, cognitive abilities, academic achievement, behaviour, and social-emotional wellbeing (Leung et al., 2017; Spittle & Orton, 2014).

Behavioural and social-emotional difficulties are elevated in VP populations (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; M S Indredavik et al., 2004; McCormick, Workman-Daniels, & Brooks-Gunn, 1996; Patton, Coffey, Carlin, Olsson, & Morley, 2004; Treyvaud et al., 2013). Behaviourally, inattention and hyperactivity problems are common, and shyness, unassertiveness, anxiety and social withdrawal contribute to social difficulties (Bhutta et al., 2002; Saigal & Doyle, 2008). The most commonly reported psychiatric diagnoses in VP populations include anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (Johnson & Marlow, 2011; Treyvaud et al., 2013). Compared with FT children, VP children are shown to be three times more likely to meet criteria for a psychiatric diagnosis during childhood (Treyvaud et al., 2013). Early social-emotional problems, severe perinatal brain injury, less sensitive parenting style, and higher social risk are shown to predict preterm social-emotional-behavioural difficulties (Clark,

Woodward, Horwood, & Moor, 2008; Treyvaud et al., 2013). Identification of VP children at risk for social-emotional-behavioural difficulties is essential, given that difficulties can persist into adolescence and adulthood, and early intervention may minimise the negative effects of these difficulties upon home life, learning, friendships and leisure pursuits (Clark et al., 2008; Hack et al., 2002; M. S. Indredavik et al., 2005; C. Nosarti, Reichenberg, Murray, & et al., 2012).

Very preterm birth is consistently associated with reduced general intellectual functioning (Kerr-Wilson, Mackay, Smith, & Pell, 2012). During early childhood, rates of general intellectual functioning impairment in VP/VLBW children far exceed those rates documented in FT children (41% versus 2% respectively; Marlow, Wolke, Bracewell, & Samara, 2005). Moreover, VP/VLBW children demonstrate persistently poorer intellectual skills than their FT peers throughout childhood and adolescence (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2015). Very preterm intelligence quotients (between 23 to 37 weeks' gestation) are documented to be up to 12 points, almost one standard deviation, lower than those of matched FT children in cohort studies (Kerr-Wilson et al., 2012). Perinatal risk factors such as reduced GA/BW in VP children are related to poorer intellectual skills (Kerr-Wilson et al., 2012; Silva, McGee, & Williams, 1984; Weisglas-Kuperus et al., 2009). In fact, a 1.5 point intelligence quotient (IQ) decrease per gestational week is documented in children born at less than 33 weeks GA (Johnson, 2007). While intelligence tests indicate that cognitive impairment is prevalent in VP populations, they do not yield adequate detail to understand specific cognitive deficits experienced by VP children.

Up to 60% of VP/ELBW children exhibit cognitive deficits in late childhood (P. J. Anderson & Doyle, 2003). Memory and language impairments are commonly experienced by preterm children. Impairments in all aspects of verbal and visual memory functioning, including encoding, storage and recall, are reported in VP/VLBW samples throughout infancy and childhood (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; P. J. Anderson & L. W. Doyle, 2004; I. S. Baron, Erickson, Ahronovich, Litman, & Brandt, 2010; Haan, Bauer, Georgieff, & Nelson, 2000; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Omizzolo et al., 2013; Rose, Feldman, & Jankowski, 2005; Rose, Feldman, Jankowski, & Van Rossem, 2011; Taylor, Klein, Minich, & Hack, 2010). Very preterm children are reported to be approximately 2 to 3.5 times more likely than their FT peers to experience memory deficits (Omizzolo et al., 2013). Generalised language impairments are also commonly experienced by VP/VLBW children, involving difficulties in both fundamental (i.e.,

phonological awareness, expressive and receptive language) and complex (i.e., pragmatics, discourse) language skills (Barre, Morgan, Doyle, & Anderson, 2011; Reidy et al., 2013; van Noort-van der Spek, Franken, & Weisglas-Kuperus, 2012).

Higher-level cognitive skills, known as executive functions (EFs), represent a key domain of cognitive impairment experienced preterm children (P. J. Anderson & Doyle, 2003). Impairments in EFs are a particularly concerning cognitive deficit given their importance for successful reasoning, goal-directed and adaptive behaviour (Burnett, Scratch, & Anderson, 2013). The following section will comprehensively review executive functioning and the deficits VP children exhibit in this cognitive domain.

1.5. Executive function impairment

The following section will begin by defining EFs, and discussing executive dysfunction (EDF) as well as several theoretical approaches to EF, with a more detailed explanation of the framework chosen to guide this dissertation. Measurement of EF will be outlined next, after which typical development of EF during childhood will be discussed. An overview of EF impairments in VP samples throughout late childhood will follow. Factors of prematurity that are related to VP executive function difficulties will then be considered.

1.5.1. Executive functions

Executive function is an umbrella term for numerous interrelated higher-order cognitive skills that are essential for complex reasoning, goal-directed activity and adaptive behaviour (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2012; P. J. Anderson, 2002). Executive function includes complex attention (i.e., working memory), impulse control, response inhibition, self-regulation, initiation, cognitive flexibility, utilisation of feedback, performance monitoring, planning and organisation, problem-solving and strategic reasoning (P. J. Anderson, 2002; V. A. Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001).

The anterior portion of the brain's frontal lobe (i.e., the prefrontal cortex) is integral for EF. Early research in patients with brain lesions and acquired brain injuries demonstrated the neuroanatomical link between prefrontal region damage and corresponding executive dysfunction (Benton, 1968; Eslinger & Damasio, 1985; Stuss & Benson, 1984). Functional neuroimaging has also demonstrated

the frontal lobe and EF connection, demonstrating significant prefrontal lobe activation during completion of EF tasks (e.g., the Tower Test; Baker et al., 1996; Morris, Ahmed, Syed, & Toone, 1993; Newman, Carpenter, Varma, & Just, 2003). The neural underpinnings of EF are complex, however, and not limited to the frontal lobe, with virtually all brain regions contributing to EF proficiency, including the brain stem, occipital, temporal and parietal lobes, limbic and subcortical structures (i.e., basal ganglia, thalamus) as well as the cerebellum (Alivisatos & Petrides, 1997; P. J. Anderson, 2002; Klinberg, O'Sullivan, & Roland, 1997; Stuss & Benson, 1984). Neuroimaging evidence indicates that white matter tracts are crucial for supporting the afferent and efferent connections that facilitate communication between the numerous brain regions underlying EF (Makris et al., 2008; Niogi et al., 2008; Schermuly et al., 2010). While a broad neural network supports EF, its reliance upon a distributed network renders it vulnerable to impairment if any one of these regions incurs injury or insult.

1.5.2. Executive dysfunction

Executive dysfunction pertains to EF difficulties that manifest as behavioural, cognitive and emotional deficits (P. J. Anderson, 2002; Godefroy et al., 2010). In developmental populations, cognitive manifestations of EDF may involve impairments in cognitive flexibility, impulse control, reasoning, feedback utilisation, working memory, performance monitoring, self-regulation, planning, organisation strategy generation, and initiation, as well as perseveration (P. J. Anderson, 2002). Emotional and behavioural difficulties may also be apparent, including disruptive, argumentative, impulsive and socially inappropriate behaviours (P. J. Anderson, 2002; Hughes, Dunn, & White, 1998). Executive dysfunction is associated with compromised ability in activities of daily living, including domains of academic achievement, social competence and occupational pursuits (Barkley & Murphy, 2010; Best, Miller, & Naglieri, 2011; Blakemore & Choudhury, 2006; Shimoni, Engel-Yeger, & Tirosh, 2012), and potentially loss of autonomy and emotional difficulties (Godefroy et al., 2010). Executive dysfunction has been reported in a range of conditions, including acquired brain trauma (e.g., traumatic brain injury; Ponsford, Sloan & Snow, 2013), congenital brain disorders (e.g., chiari malformations; Lacy, Ellefson, DeDios-Stern, & Frim, 2016), psychiatric diagnoses (e.g., schizophrenia; Semkovska, Bedard, Godbout, Limoge, & Stip, 2004) as well as neurodevelopmental disorders (e.g., ADHD; Salcedo-Marin, Moreno-Granados, Ruiz-Veguilla, & Ferrin, 2013). Executive dysfunction can be further understood in the context of theoretical models of EF.

1.6. Models of executive functions

Though numerous theoretical frameworks have conceptualised EF, no one model has been universally accepted (Burnett et al., 2013). Unitary models traditionally conceptualised EF to be a single, general cognitive construct with multiple interrelated subcomponents (i.e., the central executive hypothesis, Baddeley, 2002; self-regulation model, Barkley, 2011; supervisory attentional system, Norman & Shallice, 1986), while non-unitary models (i.e., Friedman, Miyake, Robinson, & Hewitt, 2011; Miyake & Friedman, 2012; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Pennington, 1997; Welsh, Pennington, & Groisser, 1991) postulate EFs to be a collection of multiple dissociable processes, that are modular in nature (Jurado & Rosselli, 2007). Despite a lack of consensus as to the unitary or non-unitary conceptualisation of EF, in the context of considerable criticism of unitary models, non-unitary models appear to be the most widely accepted approach.

1.6.1. Unitary models of executive functions

From the perspective of unitary models, EF is viewed as a single component representing a single underlying mechanism or ability (Baddeley, 2002). Unitary models however are largely deemed to be too simplistic to represent the breadth and complexity of EF (P. J. Anderson & Reidy, 2012). Factor analytic approaches to EF conceptualisation have revealed low intercorrelations among EF tasks measuring different EF components (i.e., usually r = .40 or less), which suggests that no core factor can represent EF, contrary to a unitary model perspective (Jurado & Rosselli, 2007; Lehto, 1996; Miyake, Friedman, Emerson, Witzki, Howerter, et al., 2000; Salthouse, Atkinson, & Berish, 2003). While tests measuring a specific component of EF tend to correlate highly with one another (e.g., Codes test and digit span backwards measuring attentional control; Anderson et al., 2011), demonstrating convergent validity, EF components also demonstrate low correlations between one another (e.g., sustained attention and goal setting; Anderson et al., 2011), therefore demonstrating discriminant validity (Alvarez & Emory, 2006; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). Evidence for convergent and discriminant validity of EF components negates a unitary model, lending support to the dissociable nature of EF components (V. A. Anderson et al., 2001; Friedman et al., 2011; Miyake & Friedman, 2012). Clinically, a unitary conceptualisation of EF deficits is not

supported, given that deficits observed are rarely global in nature (P. J. Anderson, 2002; Tim Shallice, 1988).

Developmental considerations also support a non-unitary conceptualisation of EF. During development EFs do not come “online” simultaneously, as a unitary model would posit. Instead EF development is protracted and acquired over time, with EF components maturing at different rates throughout infancy, childhood and adolescence (Anderson, 2002; Anderson et al., 2001). As well, there is ample evidence that separate EF components can be assessed individually from an early age, thus supporting EFs to be dissociable processes (Huizinga, Dolan, & van der Molen, 2006; Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003 & Pulkkinen, 2003).

1.6.2. Non-unitary models of executive functions

Non-unitary models view EF to be comprised of several individual but interrelated components of higher-level cognition. Early non-unitary models of EF were derived from observations of patients with frontal lobe damage and EDF (i.e., Lezak, 1995; Luria, 1966; Stuss & Benson, 1986). Despite demonstrating utility for identifying, assessing and managing individuals presenting with EDF, models based on clinical observations lacked theoretical validation (P. J. Anderson, 2008). A plethora of theoretically driven EF models have since followed, generally describing EF as an umbrella term for higher level cognitive processes that are necessary for goal directed behaviour. While many models have described the key components of EF using factor analytic methods (E. K. Miller & Cohen, 2001; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Zelazo, Carter, Reznick, & Frye, 1997), a minority have conceptualised EF based on its neuroanatomical underpinnings (Banich, 2009), in the context of behaviour analysis (Hayes, Gifford, & Ruckstuhl, 1996) or in response to cognitive and behavioural deficits (Godefroy et al., 2010).

Several issues prevail with the aforementioned selection of non-unitary EF theories. Overall, these theories have separately identified the numerous components that comprise EF, typically citing up to four key components, however no model has incorporated these into one cohesive model. Also, most non-unitary models fail to include goal setting (i.e., strategic reasoning, organisation and planning skills), a key component of EF. The broad range of EF theories to date highlights just how complex EF is, congruent with its complex neuroanatomical underpinnings.

1.6.3. The Executive Control System

Based on factor analytic studies of EF and current neuropsychological knowledge, P. J. Anderson (2002) proposed an integrated EF framework, the executive control system (ECS; see Figure 1.3.). The ECS has been chosen because it captures the integrated nature of EF components, based on how these cognitive skills interact. The ECS also addresses the aforementioned shortfalls of extant non-unitary EF theories (e.g., aligns with factor analytic evidence, comprises widely recognised EF components in one cohesive model, includes goal setting). The ECS proposes that executive functioning is comprised of four distinct but interrelated domains. *Attentional control* involves the ability to selectively attend to and sustain attention, inhibit responses and self-monitoring actions required to execute a plan. *Cognitive flexibility* is concerned with set shifting, learning from mistakes, creating alternative strategies, divided attention and concurrent management of information sources. *Goal setting* refers to demonstrating initiative and conceptual reasoning, planning actions in advance, as well as efficiently, and strategic organisation skills. Lastly, *information processing* refers to fluency, speed and efficiency of information processing. In this system, each EF component operates in an integrative manner to execute goal directed behaviours, though the nature of the task determines the degree of input provided by each domain and altogether represent an overall EF control system (P. J. Anderson & Reidy, 2012).

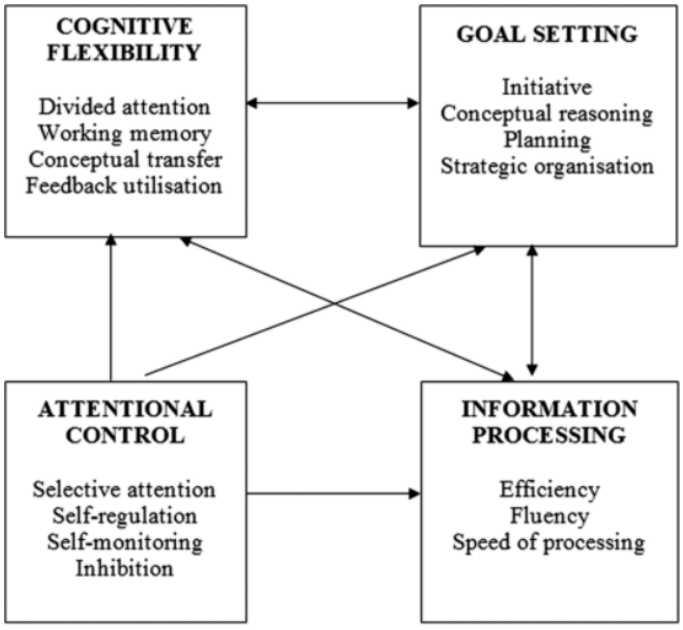

Figure 1.3. The Executive Control System. Note. Figure adapted from (P. J. Anderson, 2002).

1.6.4. Measurement of executive functions

Executive functions tend to be assessed using cognitively demanding and multifaceted neuropsychological tests. To measure EF, tests ought to be complex as well as novel, requiring an examinee to integrate information, initiate a plan, strategise and self-regulate in order to succeed (P. J. Anderson & Reidy, 2012; Walsh, 1978). Several challenges are inherent to the measurement of EF. Given that EF is a multifaceted cognitive skill, task impurity is a key challenge. It has been suggested that virtually all lower level cognitive tests are dependent on some aspect of EF, and vice versa, EF measures are reliant upon numerous lower level cognitive skills (Alexander & Stuss, 2000; Della Sala, Gray, Spinnler, & Trivelli, 1998). Thus deficits in lower level cognitive skills have the potential to confound EF test performance in the absence of pure EF deficits (P. J. Anderson, 2002; V. A. Anderson et al., 2001). Issues of task impurity also complicate EF test interpretation, although this may be circumnavigated by administering multiple measures of EF, to ascertain the pattern of EF skill level across multiple tests. Determining EF test performance solely from quantitative EF measures (i.e., using psychometric tests) is problematic however, as it overlooks qualitative observations that aid in the interpretation of test performance, such as motivation, response to increased task difficulty, attention, environmental distractions which may impact EF performance (P. J. Anderson, 2002).

Ecological validity is another challenge inherent to EF measurement. The quiet, controlled testing environment is discrepant with real-life settings, making it difficult to know whether EF test performances reflects EF abilities as they play out in everyday life (P. J. Anderson, 2002; Levine et al., 2000). Tests that mimic real-life activities requiring EF skills have been developed to address these ecological validity concerns (e.g., the Children's Cooking Task; Chevignard, Catroppa, Galvin, & Anderson, 2010; the Multiple Errands test; Shallice & Burgess, 1991; the party planning task; Shanahan, McAllister, & Curtin, 2011). Informant and self-report questionnaires have also been developed to ascertain EF abilities in everyday life and are administered in correspondence with EF tests (Hughes, 2011).

1.6.5. Development of executive functions in childhood

Historically, EF skills were thought to emerge during adolescence in correspondence with frontal lobe maturation, however there is evidence that primitive EFs are present and measurable during early infancy and the first years of life (Diamond, 1985; Diamond & Goldman-Rakic, 1989; Garon, Smith, & Bryson, 2014; Golden, 1981; Mulder, Hoofs, Verhagen, van der Veen, & Leseman, 2014). Executive functions are thought to mature in conjunction with brain development (Casey, Tottenham, Liston, & Durston, 2005). Throughout early childhood, cortical synaptic pruning takes place, nerve fibres myelinate, and white matter volumes increase (Huttenlocher, 1990; Huttenlocher & Dabholkar, 1997; Taki et al., 2013). Gray matter volumes develop continually up until middle childhood, after which time they begin to decrease (Giedd et al., 1999; Supekar et al., 2010). Frontal lobe structures develop throughout infancy, childhood and adolescence, as do the white matter tracts connecting them to distal and proximal brain regions (Asato, Terwilliger, Woo, & Luna, 2010; Case, 1992; Hale, Bronik, & Fry, 1997; Hudspeth & Pribram, 1990; Huttenlocher & Dabholkar, 1997; Jernigan & Tallal, 1990; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Thatcher, 1991).

In correspondence with brain development, executive function skills develop incrementally from early childhood, developing markedly throughout late childhood and adolescence, which is a key period of EF skill development (G. Roberts et al., 2013). Working memory, shifting and planning abilities demonstrate marked development from 5 years of age, while set shifting, temporal ordering, inhibition, organisation and strategising skills are shown to develop in stages between ages 6 to 8 and 10 to 12 years (Best, Miller, & Jones, 2009; Davidson, Amso, Anderson, & Diamond, 2006; Romine & Reynolds, 2005; Wiebe, Espy, & Charak, 2008; Willoughby, Blair, Wirth, & Greenberg, 2010). Meta-analytic data suggests the greatest advances in EF ability to occur between 5 to 8 years, followed by staggered development until age 14 (Romine & Reynolds, 2005). Some EF skills, including planning and verbal fluency skills, are thought to be underdeveloped until they reach maturity in early adulthood (Romine & Reynolds, 2005). In contrast, an altered developmental trajectory is often reported in neurologically compromised populations, such as VP children.

1.7. Executive function impairments in very preterm children

Executive function deficits in VP populations have attracted considerable attention due to their essential contribution to everyday functioning (Anderson & Doyle, 2004; Burnett et al., 2013). Executive functions are integral for academic achievement, adaptive and behavioural functioning as

well as social development (Aarnoudse-Moens et al., 2013 van Goudoever, & Oosterlaan, 2013; Alduncin, Huffman, Feldman, & Loe, 2014 & Loe, 2014). Further, EF skills are especially important for the development of independent thinking and self-management skills (Burnett et al., 2013). The following section provides an overview of EF deficits experienced by VP children, and EP or VLBW/ELBW when evidence in VP cohorts is lacking, structured according to the ECS framework (P. J. Anderson, 2002), including information processing, attentional control, cognitive flexibility and goal setting.

1.7.1. Information processing

Information processing involves the efficiency, fluency and speed of processing and responding to complex stimuli and tasks (P. J. Anderson, 2014). Information processing mediates other executive skills (Mulder, Pitchford, & Marlow, 2011), and deficits may be characterised by reduced, slowed and dysfluent responding time (Burnett et al., 2013). An overwhelming body of research has documented information processing deficits in VP children throughout development, evident during infancy and persisting throughout early to late childhood (P. J. Anderson & Doyle, 2003; Bohm, Smedler, & Forssberg, 2004; Murray et al., 2014; Rose & Feldman, 1996; Rose, Feldman, & Jankowski, 2002; Rose, Feldman, & Jankowski, 2009). Largely, VP children demonstrate slower and dysfluent response speed (i.e., reaction time) and poorer response output than their FT born peers (i.e., error prone responses). Information processing difficulties are thought to mediate other EF deficits, such as working memory (Rose, Feldman, & Jankowski, 2011).

1.7.2. Attentional control

Attentional control refers to the ability to actively attend to stimuli, tasks and problems in the external world, as well as regulate and monitor responses (Burnett et al., 2013; van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008). In the ECS model, attentional control encompasses selective attention, self-regulation, self-monitoring and inhibition skills (P. J. Anderson, 2002). Poor attentional control during childhood is characterised by difficulties attending to stimuli, maintaining focus, encoding information, directing attention between stimuli, as well as poor attention regulation and disinhibition. Attention deficits are widely documented in VP samples throughout development. Very

preterm infants demonstrate less efficient attentional control than their FT peers across tasks assessing visual orienting, habituation and novelty preference (van de Weijer-Bergsma et al., 2008). Across early to late childhood, research indicates VP/VLBW children demonstrate poorer higher level attentional control abilities than FT children, demonstrating shorter attentional capacity and difficulties switching between mental sets (Aarnoudse-Moens, Smidts, Oosterlaan, Duivenvoorden, & Weisglas-Kuperus, 2009; P. J. Anderson et al., 2011; Bayless & Stevenson, 2007; de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012; Murray et al., 2014).

1.7.3. Cognitive flexibility

Cognitive flexibility involves the ability to rapidly switch between information sets, exert mental control and transfer conceptual information (Burnett et al., 2013). Tasks assessing cognitive flexibility require examinees to navigate and adjust to changing rules/requirements, divide their attention between tasks, or hold and manipulate information (i.e., working memory). During early childhood, VP/VLBW difficulties in cognitive flexibility are evident, including working memory impairments and divided attention difficulties (Aarnoudse-Moens, Weisglas-Kuperus, et al., 2009; P. J. Anderson & L. W. Doyle, 2004; Beauchamp et al., 2008; Mulder, Pitchford, Hagger, & Marlow, 2009; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004; Woodward, Edgin, Thompson, & Inder, 2005). Across middle to late childhood, research indicates ongoing verbal and visual working memory deficits, as well as difficulties with and shifting and divided attention (P. J. Anderson et al., 2011; Bayless & Stevenson, 2007; Bohm et al., 2004; W. J. Curtis, Lindeke, Georgieff, & Nelson, 2002; Luciana et al., 1999; Ni, Huang, & Guo, 2011; Omizzolo et al., 2013; Taylor, Minich, Klein, & Hack, 2004).

1.7.4. Goal setting

Goal setting involves the ability to strategically organise a series of steps or formulate a plan in order to complete a goal. Goal setting is typically assessed by tasks requiring a participant to determine a sequence of steps or generate a strategy to achieve a goal (e.g., tower building tasks). Deficits with goal setting may result in problem solving challenges, due to poor planning, disorganisation, strategy development difficulties, overreliance on previously learned strategies, as

well as reasoning difficulties (P. J. Anderson, 2002).

Preterm goal setting deficits emerge early in childhood. Tower building tasks have been used to assess the ability to formulate a planned sequence, execute the moves and monitor/adjust the plan throughout the move (Bull, Espy, & Senn, 2004). Very preterm children are shown to underperform in comparison to their FT peers on tower measures, demonstrating a higher rate of perseverative errors, rule violations and poorer overall performance (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, Oosterlaan, & van Goudoever, 2013; J. M. Harvey, O'Callaghan, & Mohay, 1999; Marlow, Hennessy, Bracewell, & Wolke, 2007; Ni et al., 2011). In a cohort of 8 to 9 year old children, P. J. Anderson and L. W. Doyle (2004) found that ELBW/VP children scored significantly lower on a spatial organisation task compared with FT controls, with 57% of ELBW/VP children demonstrating a performance characterised by poorer problem solving strategies in comparison with poorer problem solving strategies demonstrated by 42% of FT controls. During early childhood, parents of VP/VLBW children also report significant planning and organisation difficulties in everyday functioning as reported on EF questionnaires (P. J. Anderson & L. W. Doyle, 2004; Loe, Chatav, & Alduncin, 2015; Scott et al., 2012).

Goal setting skills are of increased importance during late childhood (Burnett et al., 2013). As children approach adolescence, organisation and planning competence are required to succeed in new and increasingly complex environments (e.g., secondary school) and help to facilitate academic, social, and personal development (Luu, Ment, Allan, Schneider, & Vohr, 2011). The brain regions underpinning executive functions develop markedly during late childhood (Romine & Reynolds, 2005). For example, in the frontal lobe, processes of synaptogenesis and myelination take place, paralleling increases in executive functions (Huttenlocher & Dabholkar, 1997; Romine & Reynolds, 2005; Sowell et al., 2004; Spear, 2000). Given that the reliance upon goal setting skills becomes increasingly more important during late childhood, deficits in this skill may become more apparent during this developmental period in the context of brain development. In particular, the functional difficulties experienced by children with goal setting difficulties may be more overt in direct comparison to appropriate skill development demonstrated by their peers. For example, children showing functional signs of impaired goal setting may demonstrate planning and strategy generation difficulties that impede their ability to begin and complete large school assignments, in comparison to their peers who demonstrate proficiency in this skill (Burnett, Scratch, & Anderson, 2013).

Despite the relevance of goal setting skills during late childhood, literature examining VP goal setting abilities during this developmental period remains limited. While several studies have reported VP/VLBW children to demonstrate poorer spatial planning, organisation and problem solving skills compared with their FT peers (Aarnoudse-Moens et al., 2012; W. J. Curtis et al., 2002; Rickards, Kelly, Doyle, & Callanan, 2001; Taylor, Minich, Klein, et al., 2004), evidence for comparable abilities also exist (Mulder et al., 2011). Overall however, VP goal setting skills during late childhood have not been well characterised. Understanding the nature of preterm goal setting abilities has implications for early detection and intervention, with a preference to detect deficits before they become entrenched during adolescence (Luu et al., 2011; Rushe et al., 2001; Taylor, Minich, Bangert, Filipek, & Hack, 2004).

The sparse literature examining goal setting during late childhood has some limitations. Many of the studies comprised VP participants across a wide age range, (Aarnoudse-Moens et al., 2012; Taylor, Minich, Klein, et al., 2004), often including quite young children. Further, measures used to assess goal setting skills to date have been limited to the Stockings of Cambridge tower building test from the Cambridge Neuropsychological Test Automated Battery (CANTAB; (Aarnoudse-Moens et al., 2012; W. J. Curtis et al., 2002), and the organisation score from the Rey Complex Figure Test (Rickards et al., 2001; Taylor, Minich, Klein, et al., 2004), or a combination of these tests (Taylor, Minich, Bangert, et al., 2004). Further research using a range of planning measures with VP children is warranted, including ecologically valid measures of planning. Given goal setting research in VP children during late childhood is lacking, and the gaps and limitations of the extant research, additional research is warranted.

1.8. Factors associated with very preterm executive function

Identification of risk factors associated with EF impairments such as goal setting in VP children is important in order to classify high-risk children who warrant close surveillance and possibly require early intervention. Understanding of risk factors is important for determining why impairments may develop, which can subsequently assist in formulating and tailoring interventions to help vulnerable VP children. The following section will review factors of prematurity that are associated with poorer EF outcomes.

1.8.1. Perinatal factors

Perinatal characteristics, including being born at extremely low GA or BW are consistently shown to relate to EF deficits in VP children. Lowered BW and GA is associated with poorer conceptual reasoning, verbal fluency, inhibition, problem solving skills, planning, spatial organisation and working memory skills of VP/VLBW children during early childhood (Aarnoudse-Moens, Smidts, et al., 2009; P. J. Anderson et al., 2011; P. J. Anderson & L. W. Doyle, 2004; Duvall, Erickson, MacLean, & Lowe, 2014; J. M. Harvey et al., 1999; Loe et al., 2015; Mulder et al., 2009; Ni et al., 2011; Orchinik et al., 2011; Saavalainen et al., 2007; Taylor, Klein, Minich, & Hack, 2000), with very little research to suggest otherwise (Bohm et al., 2004). These risk factors have also been found to result in VP working memory, cognitive flexibility, and response inhibition deficits during late childhood (W. J. Curtis et al., 2002; Taylor, Minich, Klein, et al., 2004). Little research has examined factors of prematurity that relate to goal setting impairments in VP groups. Whilst in early childhood, planning and organisation (i.e., core goal setting components) appear to be related to a decrease in BW and GA, the same has not been examined during late childhood.

Respiratory illness and infection are additionally related to EF difficulties experienced by VP children. BPD is correlated with poorer working memory skills of VP children in early childhood (Potharst et al., 2013). Executive function abilities are also negatively impacted by BPD during late childhood, with an inverse relationship between increasing duration of BPD oxygen treatment and poorer planning, cognitive flexibility, working memory and self-monitoring skills (Taylor, Minich, Klein, et al., 2004). Infections associated with preterm birth appear to be closely linked to EF outcomes of ELBW/EP children in middle childhood (i.e., NEC associated with selective attention difficulties; Anderson et al., 2011), however little research has established a relationship between EF outcomes and infection in VP children during late childhood (Taylor, Minich, Bangert, et al., 2004). Therefore it is unclear whether neonatal infections are linked with EF outcomes, such as goal setting, in VP children during late childhood.

1.8.2. Neonatal brain abnormality

Neonatal brain abnormalities and volume reductions are associated with EF impairments in preterm children throughout childhood. Brain injuries experienced by the preterm infant are likely to

compromise efficient functioning of the numerous brain regions subserving executive functions, and may also disrupt brain circuits (e.g., the fronto-striatal, fronto-subcortical) that facilitate communication between the prefrontal cortex and subcortical and/or other cortical regions (e.g., cerebellum, parietal cortices; Elliot, 2003; Krienen & Buckner, 2009; Schmahmann, 1996). During early childhood, more severe neonatal white and gray matter abnormality scores and smaller deep gray matter volumes are shown to be associated poorer working memory, inhibition, cognitive flexibility, problem solving and goal setting abilities of VP/EP children (Clark & Woodward, 2010; Edgin et al., 2008; Woodward, Clark, Bora, & Inder, 2012; Woodward, Clark, Pritchard, Anderson, & Inder, 2011). Additionally, neonatal white matter injury is linked with parent rated EF difficulties of VP children in everyday life (i.e., Behavior Rating Inventory of Executive Function; BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000; Young et al., 2016). Recently, Loh et al. (2017) demonstrated an association between neonatal basal ganglia and thalamic volumes and poorer goal setting performances at 7 years. These findings in preschool and early school-aged VP children imply a relationship between neonatal brain injury and goal setting deficits in early childhood, but whether this relationship persists into late childhood remains unclear.

1.8.3. Sex

While literature examining the influence of sex upon EF deficits in VP children has yielded sex differences in early childhood, the impact of gender during late childhood remains unclear. In early childhood VLBW/EP/preterm samples, male sex is associated with deficits in response inhibition, verbal fluency, and working memory, planning, monitoring, self-regulation, and problem solving (Bohm, Katz-Salamon, Smedler, Lagercrantz, & Forssberg, 2002; Marlow et al., 2007; Pasman, Rotteveel, & Maassen, 1998; Urben et al., 2017), as well as parent reported EF difficulties (Young et al., 2016). During late childhood, there is some evidence to suggest that male sex is associated with poorer response inhibition and planning abilities, as well as higher teacher-rated inattention difficulties in VP samples (Aarnoudse-Moens et al., 2012; Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, & Oosterlaan, 2013). In contrast however, male sex was not associated with EF deficits in some VP/VLBW samples during late childhood (W. J. Curtis et al., 2002; Luu et al., 2011; Taylor, Minich, Bangert, et al., 2004). Overall, it is unclear whether sex relates to EF outcomes of VP children during late childhood given mixed findings to date.

1.8.4. Sociodemographic factors

Very preterm children are often found to be of greater social risk than their FT peers. In some regions, VP/EP infants are slightly more likely to be birthed by younger mothers, and come from non-nuclear families (i.e., single caregiver), have parents with lower education levels, working less (i.e., unemployed or part-time, compared to full-time) in low skill occupations, and come from families of a non-English speaking background (P. J. Anderson & Doyle, 2008; I. S. Baron & Rey-Casserly, 2010; Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010; G. Roberts et al., 2008; Saigal, Burrows, Stoskopf, Rosenbaum, & Streiner, 2000; Wong & Edwards, 2013). Consequently, sociodemographic factors are essential to adjust for in VP studies examining cognitive outcomes throughout development. Inhibition, verbal fluency, cognitive flexibility and working memory impairments are related to sociodemographic factors indicative of greater social risk, such as lower household income (Aarnoudse-Moens, Smidts, et al., 2009; Taylor, Minich, Klein, et al., 2004). Parent rated inattention and impulsivity of VLBW children is also reported to be negatively associated with poorer quality home environment (Robson & Pederson, 1997). In contrast, greater VP verbal fluency abilities are associated with higher levels of parental education (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, Oosterlaan, et al., 2013).

1.9. Neuroimaging and executive functions

A better understanding of the neurological underpinnings of executive functions in VP children is needed, especially goal setting in older children. The focus of this dissertation section is magnetic resonance imaging (MRI). Firstly, MRI will be introduced, followed by functional MRI (fMRI) methods, with a particular focus on resting-state functional MRI. Then, current resting state imaging findings indicating altered brain functional network architecture in preterm children will be reviewed in relation to EF skills, such as goal setting

1.9.1. Magnetic resonance imaging

Magnetic resonance imaging enables the brains entire cerebral anatomy to be identified with a high level of sensitivity and precision (Smyser et al., 2012). Magnetic resonance imaging is a safe and routinely used neuroimaging technique, used across clinical and research settings, to assess brain

architecture. An MRI scanner produces powerful magnetic fields and radio frequency pulses that generate signal from the hydrogen atoms present in body tissue (Preston, 2006). Tissue signal is transmitted to a computer to be processed, and thereafter generates detailed black and white cross-sectional images of bodily tissue, such as brain tissue. The most common MRI brain sequences are T_1- (longitudinal relaxation time of magnetic protons) and T_2-weighted (transverse relaxation time of magnetic protons) images, which produce dark and bright contrast images (See Figure 1.4.) to reveal the appearance of brain tissue (Lu, Golay, Pekar, & van Zijl, 2003).

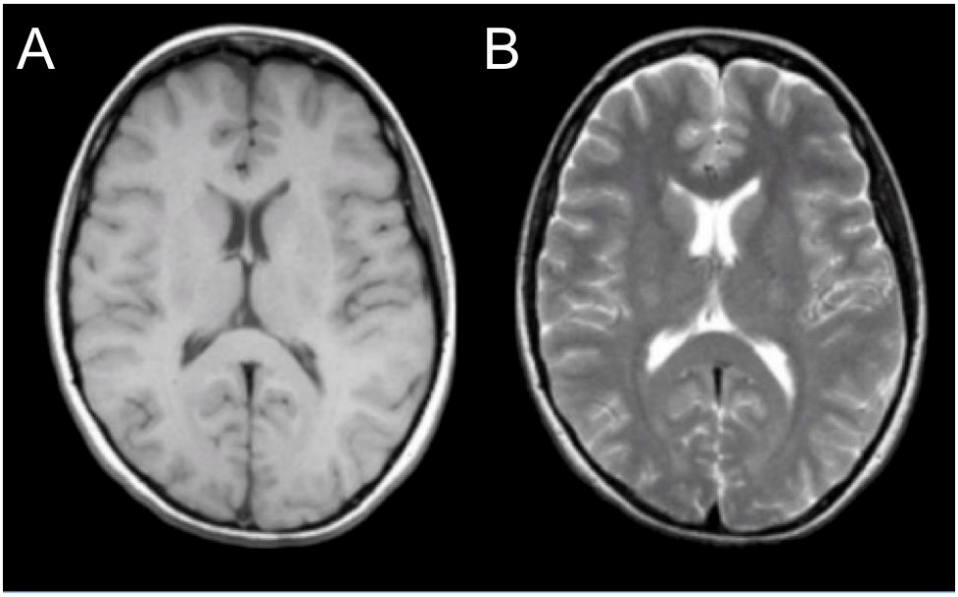

Figure 1.4. A) T_1-weighted image with dark contrast. B) T_2-weighted image with bright contrast. Note. Adapted from (Preston, 2006).

Numerous advanced MRI sequences and analysis techniques have been developed to characterise the brain and identify brain abnormalities. Volumetric segmentation analysis and surface-based morphometry methods (e.g., cortical parcellation) facilitate quantification of the size and shape of the brain overall, as well as its individual regions (see Figure 1.5.). Diffusion-weighted imaging (DWI) is a technique which measures the directional movement of water atoms (see Figure 1.6.; Mathur & Inder, 2009). Examining the trajectories of water movement around and through axons provides insight into white matter tracts throughout the brain, and the nature of structural pathways and connections between brain regions (Vettel, Cooper, Garcia, Yeh, & Verstynen, 2017). Advanced

MRI techniques are increasingly being used to characterise the relationship between brain integrity and cognition.

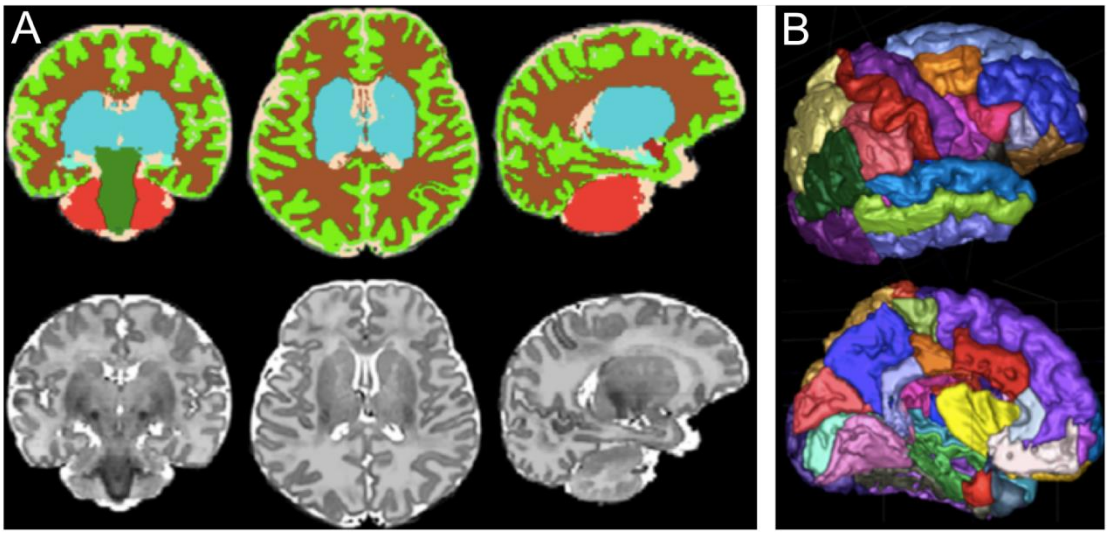

Figure 1.5. A) Top: Brain of a full-term infant's brain with tissue segmentation; Bottom: corresponding T_2-weighted images shown in coronal, axial, and sagittal planes. B) Cortical parcellation of a full-term infant's brain, shown in lateral (top) and medial (bottom) views. Note. Adapted from (P. J. Anderson et al., 2015).

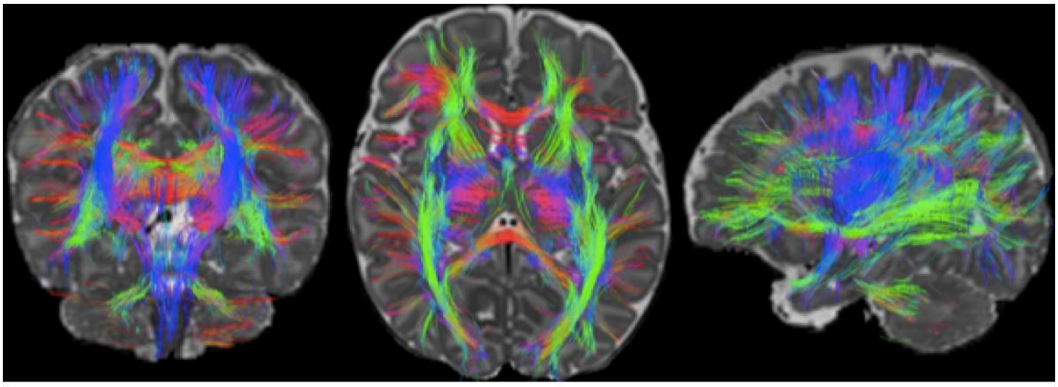

Figure 1.6. Diffusion-weighted imaging of white matter tracts within the brain of a full-term infant, overlaid on T_2-weighted images shown in coronal, axial, and sagittal planes. Note. Adapted from (P. J. Anderson et al., 2015).

1.9.2. Functional magnetic resonance imaging

Functional MRI is a non-invasive neuroimaging method that measures cerebral blood flow and oxygenation of brain cells, known as blood oxygen level dependent (BOLD) signal (see Figure 1.7.). Physiologically, oxygen is delivered to the brain's neurons by haemoglobin in the red blood cells. As neuronal brain activity increases, greater levels of oxygen are required, resulting in increased blood flow and oxygen to regions of increased neural activity (i.e., 'neurovascular coupling'; Astolfi et al., 2004). Because haemoglobin is diamagnetic (i.e., becomes magnetic) when it is oxygenated and paramagnetic (i.e., not magnetic) when it is deoxygenated, MRI can be used to indirectly measure differences in blood flow signal based on oxygenation and provide insight into brain activity (Astolfi et al., 2004; Harris, Reynell, & Attwell, 2011; Mongerson, Jennings, Borsook, Becerra, & Bajic, 2017).

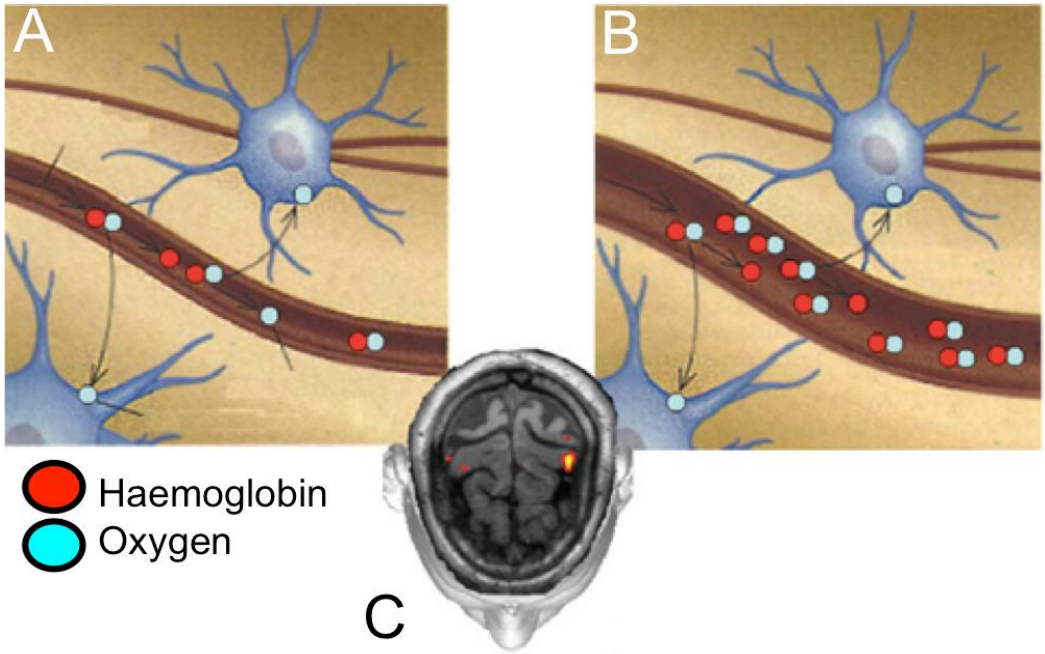

Figure 1.7. A) As neuronal activity increases, more oxygen is required. B) Blood flow increases to the areas of neuronal activity. C) Diamagnetic blood oxygen level dependent signal is measured by magnetic resonance imaging and computer processed in order to identify regions of increased neural activation (coloured highlights). Note. Adapted from (Astolfi et al., 2004).

Common fMRI imaging modalities include task based and resting state fMRI. In task-based fMRI, participants complete a task during scanning that is designed to measure a specific cognitive function. The objective is to analyse the functional brain networks being engaged during task performance (Smitha et al., 2017). Task based fMRI analyses BOLD signal during task completion in order to

characterise activity associated with, for example, attention, memory, or executive functions (Barch et al., 2013). Alternatively, in resting state fMRI (rs-fMRI) BOLD signal is analysed in the absence of a task or stimuli, while participants simply lie in an MRI scanner (Smitha et al., 2017). Fluctuations in BOLD signal measured during rest are thought to reflect functional neural brain networks, thus enabling examination of brain architecture (Lubsen et al., 2011). Resting state fMRI possesses several practical advantages over task-based fMRI. Firstly, compared with task-based fMRI, rs-fMRI does not require stimulus provoking equipment, requires minimal effort from participants, and can be administered with patients who are too cognitively impaired to complete task-based functional paradigms (Smitha et al., 2017).

1.10. Resting state functional magnetic resonance imaging

The human brain is a complex network of functionally and structurally interconnected regions (M. P. van den Heuvel & Hulshoff Pol, 2010). Connections between different brain regions are necessary to facilitate the functional communication required for complex cognitive processes (M. P. van den Heuvel & Hulshoff Pol, 2010). Resting state fMRI provides insight into such brain connectivity by defining neural resting state networks (RSNs) that may underlie functional processes of the brain. In rs-fMRI, temporal correlations between spatially remote fluctuations in low frequency (0.01 to 0.08 hertz) BOLD signal are measured (Fair et al., 2008; Fair et al., 2009). Synchronous BOLD signal fluctuations are thought to represent neuronal activity between functionally related neural networks throughout the brain (see Figure 1.8.; Fox & Raichle, 2007). Resting state fMRI is considered an established and robust measure of neuronal connectivity (Greicius, Krasnow, Reiss, & Menon, 2003; Thomason et al., 2011; M. P. van den Heuvel & Hulshoff Pol, 2010). Several analytical methods are available to identify and examine resting state networks.

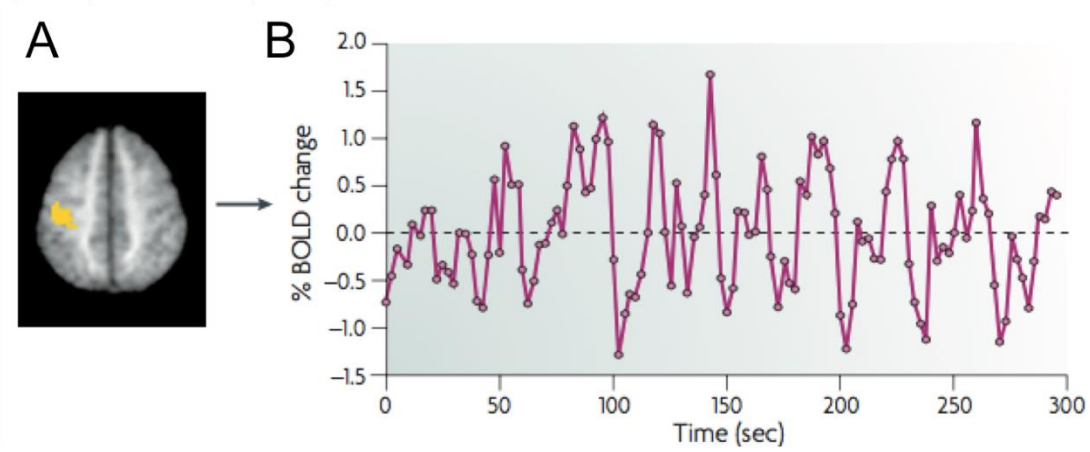

Figure 1.8. Example of blood oxygen dependent level (BOLD) signal and the corresponding region of neural activation. A) left somatomotor cortex neuronal activity. B) Time course of spontaneous blood oxygen level dependent signal fluctuations recorded during resting stating functional magnetic resonance imaging. Note. Adapted from (Fox & Raichle, 2007).

1.10.1. Resting state functional magnetic resonance imaging analysis

Model-dependent or model free methods are used to analyse rs-fMRI data. Seed-based rs-fMRI is a model-dependent method in which a specific brain region of interest is chosen (i.e., hypothesis driven). The neuronal connectivity between this region and the voxels of other brain regions is calculated, forming a functional connectivity map with z-scores that are indicative of its temporal correlations with the seed region (Smitha et al., 2017). The seed-based analysis is limited by bias that comes with the selection of seed regions, which restrict examination of whole-brain functional connectivity (Mongerson et al., 2017). Determining the anatomical region of interest accurately and specifically is another challenge in seed-based rs-fMRI (Mongerson et al., 2017). In contrast, model-free methods permit exploratory data-driven examination of whole brain connectivity. Independent component analysis (ICA) is one such model-free method that is widely used to examine neural connectivity.

1.10.2. Independent components analysis

Independent component analysis is a robust model-free method that allocates rs-fMRI data into statistically independent components that represent distinct neural RSNs (Beckmann, DeLuca, Devlin,

& Smith, 2005). A benefit of ICA is its ability to determine not only neural networks, but also non-neuronal artifactual components (i.e., head motion, physiological noise, cerebrospinal fluid; Mongerson et al., 2017), in order to remove their confounding effects. The reproducibility of rs-fMRI networks across imaging sessions, subjects and time (e.g., intraclass correlation of >0.60 for 70% of the functional networks examined by Chou, Panych, Dickey, Petrella, & Chen, 2012), suggests good reliability in RSN measurement (Biswal et al., 2010; Damoiseaux et al., 2006; Shehzad et al., 2009).

While the number of resting-state networks reported using ICA is variable, perhaps due to sample differences and analytic methodology (e.g., model-free versus model dependent), visual, auditory, sensorimotor, default mode, attention, frontoparietal and cerebellar networks are reported within the majority of rs-fMRI literature (see Figure 1.9.; (Beckmann et al., 2005; Biswal, Yetkin, Haughton, & Hyde, 1995; Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Salvador et al., 2005; Smith et al., 2009; van den Heuvel, Mandle, & Hulshoff Pol, 2008). Visual networks, often separated into one or more networks (e.g., visual-medial, visual-lateral, visual-occipital pole), generally consist of occipital cortex regions (Beckmann et al., 2005; De Luca et al., 2006; Power et al., 2011; Smith et al., 2009). The Heschel and superior temporal gyri, as well as the posterior insula cortex comprise the auditory network (Smith et al., 2009). The sensorimotor network is comprised of motor and sensory brain regions (Biswal et al., 1995). The posterior cingulate cortex, precuneus, medial frontal and inferior parietal regions comprise the default mode network (Greicius, Supekar, Menon, & Dougherty, 2008). Typically reported attention networks include the dorsal attention/executive control network, comprising intraparietal sulci, medial-frontal areas and frontal eye fields, and the ventral attention network, consisting of the temporoparietal junction and ventral frontal cortex (Fox & Raichle, 2007; Power et al., 2011; Seeley et al., 2007; Smith et al., 2009; Yeo et al., 2011). Lateral prefrontal cortices and the inferior parietal lobules comprise the frontoparietal network, often separated into left and right networks (Smith et al., 2009; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Finally, the cerebellar network consists of cerebellar regions (Smith et al., 2009).

Convergence between structural connectivity brain imaging results derived from diffusion tensor imaging, networks derived from task-based fMRI, and networks measured by rs-fMRI support the validity of functional RSNs (Damoiseaux & Greicius, 2009; Gimenez et al., 2006). White matter tracts are thought to facilitate the RSN connections between functionally linked brain regions (Damoiseaux & Greicius, 2009; M. P. van den Heuvel & Hulshoff Pol, 2010; M. P. van den Heuvel, Luigjes J, &

Hulshoff, 2008; M. P. van den Heuvel, Mandl, Kahn, Pol, & Hilleke, 2009). Within the default mode network for example, microstructural organisation of the cingulum white matter tract is directly related to the level of functional connectivity between the poster cingulate cortex and medial frontal cortex, which are key regions of this network (M. P. van den Heuvel, Luigjes J, et al., 2008).

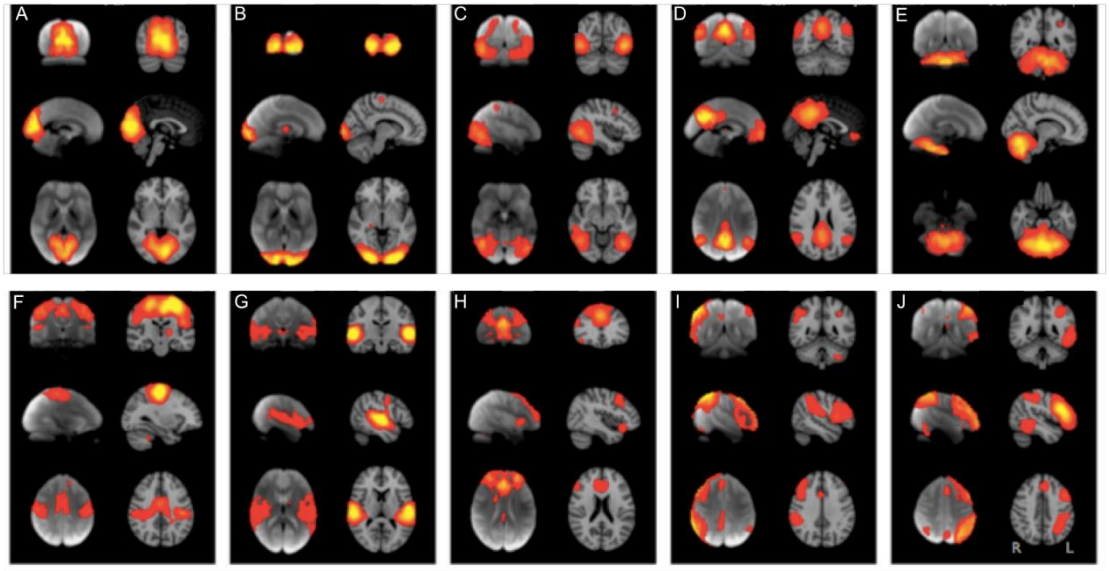

Figure 1.9. Key resting state networks. A) through C) visual networks. D) default mode network. E) cerebellar network. F) sensorimotor. G) auditory network. H) executive control network. I and J) frontoparietal networks. Note. Figure adapted from (Smith et al., 2009).

1.11. Applications of resting state neuroimaging

Resting state fMRI has demonstrated utility for examining large-scale brain networks of neurologically compromised samples. Connectivity of RSNs is thought to be affected in neurological insult or injury, altering the brains architecture and consequently RSNs (Bonnelle et al., 2011; Li et al., 2015). In adult samples with neurodegenerative diseases (e.g., Alzheimer's, Parkinson's disease, mild cognitive impairment), as well as paediatric samples with neurodevelopmental disorders (e.g., autism, ADHD, traumatic brain injury, epilepsy) altered RSNs characterised by increased or decreased regional connectivity have been identified (Amboni et al., 2015; Binnewijzend et al., 2012; Cherkassky, Kana, Keller, & Just, 2006; Greicius, Srivastava, Reiss, & Menon, 2004; H. Lin, Tseng, Lai, Matsuo, & Gau, 2015; Palacios, Sala-Llonch, Junque, & et al., 2013; Widjaja, Zamyadi, Raybaud, Snead, & Smith, 2013). Widjaja et al. (2013) for example, found children with temporal lobe epilepsy

to exhibit reduced connectivity in the right superior frontal gyrus of the frontoparietal network when compared with typically developed children. Increased functional connectivity in patients compared with controls has been interpreted to be a compensatory mechanism or network reorganisation, whereas reduced connectivity is postulated to reflect RSN dysfunction (Bettus et al., 2009). Resting state fMRI has also been applied in preterm samples to determine whether prematurity impacts neural networks of the brain, as reviewed in the following section.

1.11.1. Resting state neuroimaging in preterm samples

Resting state networks undergo rapid growth during the third trimester of gestation (Doria et al., 2010; Smyser et al., 2010). During the neonatal period, immature forms of infant RSNs are apparent (Doria et al., 2010; Fransson et al., 2009; Gao et al., 2009; W. Lin et al., 2008; Smyser et al., 2010). In the preterm infant, RSNs reported at term-equivalent age include the visual, auditory, sensorimotor, default mode, frontoparietal and executive control networks (Doria et al., 2010; Smyser et al., 2010). While there is no overall consensus as to whether the RSNs exhibited by preterm and FT infants are similar, perhaps owing to differing analytic techniques (Smyser et al., 2016), the majority of studies have identified differences. In a sample of VP/EP infants without significant brain abnormalities *(n* = 80), Smyser et al. (2010) reported network-specific reductions in functional connectivity of VP/EP infants at term-equivalent age in comparison to FT infants (*n* = 10), involving less mature and abnormally formed networks, particularly thalamo-cortical networks (Kostovic & Jovanov-Milosevic, 2006). Moreover, less complex RSN structure, as well as weaker functional connectivity, is also observed in preterm infants compared with their FT peers using both quantitative (i.e., covariance matrices) and qualitative (i.e., correlation analyses) analysis techniques. During infancy, altered VP/EP RSN connectivity has been found to be associated with diffuse white abnormalities (Smyser et al., 2013), particularly in executive control and frontoparietal networks (He & Parikh, 2014). In contrast, in a study by Doria et al. (2010), no major differences were identified between the RSNs of preterm/VP and FT infants at term-equivalent age (*N* = 70) across visual, auditory, somatosensory, sensorimotor, default mode, frontoparietal and executive control networks.

Resting state networks are thought to undergo intermittent maturation throughout childhood (Smyser & Neil, 2015). Few studies have examined RSNs of VP populations during childhood, and there are no conclusive results as to whether RSNs differ between VP and FT children during this

developmental period. While RSNs between VP and FT children are shown to be comparable at 1 through 4 years of age (Lee, Morgan, Manohar, Sled, & Taylor, 2013; Padilla et al., 2014), one study has shown differences in visual and motor network connectivity of VLBW and FT children at 3 years of age (Damaraju et al., 2010). This research to date has been criticised however for predominantly including only preterm samples without or with only a small degree of brain abnormality, which may dilute findings, and thus may not be representative of premature RSNs, given the high rates of brain injury in preterm populations (Hoff, van den Heuvel, Benders, Kersbergen, & De Vries, 2013).

In late childhood, aberrant preterm RSN connectivity has been documented. In a sample of late preterm (*n* = 11) and FT (*n* = 14) children approximately 10 years of age, Degnan et al. (2015) documented altered posteromedial and lateral parietal functional connectivity in the default mode and central-executive networks. It is possible that clear differences in preterm RSNs may emerge during late childhood, as a result of alternative processes of network maturation (Fair et al., 2008; Fair et al., 2009; Fair et al., 2007; Supekar, Musen, & Menon, 2009). It is postulated that white matter injury associated with altered RSNs may prohibit the most parsimonious RSN formation, resulting in neural reorganisation and thus alternative network connections (He & Parikh, 2014; Schafer et al., 2009). Having said that, further research is required to characterise the RSNs of VP children in comparison to typically developing samples during late childhood, as research on this topic is limited to the one aforementioned study.

1.12. Resting state neuroimaging and executive functions

Resting state fMRI has demonstrated utility for examining neural connectivity networks in association with cognitive function, to better understand the neural architecture underlying cognitive impairment (Baggio et al., 2015). Altered resting state network connectivity has been documented in neurologically compromised paediatric samples with cognitive impairment, including dyslexia, ADHD, epilepsy and autism (Amboni et al., 2015; Binnewijzend et al., 2012; H. Lin et al., 2015; Mennes et al., 2011; Palacios et al., 2013; Schurz et al., 2015; Weng et al., 2010; Widjaja et al., 2013; Yu-Feng et al., 2007). Several of these studies have linked executive function difficulties with altered RSN connectivity in the default mode network (DMN), executive control network (ECN) and frontoparietal network (FPN). For example, H. Lin et al. (2015) found a sample of children with ADHD to exhibit weaker frontoparietal network connectivity compared with FT controls, which was shown to be

associated with impaired response inhibition and attentional control performances on cognitive testing, suggesting that atypical frontoparietal network connectivity contributes to the executive dysfunction seen in ADHD (H. Lin et al., 2015). In consideration of RSN alterations in preterm samples and the extensive EF deficits they exhibit, the following section will review literature that has examined RSNs of preterm children in association with EF abilities, and goal setting in particular.

1.12.1. Resting state neuroimaging and executive functions in preterm samples

Reduced connectivity strength in executive networks is suggested to predispose VP infants to executive function deficits during childhood (He & Parikh, 2015). One study has examined VLBW/ELBW RSNs relative to executive function deficits on neuropsychological testing in VLBW/ELBW children. Lubsen et al. (2011) examined performances of 16 year old preterm (*n* = 20) and FT (*n* = 23) children using the Total Achievement score from the Delis-Kaplan Executive Function System (D-KEFS) in relation to RSNs. While better EF performance was positively associated with increased connectivity in the right temporal, right hippocampal and basal ganglia regions in FT children, for VLBW/ELBW participants, increased connectivity in the left temporal region was associated with better scores, while increased connectivity in frontal regions was associated with poorer EF performance (Lubsen et al., 2011). These findings suggest that executive functioning deficits may be associated with altered connectivity in VLBW/ELBW adolescents (Lubsen et al., 2011).

Replication of these preliminary results is required, particularly within a larger sample. It would also be beneficial to use several psychometric tests designed to measure a specific component of EF, rather than a single test, as it is best practice to interpret ability based on a pattern of performances, and increases robustness. Examining RSNs related specifically to VP goal setting is of interest, particularly in late childhood when RSN differences between VP and FT samples are apparent and the neural architecture of EFs is established, and when goal-setting skills are of particular functional relevance (Engelhardt, Harden, Tucker-Drob, & Church, 2018).

1.12.2. Goal setting resting state networks

Task-based fMRI studies have provided insight into which resting state neural networks may be involved in goal setting skills. Functional MRI indicates that the FPN, ECN and DMN activate during

completion of tasks that involve core cognitive components of goal setting (i.e., strategic reasoning, organisation, planning). Studies supporting the involvement of the FPN, ECN and DMN are outlined below.

The FPN is reported to be integral for executive functions, responsible for generating internal representations for the updating, adaption and implementation of problem solving for goal-directed behaviour (Dosenbach et al., 2007; E. K. Miller & Cohen, 2001; Ramnani & Owen, 2004; Vincent et al., 2008). For example, when completing the Tower of London, the anterior prefrontal cortex of the FPN is activated while generating, assessing and problem solving the sub-goals (i.e., moving the disks across the pegs) required to build a tower (Baker et al., 1996; Ramnani & Owen, 2004). Additionally, bilateral frontoparietal regions are activated during the performance of planning and strategic reasoning tasks (Boghi et al., 2006; Coricelli & Nagel, 2009; Fincham, Carter, van Veen, Stenger, & Anderson, 2002).

The ECN is thought to be important for higher level cognition and attentional control. During completion of tasks reliant on higher level attention skills, such as working memory, attention shifting, and cognitive flexibility, the ECN is activated (C. E. Curtis & D'Esposito, 2003; Dreher & Berman, 2002; Smith et al., 2009), including the anterior cingulate cortex and lateral parietal cortices (Markett et al., 2014; Seeley et al., 2007). The ECN is likely to be essential for supporting goal setting, considering the integrated nature of attentional control and goal setting skills, and higher level attention is required to execute a plan (P. J. Anderson, 2002).

The DMN is largely thought to support internally directed thought and self-generated cognition (Beaty, Benedek, Barry Kaufman, & Silvia, 2015; Smith et al., 2009), but there is also evidence for its involvement in goal-directed behaviour (Gerlach, Spreng, Gilmore, & Schacter, 2011). Within the DMN, the dorsolateral prefrontal cortex in particular is shown to activate during the encoding action sequences, coordinating actions in relation to goals, and maintaining abstract sequential movement plans (Badre, Hoffman, Cooney, & D'Esposito, 2009; Gerlach et al., 2011). The medial prefrontal cortex, posterior cingulate cortex, posterior temporoparietal junction, inferior parietal lobule, and middle temporal gyrus activations are also shown to be associated with problem-solving skills (Gerlach et al., 2011).

While regions comprising the ECN, DMN, and FPN are individually shown to contribute to goal setting skills, they appear to work together in order to support this executive skill. Specifically, the

DMN and ECN are thought to be mediated by the FPN in goal directed cognition (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Vincent et al., 2008). Though the ECN, DMN, and FPN may not be the sole RSNs underlying goal setting skills, their role in this aspect of higher level cognition is evident, and therefore these networks will form the basis of the current study.

1.13. Chapter summary

While evidence to date suggests VP goal setting skills are impaired in early childhood, these studies have examined goal setting in relatively young children when EF skills are developing rapidly (V. A. Anderson et al., 2001). Additionally, studies to date have failed to assess goal setting comprehensively, instead relying on a single measure. Furthermore, ecological valid measures of goal setting have not been administered. Accordingly, this study aimed to comprehensively examine and describe the goal setting abilities of VP children during late childhood, in comparison to their FT peers, in a large, representative cohort using multiple and ecologically valid measures of goal setting. This study will also attempt to identify factors associated with goal setting skills of VP children during late childhood, specifically neonatal risk factors and sex.

Though neonatal MRI parameters associated with cognitive impairment and aspects of EF in VP children are known, few studies have examined these in association with EF skills such as goal setting. Diffuse brain pathology associated with VP birth affects typical development and maturation of brain structures, resulting in brain abnormalities and reduced brain volumes. Given that a plethora of brain structures are integral to EFs such as goal setting, compromised brain development may explain proficiency or impairment in these skills later in childhood. Accordingly, using neonatal MRI this study aimed to examine the association neonatal brain abnormalities and volumes have with goal setting abilities of VP children at 13 years of age.

While RSN connectivity of preterm populations is shown to differ during infancy and early childhood, little is known about the RSNs of VP children in comparison to their FT peers during late childhood. Furthermore, examination of preterm RSN connectivity during late childhood may contribute to understanding goal setting skills during this developmental period. Alterations in RSN connectivity may be related to EF abilities at this time, revealing an enduring impact of prematurity upon the brain architecture and associated functional skills. Therefore, the present study aimed to examine group differences between VP and FT children in networks thought to be involved in goal

setting, including frontoparietal, executive control and default mode RSNs of VP and FT children, and to examine network associations with goal setting skills at 13 years of age.

Data from the Victorian Infant Brain Study (VIBeS), a longitudinal project studying brain injury, brain development and neuropsychological outcomes in VP children, was utilised to address the aforementioned research gaps. The aims and hypotheses that will be addressed in this dissertation are outlined below.

1.14. Thesis aims and hypotheses

The aims of the dissertation were to:

1) Examine goal setting skills in a cohort of VP children at 13 years of age compared with FT controls, and neonatal factors associated with VP goal setting performance.
2) Examine the association between neonatal brain abnormalities and volumes, with goal setting abilities in VP 13 year olds.
3) Compare the frontoparietal, executive control and default networks between VP and FT 13-year-old children, as well as the association between these networks and goal setting ability, and determine whether associations differed between VP and FT groups.

It was hypothesised that:

1) In comparison to their FT peers, VP children would perform more poorly across goal setting measures. It was also hypothesised that within the VP group, moderate to severe brain injury, complicated neonatal course, and male sex would be associated with poorer goal setting performance.
2) More severe brain abnormality (specifically white matter, deep gray matter, and cerebellum), and decreased brain volumes (specifically white matter, corpus callosum, thalamus, basal ganglia, and cerebellum) at term-equivalent age would be associated with poorer goal setting performance in 13-year-old VP children.
3) Frontoparietal, executive control and default network connectivity strength would differ between VP and FT groups, and that the frontoparietal, executive control and default networks would be associated with goal setting ability at 13 years in both groups, but that VP and FT children would demonstrate differences in connectivity strength within resting state connectivity networks.

Chapter 2. General methods

Chapter 2

2.1. Participants

This dissertation uses data from the Victorian Infant Brain Study (VIBeS) cohort, a longitudinal prospective study comprising 227 infants born very preterm (VP; ≤ 30 weeks' and/or with birth weight <1250g) and 77 infants born full-term (FT; ≥ 37 to ≤ 42 weeks' gestational age and/or birth weight ≥ 2500g). Very preterm cohort participants were originally recruited between July 2001 and December 2003 at the Royal Women's Hospital, Melbourne. Infants with congenital and/or chromosomal abnormalities at birth were excluded from the VIBeS cohort. The 77 participants comprising the FT cohort were recruited across two time points. During the neonatal period, 46 term control children were recruited in conjunction with the VP group at the Royal Women's Hospital. To help balance the sample size between the groups, 31 additional FT control children were recruited from Maternal and Child Health Centres at 2 years of age.

2.2. Overview of data collection

As part of the VIBeS study, children and their parents were invited to participate in comprehensive follow-up assessments during the neonatal period, as well as at 2, 5, 7 and 13 years of age (see Figure 2.1). At each follow-up assessment, child age was corrected for prematurity to eliminate potential bias upon cognitive test results that may occur from using chronological age (Wilson-Ching, Pascoe, Doyle, & Anderson, 2014). At term-equivalent age (≥ 37 and ≤ 42 weeks' gestation), perinatal data were collected from hospital records and neonatal magnetic resonance imaging (MRI) was performed on all VP and FT participants recruited at birth. At 2 years of age children were invited for a formal developmental and medical assessment, and sociodemographic information was collected via parent questionnaires. At 5, 7 and 13 years, children were invited for a neuropsychological assessment. While executive functions were assessed as part of the neuropsychological assessment at 5, 7 and 13 years of age, goal setting skills were only assessed at 13 years of age. At 7 and at 13 years of age children were offered an optional MRI brain scan.

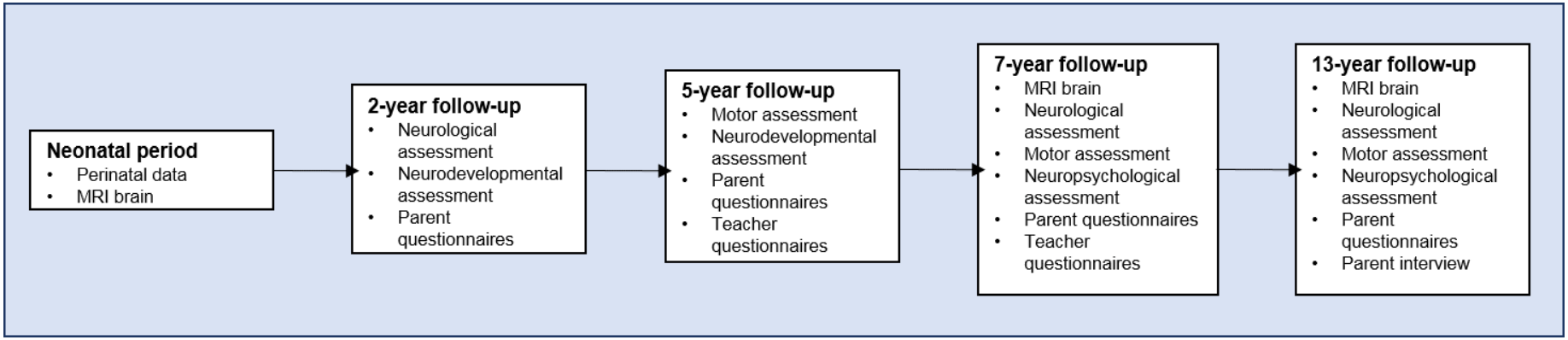

Figure 2.1. Victorian Infant Brain Study neonatal and follow-up assessments with outcome measures.

2.3. Procedure

For each follow-up, approximately one month prior to the child's birthday the family received a letter of invitation from the VIBeS team inviting the family to participate in the next data collection wave. A couple of weeks later, the research coordinator nurse, known to the families from the initial recruitment into the study, contacted the families via phone to determine their interest to participate. Willing families provided written consent. Participant assent was obtained from caregivers at 7 and 13 years, since participants were deemed to have insufficient maturity to adequately evaluate and make an informed decision regarding their participation.

Each follow-up took place at the Murdoch Children's Research Institute (MCRI) within the Royal Children's Hospital. Medical assessments were performed by a paediatrician, and neuropsychological assessments were conducted by trained psychologists blinded to participant birth group (VP versus FT). During the follow-up sessions, regular breaks and refreshments were offered to participants. Families living outside of the Melbourne metropolitan region were reimbursed for their travel and accommodation costs.

After completion of the follow-up session, each participant's family received an individual report outlining their child's strengths and weaknesses. For sessions involving an MRI, any incidental findings from the MRI scan were also communicated as part of these reports. Parents whose self-reported Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) responses were rated within the clinical range (i.e., 8 points or more on either the anxiety or depression scale; Bjelland, Dahl, Haug, & Neckelmann, 2002) were contacted by a clinical psychologist from the VIBeS study team to ensure they had adequate information to seek professional support. Thank-you cards were sent to all families after their participation. Throughout the study, regular newsletters outlining the progress of the VIBeS study were sent to families.

2.4. Drop-outs and retention rates

From the original VIBeS cohort, 2 VP infants died during the neonatal period and 1 VP infant withdrew prior to the 2-year follow up, leaving a sample of 224 VP and 77 FT participants. Retention rates of the VIBeS cohort for each follow-up are shown in Figure 2.2. Retention rates for both the VP and FT groups decreased across each follow-up but remained high. At the 13-year follow-up, the retention was 79% and 80% for the VP and FT groups respectively.

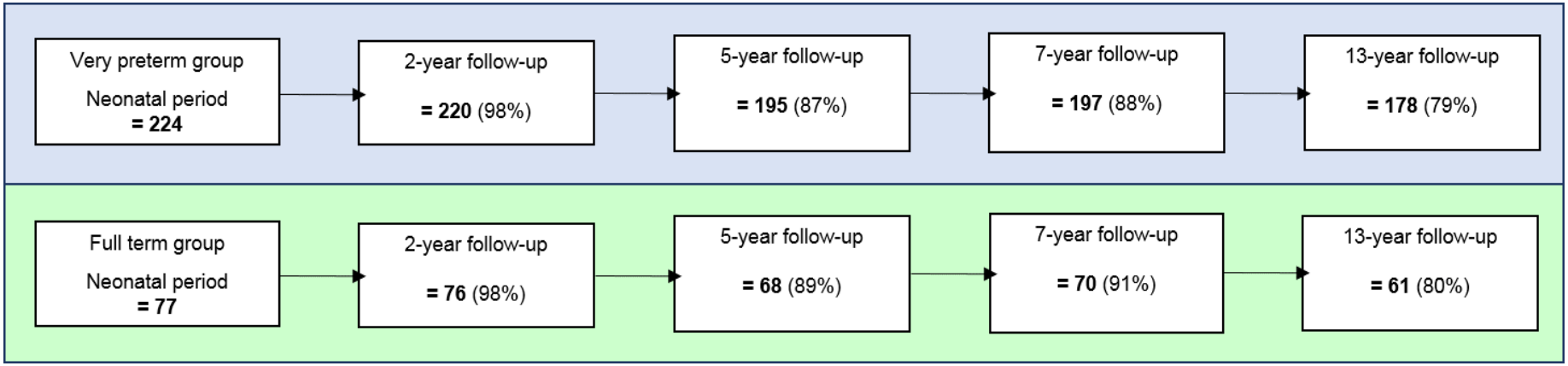

Figure 2.2. Flow-chart of participation numbers and retention rates of very preterm and full-term Victorian Infant Brain Study participants at the neonatal period, 2, 5, 7 and 13 year follow-up studies

2.5. Measures

The measures used in this dissertation were developmentally appropriate for both clinical and research settings. In order of age at follow-up assessment, the following section describes medical, social, general intellectual functioning and goal setting measures relevant to this dissertation, as shown in Table 2.1.

Table 2.1. Relevant Victorian Infant Brain Study study measures

Follow-up time point	Type of assessment	Domain assessed	Measures	Executive function component
Neonatal	***Perinatal***	*Neonatal medical risk*	-Medical record	
	Brain MRI	*Brain structure*	-3D spoiled gradient recalled T_1	
			-3D T_2 fast spin echo	
7-year	***Neurological***	*Neurosensory impairment*	-Assessment for cerebral palsy	
			-Vision/hearing	
13-year	***Neuropsychological***	*General intellectual functioning*	Kaufman Brief Intelligence Test - Second Edition:	
			-Verbal Knowledge	
			-Matrices	
			-Riddles	
		Executive functions	Delis-Kaplan Executive Function System:	
			-Tower Test	Spatial planning, rule learning, response inhibition
			Rey Complex Figure Test:	
			-Copy	Spatial accuracy, organisational strategy
			Behavioural Assessment of the Dysexecutive Syndrome in Children	
			-Zoo Map	Formulate plan, execute plan
			-Six Part Test	Planning, task/time scheduling, performance monitoring
	Parent questionnaires	*Executive functions*	-Behavior Rating Inventory of Executive Function	Executive function behaviours
		Anxiety and depression	-Hospital Anxiety and Depression Scale	
		Social risk and use of intervention services	-Family Information Questionnaire	

Follow-up time point	Type of assessment	Domain assessed	Measures	Executive function component
	Brain MRI	*Brain structure*	-3D Magnetisation Prepared Rapid Gradient Echo T_1	
			-3D T_2 Sampling Perfection with Application optimised Contrasts using different flip angle Evolution	
		Brain connectivity	-Resting state functional magnetic resonance imaging	

2.5.1. Neonatal medical risk

From the neonatal follow-up, perinatal data obtained was used to assign children a neonatal medical risk classification using the following risk factors: small for gestational age (GA; defined as birth weight standard deviation (*SD*) score >2 *SD* below mean (*M*) weight for GA computed relative to the British growth reference data; Cole, Freeman, & Preece, 1998), bronchopulmonary dysplasia (BPD; defined as oxygen dependency at 36 weeks' GA), administration of postnatal corticosteroids, proven necrotising enterocolitis (NEC) or sepsis, and cranial ultrasound brain injuries (grade 3/4 intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL). Children with at least one of these medical complications were classified as higher medical risk (P. J. Anderson et al., 2015), while the remainder were classified as lower medical risk (P. J. Anderson & Doyle, 2008).

2.5.2. Neurosensory impairment at 7 years

At the 7 year follow-up, children were assessed by a paediatrician. Children with the presence of cerebral palsy, deafness, or blindness were classified as having a neurosensory impairment.

2.5.3. Social Risk at 13 years

As part of the 13-year follow-up, parents completed a questionnaire to assess family social risk based on 6 factors: family structure, language spoken at home, education of primary caregiver, occupation of the primary income earner, employment status of primary income earner, and maternal age at birth (G. Roberts et al., 2008). Each factor was given a score of 0, 1 or 2 (see Table 2.2), which were summed together to form a total Social Risk Index score (range 0 to 14), with higher scores representative of higher social risk. The total social risk score was used to categorise participants around the median into "lower social risk" versus "higher social risk" groups.

Table 2.2. Scoring system for social risk index

Variable	Score = 0	Score = 1	Score = 2
Family structure	Two caregivers	Separated parents with dual custody/cared for by other intact family	Single caregiver
Education of primary caregiver	Tertiary education	Education up to year 11	Less than year 11
Occupation of primary income earner	Skilled/professional	Semi-skilled	Unskilled
Employment status of primary income earner	Full-time employment	Part-time employment	Unemployed/pension
Language spoken at home	English	Some English	No English
Maternal age at birth	More than 21 years	18 to 21 years	Less than 18 years

2.5.4. General intellectual functioning at 13 years

At 13 years of age, intellectual quotient (IQ) was estimated using the Kaufman Brief Intelligence Test - Second Edition (KBIT-2; Kaufman & Kaufman, 2004). The KBIT-2 includes 3 subtests: Verbal Knowledge, Matrices and Riddles. Verbal Knowledge assesses receptive vocabulary and general knowledge. Matrices assesses the ability to solve new problems, perceive relationships and complete visual analogies. Riddles assesses verbal comprehension, reasoning and vocabulary skills. Scoring of each subtest involves firstly scoring each item (0 or 1 point), then summing raw score totals. Verbal Knowledge and Riddles subtest total raw scores are summed together to form a verbal composite raw score. The Matrices subtest comprises the non-verbal raw score. Using normative test data, the verbal and non-verbal raw scores are then converted into to standard scores for interpretation (M = 100; SD = 15).

2.5.5. Goal setting measures at 13 years

Delis-Kaplan Executive Function Systems

The Delis-Kaplan Executive Function Systems (D-KEFS) test is designed to assess core components of executive function skills across 9 subtests (Delis, Kaplan, & Kramer, 2001). The Tower Test subtest has been found to be a useful measure in clinical paediatric populations, including attention deficit hyperactivity disorder (ADHD) and traumatic brain injury (Chevignard, Catroppa, Galvin, & Anderson, 2010; Holmes et al., 2010). It is administered to assess spatial planning, rule learning, inhibition of impulsive and perseverative responding, and the ability to follow and adhere to several rules.

In the Tower Test, the participant is required to move 1 to 5 disks of different sizes across 3 pegs in order to build the tower pictured in a stimulus booklet. Across 9 possible items, participants were instructed to build the pictured tower in the fewest number of moves possible, while following two rules: 1) move only one piece at a time using just one hand, and 2) never place a big disk on top of a smaller disk. The subtest is discontinued after 3 consecutive failures. In this study performance was judged using the total achievement score. The total achievement score (range 0 to 30) is the sum of the individual item achievement scores, which are based on the moves in which the tower is correctly built within an item-specific time limit. Using normative data, total achievement raw scores are converted into standard scores for interpretation (1 to 19).

Rey Complex Figure Test

The Rey Complex Figure Test (RCFT) involves reproducing a complicated line drawing (Anderson, Anderson, & Garth, 2001). The RCFT is a popular measure for assessing executive function in clinical paediatric samples, including premature birth or brain injury (V. A. Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Gimenez et al., 2005; Jacobs, Harvey, & Anderson, 2011). The RCFT was used to assess spatial ability and organisational strategy. To complete the RCFT, participants were provided with a blank piece of paper, coloured marker and a stimulus card picturing the complex figure. Participants were instructed to copy the picture as accurately as possible on the blank paper. Participants were informed that they would be provided with a different coloured marker throughout the test (every 45 seconds), but that this was not part of the test, but rather to document the order in which they drew the figure. Performance was judged according to two scores: 1) accuracy, and 2) organisational strategy. Copy accuracy was assessed using the 18 element accuracy criteria established by Osterreith (1944), whereby each individual element was scored as follows: 2 = accurately drawn and placed; 1 = accurately drawn and incorrectly placed, or, inaccurately drawn and correctly place; .5 = inaccurately drawn but recognisable and incorrectly placed; or 0 = inaccurately drawn and unrecognisable, or omitted, and incorrectly placed. Accuracy score is the sum of the 18 element scores (range 0 to 36). Organisational strategy was assessed using the RCFT Organizational Strategy Score (RCFT-OSS; Anderson, Anderson, & Garth, 2001), which classifies the order of a child's copy into 7 organisational categories according to the following criteria: 1 = unrecognizable/substitution; 2 = poor organization; 3 = random organization; 4 = piecemeal/fragmented organization; 5 = part-configural organization; 6 = conceptual organization; or 7 = excellent organization.

Behavioural Assessment of the Dysexecutive System for Children

Two subtests from the Behavioural Assessment of the Dysexecutive System for Children (BADS-C; Emslie, Wilson, Burden, Nimmo-Smith, & Wilson, 2003) were selected, Zoo Map (ZM) and Six Part Test (6PT). The BADS-C has been validated in children aged between 8 to 15 years of age and is considered a novel, ecologically valid and complex measure of planning (I. E. Baron, 2003; Engel-Yeger, Josman, & Rosenblum, 2009). The BADS-C has found to be a useful measure in other clinical paediatric populations, including ADHD and autism (Shimoni, Engel-Yeger, & Tirosh, 2012; White, Burgess, & Hill, 2009).

Zoo Map was used to assess the ability to formulate and execute a plan across both unstructured and structured formats. Participants are required to plan and complete an eight-location sequence across two task parts: ZM 1 (unstructured) and ZM 2 (structured). In ZM 1, children are asked to plan and draw a pathway on a zoo map, visiting target places listed on an instruction card, in accordance with several rules (e.g., only take camel ride pathway once). Zoo Map 1 is open-ended, requiring the child to independently plan and organise their path to visit the target places while following the rules listed on the instruction card. In ZM 2 however, the instruction card that lists the sequence in which to visit the targets on a new zoo map. Across both parts, participants are given a different coloured marker after they have visited each target place, although they are informed that this is not part of the test. Planning time and total time taken are recorded. Performance was judged using the following scores: total time taken; total number of errors; and total raw score. Total time is recorded in seconds, with longer time indicating a slower performance. For the total number of errors, rule break errors are tallied (1 point each) and summed together. In ZM 1, the total raw score is the sum of correct places visited (1 point each), with the total error score deducted. The ZM 2 total raw score is the sum of correct places visited (1 point each), with additional point deductions when planning time exceeds 25 seconds, and/or total completion time exceeded 130 seconds (1 point each). Total achievement scores on ZM 1 range from -10 to 8, and for ZM 2 range from -4 to 8. Using normative test data, total achievement raw scores may be converted into standard scores for interpretation (1 to 19).

The Six Part Test (6PT) was used to assess independent planning, task/time scheduling and performance monitoring skills. In 6PT, participants are asked to complete 6 simple tasks in 5 minutes in accordance with several rules. The 6 tasks consist of three different 2-part colour-coded card tasks: green “How many?” (simple arithmetic); blue “What is it?” (picture naming); and red “Sort me” (sorting objects). Children are asked to complete as much of each task as possible in 5 minutes, ensuring that they complete at least 1 task from each of the 6 parts. Participants must follow 1 rule: do not complete two parts of a same-coloured task one after the other (i.e., do not complete blue part 2 immediately after blue part 1). Children are provided with an instruction card, paper, pencil, eraser, 6 stacks of task cards, and a countdown timer. Performance was judged using the following scores: total rule break errors; utilised a pattern strategy total score; and total test raw score. The total rule break error score represents whether the child has returned to the coloured parts consecutively, scored as 1 or 0 for each coloured part (range 0 to 3). Utilised a pattern strategy total score is the sum of effective strategy scores awarded

across two items: 1) child uses a clear pattern to avoid breaking the order rule, and 2) child uses a set amount of time/number of items/number and time combination to attempt all six parts. Children are awarded 2 points for use of an effective strategy, or 0 points for no strategy (range 0 to 4). This score was assessed dichotomously: ≥ 2 = strategy use; or 0 = no strategy. The total test raw score is the sum of the parts attempted, scored at 2 points per part (range 0 to 12), and the utilised a pattern strategy total score, with total rule break errors deducted. An additional 1 point may be deducted from the total test raw score if a child returned to any coloured part 3 or more times. Using normative test data, the total test raw scores (range 1 to 16) were converted into standard scores for interpretation (1 to 19).

Behaviour Rating Inventory of Executive Function

The Behavior Rating Inventory of Executive Function (BRIEF) is a widely used behavioural rating measure for children, designed to assess executive function behaviours in real-life settings, as observed in natural, everyday environments (Gioia et al., 2000). The BRIEF asks parents to rate whether their child has had problems with statements regarding behaviour over the past 6 months, across a 3-point Likert Scale ranging from: 1 = never a problem; 2 = sometimes a problem; or 3 = often a problem. The "Plan/organize" scale was used to assess a child's ability to use strategies to attain goals (e.g., "becomes overwhelmed by large assignments") over 12 items (range 12 to 36). The "Organization of materials" scale was used to assess a child's ability to keep their belongings tidy (e.g., "leaves a trail of belongings wherever he/she goes") over 6 items (range 6 to 18). Item scores were summed for each scale to provide total raw scores, which were then separately converted into a T scores using normative test data (mean *T* score = 50; *SD* = 10). Scores were assessed in terms of categorical ranges, with higher scores reflecting greater endorsement of difficulties (normal ≤ 59; at risk = 60 to 64; clinically significant ≥ 65).

2.6. MRI sequences

The following section outlines the MRI sequences relevant to this dissertation from the neonatal and 13 year follow-up, in order of age at follow-up assessment.

2.6.1. Neonatal MRI

During the neonatal period, infants were fed and placed in a Vacuum Fixation beanbag to reduce movement prior to the MRI scanning. A pair of earmuffs was fitted on the infant to avoid damage to the ears. Infants were scanned while sleeping without the use of sedation.

Neonatal MRI was acquired at the Royal Children's Hospital using a 1.5 Tesla MRI scanner (Signa LX Echospeed System; General Electric, Milwaukee, WI). Sequences included T_1-weighted spoiled gradient recalled (coronal slices=0.8-1.6mm, repetition time (TR)=35ms, echo time (TE)=9ms; flip angle=45°, field of view=210×158mm, matrix=256×192) and T_2 proton density-weighted dual echo fast recovery fast spin echo with interleaved acquisition (coronal slices=1.7-3.0mm, TR=4000ms, TE=60/160ms, flip angle=90°, field of view=220×160mm, matrix=256×192, interpolated=512×512).

2.6.2. Qualitative neonatal MRI scoring

A neonatal neurologist assessed the T_1 and T_2 sequences acquired during the neonatal period, using a reliable qualitative scoring system (Kidokoro et al., 2013). Scores of brain abnormalities included 1) white matter 2) cerebral gray matter 3) deep gray matter, 4) cerebellum, and 5) overall brain abnormalities. The scores ranged from 0 to 4 for each brain tissue or region, except for cortical gray matter, for which the scores ranged from 0 to 3. The total possible overall score ranged from 0 to 17. A higher score indicated more brain abnormalities. For specific details on the scoring system, see Table 2.3.

Table 2.3. Qualitative MRI Scoring System, adapted from Kidokoro et al., (2013).

Variables	Score 0	Score 1	Score 2	Score 3	Score 4
White matter					
Cystic lesions	None	Focal unilateral	Focal bilateral	Extensive unilateral	Extensive bilateral
Focal signal abnormality	None	Focal punctate	Extensive punctate	Linear	
Myelination delay	PLIC & corona radiata	Only PLIC	Minimal—no PLIC		
Thinning of the corpus callosum	None	Partial (genu/body < 1.3 mm or splenium < 2.0 mm)	Global (genu/body < 1.3 mm and splenium < 2.0 mm)		
Dilated lateral ventricles	Both sides VD < 7.5 mm	One side 7.5 mm ≤ VD < 10 mm	Both sides 7.5 mm ≤ VD < 10 mm or one side VD ≥ 10 mm	Both sides VD ≥ 10 mm	
Volume reduction	cBPW ≥ 77 mm	77 mm > cBPW ≥ 72 mm	72 mm > cBPW ≥ 67 mm	67 mm > cBPW	
Cortical gray matter					
Gyral maturation	Delay < 2 weeks	2 ≤ delay < 4 weeks	Delay ≥ 4 weeks		
Increased extracerebral space	IHD < 4 mm	4 mm ≤ IHD < 5 mm	5 mm ≤ IHD < 6 mm	IHD ≥ 6 mm	
Deep Gray Matter					
Signal abnormality	None	Focal unilateral	Focal bilateral	Extensive unilateral	Extensive bilateral
Volume reduction	cDGMA ≥ 9.5	9.5 > cDGMA ≥ 8.5	8.5 > cDGMA ≥ 7.5	7.5 > cDGMA	
Cerebellum					
Signal abnormality	None	Punctate unilateral	Punctate bilateral	Extensive unilateral	Extensive bilateral
Volume reduction	cTCD ≥ 50 mm	50 mm > cTCD ≥ 47 mm	47 mm > cTCD ≥ 44 mm	cTCD < 44 mm	

*Note***.** PLIC = posterior limb of internal capsule; cBPW = corrected biparietal width; VD = ventricular diameter; cDGMA = corrected deep gray matter area (cm^2); cTCD = corrected transcerebellar diameter; IHD = interhemispheric distance.

2.6.3. Quantitative neonatal MRI volumes

Neonatal volumes of white matter, cortical gray matter, cerebellum, total brain tissue and intracranial cavity were derived from the Morphologically Adaptive Neonatal Tissue Segmentation (MANTiS) technique, applied to T_2 structural images at term equivalent age (Beare et al., 2016). Basal ganglia and thalamus volumes were obtained from the combined T_2- and proton density-weighted images (Thompson, Ahmadzai, et al., 2012) using the Pediatric Subcortical Segmentation Technique (Loh et al., 2016), as previously described (Loh et al., 2017). Hippocampi were manually traced with 3D slicer 2.5 software (http://slicer.org/) by a single operator on the combined raw T_2- and proton density–weighted images, as previously described (Thompson, Ahmadzai, et al., 2012). The corpus callosum area was traced on the mid-sagittal slice of the structural T_1 scan that had been manually aligned along the anterior–posterior commissure line, as previously described (Thompson et al., 2011). Across these measures, poorer brain growth is indicated by smaller volumes (R. W. Cooke, 2010).

2.6.4. Magnetic resonance imaging at 13 years

At the 13-year follow-up, children had a familiarisation session in a mock MRI prior to their scan. As part of this process, pictures of the brain as captured by the MRI were shown, and children practiced laying down in a practice MRI scanner while sounds from the MRI machine were played, to familiarise children with noises they would hear in the scanner. Children also practiced looking at the resting-state fMRI (rs-fMRI) cross on a screen.

For the MRI scan, children were offered a blanket and a pillow under their legs for comfort. Children could watch a movie during the scanning period, except during the rs-fMRI scan during which children were instructed to look at a cross on the screen, while thinking about nothing in particular.

Magnetic resonance imaging sequences were acquired at the Royal Children's Hospital using a 3Tesla Trio Siemens scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. Neuroanatomical sequences included T_1-weighted multi-echo Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence with echo planar image (EPI) navigated prospective motion compensation sequences with the following acquisition parameters: repetition time (TR) = 2530ms, echo time (TE) 1= 1.77, TE 2= 3.51, TE 3= 5.32,

TE 4= 7.2ms, flip angle= 7°, field of view (FOV) = 230 x 209mm, matrix= 256 x 230 (interpolated 256 x 256), 0.9mm^3 isotropic voxels). Resting-state functional MRI connectivity images were acquired via a BOLD contrast sensitive sequence using a multiband EPI sequence with the following acquisition parameters: multiband acceleration factor = 3, TR = 1500ms, TE = 33ms, flip angle = 85°, FOV = 255 x 255mm, matrix = 104 x 104, voxel size= 2.5mm^3 isotropic

2.6.5. MRI preprocessing at 13 years

Prior to MRI data preprocessing, datasets were assessed to exclude T_1 and rs-fMRI data of insufficient quality for further analysis (i.e., incomplete datasets, significant motion or other imaging artifact). Data preprocessing was undertaken using the CONN toolbox from the SPM12 software package (Gabrieli Lab McGovern Institute for Brain Research, 2014) in MATLAB Statistics Toolbox Release R2016b (MATLAB version 8.5.1., 2016) to analyse and correct for motion artifact, as well as the TOPUP tool to estimate and correct for susceptibility induced distortions within the data set. Using the CONN pipeline, functional volumes were subjected to time shift correction (TR 2.53) and then each participant's functional image was registered linearly to their T_1 structural image and converted to the MNI152 adult brain atlas space (Evans et al., 2001). Next, the spatial volumes of the functional images were smoothed with full width at half maximum (FWHM) Gaussian kernel of 8mm. The T_1 structural images were segmented into cerebrospinal fluid (CSF), white and gray matter, in order to mask out the effect of the CSF and white matter from the fMRI image. This denoising process was achieved by regressing out the signal from the CSF and white matter to preserve the gray matter BOLD signal only. The final step involved applying temporal filtering of low frequency signal whereby the residual time series were band pass filtered (0.008 - 0.09 Hz).

Chapter 3. Goal setting deficits at 13 years in very preterm born children

Chapter 3

3.1. Declaration for thesis chapter 3

Monash University

Declaration for Thesis chapter 3

Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Data collection, generation of research questions, literature review, data analysis, results, interpretation, manuscript	65

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Catherine Willmott	Generation of research questions, data analysis, input into manuscript	7.5
Rachel Ellis	Data collection, input into manuscript	5 collectively
Alice Burnett	Input into manuscript	
Shannon Scratch	Data collection, input into manuscript	
Leona Pascoe	Data collection, input into manuscript	
Megan Spencer-Smith	Input into manuscript	
Jeanie Cheong	Input into manuscript	
Terrie Inder	Input into manuscript	
Lex Doyle	Input into manuscript	
Deanne Thompson	Generation of research questions, data analysis, input into manuscript, interpretation	10
Peter Anderson	Generation of research questions, data analysis, input into manuscript, interpretation	12.5

Candidate's signature: [redacted] **Date:** 2nd July 2018

Main supervisor's signature: [redacted] **Date:** 2nd July 2018

3.2. Overview

This chapter presents an empirical paper titled *"Goal setting deficits at 13 years in very preterm born children",* published in the Journal of the International Neuropsychological Society (JINS). This paper investigated goal setting skills of very preterm born children in comparison to full-term born control children at 13 years of age, characterising these abilities in the context of numerous executive functioning deficits documented in very preterm populations during late childhood. Additionally, we investigated neonatal medical complications associated with goal setting abilities of very preterm children at 13 years of age. We identified early risk factors associated with outcomes during late childhood, contributing to the early identification of children at risk for difficulties.

3.3. Abstract

Objective: Preterm children demonstrate deficits in executive functions including inhibition, working memory and cognitive flexibility, however their goal setting abilities (planning, organisation, strategic reasoning) remain unclear. This study compared goal setting abilities between very preterm (VP: <30 weeks/<1250 grams) and term born controls during late childhood. Additionally, early risk factors (neonatal brain abnormalities, medical complications, and sex) were examined in relationship to goal setting outcomes within the VP group.

Method: Participants included 177 VP and 61 full-term born control children aged 13 years. Goal setting was assessed using several measures of planning, organisation and strategic reasoning. Parents also completed the Behavior Rating Inventory of Executive Function (BRIEF). Regression models were performed to compare groups, with secondary analyses adjusting for potential confounders (sex and social risk), and excluding children with major neurosensory impairment and/or IQ<70. Within the VP group, regression models were performed to examine the relationship between brain abnormalities, medical complications, and sex, on goal setting scores.

Results: The VP group demonstrated a clear pattern of impairment and inefficiency across goal setting measures, consistent with parental report, compared with their full-term born peers. Within the VP group, moderate/severe brain abnormalities on neonatal MRI predicted adverse goal setting outcomes at 13.

Conclusions: Goal setting difficulties are a significant area of concern in VP children during late childhood. These difficulties are associated with neonatal brain abnormalities, and are likely to have functional consequences academically, socially and vocationally.

3.4. Introduction

Children born very preterm (VP; <32 weeks' gestation) demonstrate prominent executive functioning (EF) deficits compared with full-term (FT) born children (Burnett, Scratch, & Anderson, 2013). Executive functioning is an umbrella term for numerous interrelated, higher-order cognitive skills essential for complex reasoning, goal-directed activity and adaptive behaviour (Anderson, 2002; Lezak, 2012). While difficulties in various EF domains, including complex attention, impulse control, working memory, verbal fluency, cognitive flexibility, and reasoning abilities, have been well documented throughout childhood in VP cohorts (Anderson et al., 2011; Anderson & Doyle, 2004; Bohm, Smedler, & Forssberg, 2004; Luu, Ment, Allan, Schneider, & Vohr, 2011; Taylor, Hack, & Klein, 1998), the nature of goal setting skills in VP children remains unclear due to limited research.

Goal setting can be considered a core component of EF (Anderson, 2008). It pertains to the ability to organise a series of steps or a plan towards goal completion, with deficits resulting in problem solving challenges due to poor planning, disorganisation, strategy development difficulties, overreliance on previously learned strategies, as well as reasoning difficulties (Anderson, 2002). Goal setting skills are essential to the development of independent thinking and self-management, and are therefore especially important during late childhood (Burnett et al., 2013). Organisation and planning competence, both components of goal setting, may assist children to succeed in new and increasingly complex environments (e.g., secondary school) and facilitate academic, social, and personal development (Luu et al., 2011). Since goal setting skills become increasingly important for successfully and independently completing activities of daily living during late childhood and adolescence, deficits may become more overt during this developmental period. Understanding the nature of these abilities in VP children has implications to early detection and intervention, with a preference to detect deficits before they become entrenched.

Though limited, research suggests that VP children are at greater risk for goal setting difficulties than FT born children. Poorer planning and spatial organisation abilities of VP cohorts have been reported during early childhood using performance based measures (Anderson & Doyle, 2004; Harvey, O'Callaghan, & Mohay, 1999; Marlow, Hennessy, Bracewell, & Wolke, 2007) as well as parent report behavioural questionnaires (Anderson &

Doyle, 2004; Loe, Chatav, & Alduncin, 2015; Scott et al., 2012). In late childhood, several studies have reported poorer VP spatial planning and strategy formulation (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2012; Curtis, Lindeke, Georgieff, & Nelson, 2002; Taylor, Minich, Bangert, Filipek, & Hack, 2004), but others have found no goal setting deficits in VP groups (Mulder, Pitchford, & Marlow, 2011).

To date, no study has undertaken a comprehensive assessment of goal setting in VP children, with current knowledge limited to studies that have utilised a single goal setting measure. Experimental measures with unclear ecological validity (i.e., CANTAB Stockings of Cambridge test; Cambridge Cognition, 2016) bring into question the generalisability of the findings to real life functioning (Burgess, Alderman, Evans, Emslie, & Wilson, 1998). Another limitation of the research to date on goal setting in VP survivors is that most studies have focused on samples under 11 years of age, when these skills are still emerging and are of only modest functional importance (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). Further, risk factors of goal setting deficits in VP groups are unknown, yet important for classifying high-risk children who warrant close surveillance and possibly early intervention. In VP groups, neonatal medical complications (Curtis et al., 2002; Duvall, Erickson, MacLean, & Lowe, 2014; Orchinik et al., 2011), including brain injury and altered brain development (Clark & Woodward, 2010; Edgin et al., 2008; Woodward, Anderson, Austin, Howard, & Inder, 2006; Woodward, Clark, Pritchard, Anderson, & Inder, 2011; Young et al., 2016) are known to be related to poorer outcome in other EF domains. Sex is another important consideration given the higher mortality and morbidity in preterm males (Costeloe, Hennessy, Gibson, Marlow, & Wilkinson, 2000), and their poorer performance on executive measures (Böhm et al., 2004; Marlow et al., 2007; Urben et al., 2017).

The current study sought to examine goal setting skills in a cohort of VP children at 13 years of age compared with FT controls. It was hypothesised that in comparison to their FT born peers, VP children would perform more poorly across goal setting measures, and within the VP group, moderate to severe brain injury, complicated neonatal course, and male sex would be associated with poorer goal setting performance.

3.5. Methods section

3.5.1. Participants and procedure

Participants were part of the Victorian Infant Brain Study (VIBeS) cohort, a longitudinal study examining the development of children born VP (<30 weeks' gestation) and/or very low birth weight (<1250 g). Two hundred and twenty-seven participants fitting eligibility criteria and without genetic or congenital abnormalities known to affect development were originally recruited between July 2001 and December 2003 at the Royal Women's Hospital, Melbourne. Three infants subsequently died, leaving 224 survivors. Seventy-seven healthy control children born at term (≥ 37 to ≤ 41 weeks' gestation) and of normal birth weight (≥ 2500 g) were also recruited, 46 from the Royal Women's Hospital at birth and 31 from Maternal and Child Health Centres at 2 years of age. Neonatal brain MRI was performed on all VP survivors and the control children recruited at birth.

Children were followed up at 2, 5, 7 and 13 years of age, with age corrected for prematurity at all time points to avoid a known bias in cognitive test scores (Wilson-Ching, Pascoe, Doyle, & Anderson, 2014). This study was approved by the Human Research and Ethics committees of the Royal Women's Hospital and the Royal Children's Hospital, and informed written consent was obtained from the parents at all time points.

At the 13 year follow up, 179 (80%) of the 224 eligible children in the VP cohort agreed to participate. Eleven participants did not consent, and 34 were lost to follow up (uncontactable, *n* = 10; declined/failed to attend, *n* = 24). Goal setting measures could not be administered to 2 VP participants due to intellectual and physical impairment, resulting in n = 177.Of the 77 eligible FT children, 61 (79%) participated, with 11 deciding not to consent and 5 lost to follow up (uncontactable, *n* = 4; overseas, *n* = 1).

3.5.2. Goal setting measures at 13 years of age

From the Delis-Kaplan Executive Function Systems (D-KEFS; Delis, Kaplan, & Kramer, 2001) the *Tower Test* was administered to assess spatial planning, rule learning, inhibition of impulsive and perseverative responding, and the ability to establish and maintain instructional set. Performance was judged according to the total achievement score, which is based on the number of correct towers assembled within an item-specific time limit.

The *Rey Complex Figure Test* (RCFT) involves reproducing a complicated line drawing (Anderson, Anderson, & Garth, 2001). Performance was judged according to 1) accuracy, and 2) organisational strategy. Copy accuracy was assessed using the 18 item accuracy criteria established by Osterreith (1944). Organisational strategy was assessed using the RCFT-Organizational Strategy Score (RCFT-OSS; Anderson, Anderson, & Garth, 2001), which classifies drawings into 7 categories according into set criteria: 1 = unrecognisable/substitution; 2 = poor organization; 3 = random organization; 4 = piecemeal/fragmented organization; 5 = part-configural organization; 6 = conceptual organization; or 7 = excellent organization. For the purposes of this analysis, performance was dichotomised into part-configural organisation or better (levels 5 to 7) versus the rest (levels 1 to 4).

Two subtests from the *Behavioural Assessment of the Dysexecutive System for Children* (BADS-C; Emslie, Wilson, Burden, Nimmo-Smith, & Wilson, 2003) were selected, *Zoo Map* (ZM) and *Six Part Test (6PT).* Zoo Map is a test of planning that captures the ability to plan and execute a specific eight location sequence in accordance with several rules across 2 parts: ZM 1 unstructured, requiring independent planning; ZM 2 structured, with the sequence provided. Across both parts, points are accumulated and deductions are made for rule breaks. On ZM 2, points were additionally deducted when planning time exceeded 15 seconds, and/or total completion time exceeded 120 seconds. The *Six Part Test (6PT)* examines planning, task scheduling and performance monitoring skills by asking participants to complete 6 simple tasks in 5 minutes in accordance with several rules. Points are awarded for an effective strategy and pattern, and deducted when a participant returns to any part consecutively. The BADS-C is a novel, ecologically valid and complex measure of planning (Baron, 2003). The BADS-C has been validated in children aged between 8 to 15 years of age (Baron, 2003; Engel-Yeger, Josman, & Rosenblum, 2009) and been found to be a useful measure in other clinical paediatric populations, including ADHD and autism (Shimoni, Engel-Yeger, & Tirosh, 2012; White, Burgess, & Hill, 2009).

3.5.3. Behavioural questionnaire

The parent form of the *Behavior Rating Inventory of Executive Function* (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) was administered to the primary caregiver at the 13 year follow up. This questionnaire assesses executive function behaviours in real-life settings. The Plan/organize (i.e., using strategies for attaining goals) and Organization of materials (i.e., keeping belongings tidy) scales were examined (Mean *T* score = 50, *SD* = 10) and reported in categorical ranges, with higher scores reflecting greater endorsement of difficulties (normal ≤ 59; at risk = 60 to 64; clinically significant ≥ 65).

3.5.4. Neonatal brain abnormalities

At term-equivalent age (37 to 42 weeks' GA), T_1 and T_2 images were acquired with a 1.5 Tesla General Electric MRI scanner (Signa LX Echospeed System; General Electric, Milwaukee, WI). Two VP infants who were scanned outside of the term-equivalent window (40 weeks' gestation, +/- 2 weeks) were excluded from imaging analysis. Unsedated infants were placed in a Vacuum Fixation beanbag to reduce motion. Using the rating system described by Kidokoro, Neil, and Inder (2013), brain scans were assessed for pathology by an experienced neonatal neurologist. The scoring system has sub- scales for rating white matter, cortical gray matter, deep gray matter and cerebellar abnormality, as well as a total abnormality scale that is the sum of the sub-scales. Higher scores reflect greater brain abnormalities. The total sub-scale score was classified into 4 groups, reflecting the following abnormality categories: none, mild, moderate or severe (Kidokoro et al, 2013). For our analysis, we contrasted those with no and mild brain abnormalities with those with moderate to severe abnormality.

3.5.5. Social Risk

As part of the 13-year follow-up, parents completed a questionnaire to assess family social risk based on a number of indicators (i.e., family structure, language spoken at home, education of primary caregiver, occupation of the primary income earner, employment status of primary income earner, and maternal age at birth). In accordance with previous follow up of this cohort, a social risk total score was calculated (Roberts et al., 2008; Treyvaud et al., 2013) which was then used to categorise participants around the median into lower or higher risk groups.

3.5.6. Neonatal medical risk and neurosensory impairment

Data obtained during neonatal follow up of the VP sample was used to assign children a neonatal medical risk classification. Children were classified as being of higher medical risk if they had one or more of the following risk factors: small for gestational age (GA; defined as birth weight SD score > 2 standard deviations below mean weight for GA computed relative to the British growth reference data; Cole, Freeman, & Preece, 1998), bronchopulmonary dysplasia (BPD; defined as oxygen dependency at 36 weeks' GA), administration of postnatal corticosteroids, proven necrotising enterocolitis (NEC) or sepsis, and cranial ultrasound brain injuries (grade 3/4 intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL). Children with at least one of these medical complications were classified as higher medical risk (Anderson, Cheong, & Thompson, 2015), while the remainder were classified as lower medical risk (Anderson & Doyle, 2008).

Neurosensory impairment was defined as the presence of cerebral palsy, deafness, or blindness, as diagnosed at the 7 year follow up.

3.6. Statistical analysis

Data were analysed using Stata 14.2 (StataCorp, College Station, Texas. Significantly skewed variables were log transformed to provide a better model fit prior to analysis.

Group differences in goal setting outcomes at 13 years of age between VP and term-born children were compared using both linear and logistic regression, with both unadjusted and adjusted models. The adjusted model included sex and social risk as potential confounders, and excluded children with significant neurosensory impairment or an IQ less than or equal to 70 (n = 14), to ensure that group differences and/or associations were not due to a small number of significantly impaired VP children.

Additional regression analyses were conducted within the VP group. These models separately assessed the relationship between neonatal brain abnormalities (none/mild vs. moderate/severe), neonatal medical risk (high versus low) and sex, and goal setting outcomes.

Models were fitted using Generalised Estimating Equations reported with robust standard errors to allow for clustering of multiple births within a family (i.e., twins/triplets). A critical value of less than or equal to .05 was used to evaluate statistical significance, but acknowledging

the number of comparisons, findings are interpreted based on the pattern of the results (direction and magnitude of differences across measures). The Benjamini-Hochberg False Discovery Rate (FDR) correction procedure was applied to all p values to address the issue of multiple comparisons (Benjamini & Yekutieli, 2001). Effect sizes were calculated to determine the magnitude of the group comparisons (Olejnik & Algina, 2003), with 0.2 being considered a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen, 1973).

3.7. Results

3.7.1. Sample characteristics

There were no differences between VP participants and non-participants, or FT participants and non-participants across the available neonatal variables (presented in Table 3.1.). As expected the VP and FT groups differed on antenatal and neonatal variables (i.e., birth weight, GA, BPD, sepsis, postnatal corticosteroids, brain injuries). Regarding sociodemographic characteristics, the VP group demonstrated higher social risk (fewer intact families and primary caregivers with a tertiary education), had a lower mean IQ, and were more likely to have received allied health intervention, compared with the FT group.

Table 3.1. Sample characteristics

	VP (*n* = 177)	FT (*n* = 61)	Statistics for group comparisons	
	n (%)	*n* (%)	[95% CI]	*p*
Neonatal Characteristics				
GA (weeks)	27.4 (2.0)†	39.1 (*1.3)*†		
GA <28 weeks	102 (*58)*	0		
BW (g)	961.28 (*225.5)*†	3305.39 (*524.4)*†		
BW <1000 g	99 (*56)*	0		
Small for gestational age	15 (*9)*	1 (*3)*		
Male sex	91 (*51)*	25 (*41)*		
Multiple birth	79 (*45)*	4 (*7)*		
Postnatal corticosteroids	17 (*10)*	0		
Necrotising enterocolitis	9 (*5)*	0		
Bronchopulmonary dysplasia	63 (*36)*	0		
Any sepsis	60 (*34)*	0		

Grade 3/4 intraventricular haemorrhage	7 (*4)*	0			
Cystic periventricular leukomalacia	6 (*3)*	0			
Sociodemographic Characteristics at 13					
Maternal age at birth (years)	30.4 (*5.5)*†	31.2 (*4.2)*	0.87[b]	[-0.66, 2.40]	.26
Intact family	116 (*67)*	50 (*83)*†			.002**
Primary caregiver with tertiary education	65 (*41)*	36 (*62)*†	0.21[a]	[0.07, 0.36]	.005**
Higher social risk score at 13yo	99 (*59)*	21 (*35)*†	-0.24[a]	[-0.38, -0.09]	.001**
Recipient of allied health services since 7yo (ST, psych, OT, physio)	64 (*39)*	13 (*23)*†	-0.16[a]	[-0.29, -0.03]	.02*
General Outcomes at 13					
Corrected age at testing (years)	13.3 (0.*4)*†	13.2 (0.*5)*	-0.0[b]	[-0.2, 0.10]	.47
FSIQ	100.2 (*18.3)*†	110.2 (*13.0)*	10[b]	[5.0, 15.0]	<.001

Note. n = number; *%* = percentage; GA = gestational age; BW = birth weight; † = M *(SD)*; ST = speech therapy; OT = occupational therapy; CI = confidence interval; [a]proportional difference; [b]mean difference; FSIQ = full scale intelligence quotient.

Some sample sizes are less than the total sample due to missing data (social risk [VP = 169, FT = 60], recipient of allied health services since 7yo [VP = 164, FT = 57], primary caregiver with tertiary education [VP = 160, FT = 58], maternal age at birth [VP = 176, FT = 59], FSIQ [VP = 2]).

**$p < .05$; ***$p < .01$.

3.7.2. Goal setting

The VP group performed more poorly across all goal setting measures compared with the FT group, with group differences reaching significance on the majority of outcome measures, including poorer summary scores, slower completion times, and a greater number of errors (presented in Table 3.2.). Types of errors involved excessive planning/total completion time and rule breaks (i.e., deviating from a path, visiting inappropriate locations). On the BRIEF, parents of the VP group endorsed a greater proportion of planning and organisational difficulties, compared with parents of FT controls. Group differences largely persisted after adjustment for sex and social risk, and following false discovery rate correction to address the multiple comparisons.

Table 3.2. Goal setting group differences, unadjusted and adjusted models

	VP	FT	Unadjusted				Adjusted[a]			
	M *(SD)*	M *(SD)*	*b*	[95% CI]	*p*	*η2*	*b*	[95% CI]	*p*	*η2*
BADS-C										
ZM1 total time taken (seconds)^	180.96 (*128.14)*	143.06 (*53.73*)	36.71	[13.29, 60.13]	*.002***	*.021*	41.51	[15.49, 67.52]	*.002***	*.025*
ZM1 total number of errors^	2.67 *(3.48)*	1.30 *(2.06)*	0.73	[0.29, 1.16]	*.001***	*.035*	0.59	[0.13, 1.06]	*.013**	*.033*
ZM1 total raw score	2.02 *(5.06)*	4.85 *(3.75)*	-2.84	[-4.05, -1.63]	*<.001*	*.064*	-2.27	[-3.55, -.01.0]	*<.001*	*.044*
ZM2 total time taken (seconds)^	69.16 *(29.92)*	60.84 *(18.76)*	8.35	[1.94, 14.76]	*.01***	*.017*	7.66	[0.09, 15.23]	*.04**	*.014*
ZM2 total number of errors^	0.89 *(2.3)*	0.11 *(0.45)*	2.04	[0.99, 3.10]	*<.001*	*.028*	1.78	[0.60, 2.96]	*.003**	*.027*
ZM2 total raw score	6.72 *(3.03)*	7.74 *(0.91)*	-1.03	[-1.55, -0.51]	*<.001*	*.028*	-0.71	[-1.08, -0.34]	*<.001*	*.019*
6PT total rule break errors^	0.43 (*.77)*	0.37 (0.*71)*	0.14	[-0.41, 0.70]	*.61*	*.001*	0.18	[-0.41, 0.78]	*.54*	*.001*
6PT utilised a pattern strategy	65 (*37)*†	27 *(44)*†	-0.31	[-0.93, 0.32]	*.33*		-0.14	[-0.78, 0.50]	*.67*	
6PT test total raw score	11.06 (*3.54)*	12.10 *(2.90)*	-1.04	[-1.92, -0.16]	*.02**	*.018*	-0.81	[-1.66, 0.05]	*.06*	*.013*

DKEFS										
Tower Test total achievement raw score	16.73 (*3.08)*	18.36 (*3.02)*	-1.67	[-2.56, -0.78]	*<.001*	*.052*	-1.28	[-2.19, -0.38]	*.005***	*.038*
RCFT										
Copy raw score	24.94 (*4.93)*	27.28 (*3.80)*	-2.39	[-3.61, -1.17]	*<.001*	*.046*	-1.33	[-2.53, -0.13]	*.03**	*.021*
Utilised part-configurable strategy or better	90 *(52)*†	37 *(62)*†	-0.59	[-1.56, 0.39]	*.23*		-0.31	[-1.30, 0.68]	*.54*	
BRIEF										
Plan/organize difficulties; at risk and above range^	63 *(39)*†	13 *(22)*†	2.54	[0.34, 4.73]	*.02**		1.05	[-0.45, 2.55]	*.17*	
Organization of materials difficulties; at risk and above range^	30 (*19)*†	*10 (17)*†	0.29	[-1.05, 1.62]	*.67*		-0.02	[-0.93, 0.88]	*.96*	

Note. N ranges from 221 to 238 depending on the outcome; VP = very preterm; FT = full-term; M = mean; *SD* = standard deviation; ^ = higher scores reflects worse performance; † = *n* (%); BADS-C = Behavioural Assessment of the Dysexecutive System for Children; ZM 1 = Zoo Map 1; ZM 2 = Zoo Map 2; 6PT = 6 Part Test; DKEFS = Delis-Kaplan Executive Function Systems; RCFT = Rey Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Function; *b* = coefficient for group from the regression model representing the difference in means between the VP and FT groups; CI = confidence interval.

[a]Adjusted for sex, social risk, and excludes participants with significant neurosensory impairment and/or IQ<=70.

**$p < .05$; ***$p < .01$.

3.7.3. Risk factors and goal setting in VP group

Within the VP group, children with moderate/severe neonatal brain abnormalities performed poorer on Zoo Map 1 (slower and more errors), Tower Test, and RCFT (accuracy and organizational strategy; presented in Table 3.3.). Higher neonatal medical risk was not significantly associated with goal setting performances. While sex was not strongly associated with goal setting performance, males demonstrated poorer visuospatial organisation, and parents of females reported a higher proportion of difficulties with 'organization of materials'. There was also a trend for males to utilise less effective planning strategies (6PT, RCFT). Results were unchanged following the application of the false discovery rate correction procedure.

Table 3.3. Early predictors of goal setting outcomes within the very preterm group

	Brain abnormality None/mild (*n* = 147) vs. Moderate/severe (*n* = 30)				Medical risk Low (*n* = 72) vs. High (*n* = 105)				Sex Female (*n* = 86) vs. Male (*n* = 91)			
	b	[95% CI]	*p*	*η2*	*b*	[95% CI]	*p*	*η2*	*b*	[95% CI]	*p*	*η2*
BADS-C												
ZM1 total time taken (seconds) ^	65.22	[-12.37, 142.82]	*.09*	.044	24.87	[-8.39, 58.12]	*.14*	.010	-18.44	[-54.65, 17.77]	*.31*	.007
ZM1 total number of errors ^	0.45	[0.07, 0.84]	*.02**	.023	0.17	[-0.21, 0.54]	*.38*	.004	-0.00	[-0.37, 0.38]	*.98*	
ZM1 total raw score	-1.92	[-3.67, -0.18]	*.03**	.021	-0.23	[-1.73, 1.27]	*.76*	.001	0.40	[-1.05, 1.86]	*.58*	.001
ZM2 total time taken (seconds) ^	19.05	[8.15, 29.95]	*.001***	.058	4.18	[-4.64, 12.99]	*.35*	.005	0.80	[-7.97, 9.57]	*.85*	.000
ZM2 total number of errors ^	0.34	[-0.36, 1.05]	*.33*	.003	0.02	[-0.79, 0.84]	*.96*	.000	0.43	[-0.31, 1.17]	*.25*	.007
ZM2 total raw score	-1.03	[-2.41, 0.35]	*.14*	.015	-0.38	[-1.29, 0.53]	*.41*	.004	-0.46	[-1.33, 0.41]	*.29*	.006
6PT total rule break errors ^	0.17	[-0.46, 0.81]	*.59*	.002	-0.25	[-0.78, 0.27]	*.34*	.005	0.05	[-0.50, 0.60]	*.86*	.000
6PT utilised a pattern strategy	-0.23	[-1.14, 0.67]	*.61*		0.50	[-0.17, 1.17]	*.14*		-0.64	[-1.29, 0.01]	*.053*	
6PT total raw score	-0.71	[-2.13, 0.70]	*.32*	.007	0.93	[-0.03, 1.90]	*.057*	.018	-0.68	[-1.70, 0.33]	*.18*	.011

DKEFS												
Tower Test total achievement raw score	-1.57	[-2.87, 0.27]	*.018***	.037	0.19	[-0.72, 1.10]	*.68*	.000	-0.64	[-1.56, 0.29]	*.17*	.011
RCFT												
Copy raw score	-1.98	[-3.95, -0.00]	*.05**	.025	-1.13	[-2.59, 0.33]	*.12*	.010	-2.36	[-3.72, 0.99]	*.001***	.052
Utilised part configurable strategy or better	-1.87	[-3.39, -0.35]	*.016**		-.45	[-1.66, 0.75]	*.46*		-0.91	[-1.97, 0.15]	*.09*	
BRIEF												
Plan/organize difficulties; at risk and above range ^	2.50	[-1.89, 6.88]	*.26*		1.62	[-0.93, 4.16]	*.21*		4.07	[-0.87, 9.01]	*.10*	
Organization of materials difficulties; at risk and above range ^	1.30	[-2.10, 4.70]	*.45*		1.22	[-1.54, 3.98]	*.38*		-2.74	[-5.25, -0.22]	*.03**	

Note. Outcome *measure n* ranges from 162 to 175 depending on the outcome; ^ = higher scores reflects worse performance; BADS-C = Behavioural Assessment of the Dysexecutive System for Children; ZM 1 = Zoo Map 1; ZM 2 = Zoo Map 2; 6PT = 6 Part Test; DKEFS = Delis-Kaplan Executive Function Systems; RCFT = Rey Complex Figure Test; BRIEF = Behavior Rating Inventory of Executive Function; *b* = coefficient for group from the regression model representing the increase in the dependent variable for every 1 unit increase in the independent variable; CI = confidence interval.

$^{**}p < .05$; $^{***}p < .01$.

3.8. Discussion

In the current study, VP 13-year-olds exhibited poorer goal setting than their FT born peers with a clear pattern of impairment and inefficiency across multiple measures, including parent report of everyday behaviour. Brain abnormality on neonatal MRI at term equivalent age was significantly associated with adverse performance on some goal setting measures.

Our findings provide further support that the VP population underperforms on goal setting measures (Aarnoudse-Moens et al., 2012; Anderson & Doyle, 2004; Curtis et al., 2002; Harvey et al., 1999; Loe et al., 2015; Marlow et al., 2007; Scott et al., 2012; Taylor et al., 2004). However, our study adds to the existing literature in that we performed a detailed assessment of goal setting in later childhood, enabling examination of group differences on multiple measures. Regardless of the degree of structure inbuilt into the task, the VP group generally displayed slower completion times and higher error rates than full-term controls, which may reflect slower information processing speed (Murray et al., 2014; Rose & Feldman, 1996) and/or poorer attention (i.e., shifting; Anderson et al., 2011; Mulder et al., 2010; Shum, Neulinger, O'Callaghan, & Mohay, 2008). Working memory difficulties in VP groups (Anderson & Doyle, 2003; Böhm et al., 2004; Omizzolo et al., 2013) are well recognised and may have contributed to difficulties maintaining an instructional set across goal setting tasks. Variables measuring strategy use failed to reach significance, despite the VP children performing more poorly across these tasks overall. Goal setting can be considered a top-down cognitive process. Strategic planning is required to achieve a goal, followed by the implementation of the plan which often involves a number of steps integrating and coordinating other cognitive domains (Friedman et al., 2006; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). Accordingly, deficits in other cognitive domains are likely to impede effective goal setting. For example, working memory is required to remember and execute each step, and active shifting of one's attention is required between the planning and execution of the goal. An alternative explanation however might be that the variables assessing strategy use failed to reach significance due to their qualitative nature which lacks the sensitivity necessary to detect subtle differences in higher level reasoning.

Planning/organisation difficulties in everyday settings (e.g. home and school) have been previously reported by parents of VP children (Anderson & Doyle, 2004; Loe et al., 2015), as

well as by teacher report (Scott et al., 2012). Performance decrements on neuropsychological measures that align with parent and teacher reports provide reassurance that the findings are robust. Parent reported planning and organisation difficulties of VP children are likely to reflect functional consequences, such as underestimating time needed to finish tasks, difficulties studying to achieve sound grades, or being overwhelmed by large tasks (e.g., school assignments; Gioia et al., 2000). As this is a cross-sectional analysis, we cannot comment on the trajectory of goal setting deficits in the VP population. The deficits documented are similar to that reported in preschool and early school-aged children born VP (Anderson & Doyle, 2004; Harvey et al., 1999; Loe et al., 2015; Marlow et al., 2007; Scott et al., 2012), and while this suggests an ongoing impairment, it is possible that developmental catch-up occurs later in adolescence and early adulthood.

The overall findings were largely robust, with the majority of group differences remaining unaltered when accounting for sex and social risk, factors known to be associated with cognitive outcomes (Anderson, Anderson, Northam, et al., 2001). It was also demonstrated that goal setting deficits cannot solely be explained by low IQ or significant neurosensory impairment (i.e., cerebral palsy, blindness, deafness), consistent with previous studies examining executive outcomes of VP children during late childhood (Aarnoudse-Moens et al., 2012; Anderson & Doyle, 2004; Bohm et al., 2004; Marlow et al., 2007).

This is the first study that we are aware of that demonstrates an association between moderate to severe brain abnormalities on neonatal MRI and poorer goal setting performances in late childhood, in terms of overall accuracy as well as inefficiency. While this is a new finding, it adds to previous research documenting the capacity of brain abnormalities to predict other executive functioning difficulties during early childhood (Clark & Woodward, 2010; Edgin et al., 2008; Woodward et al., 2006; Woodward et al., 2011; Young et al., 2016). VP birth is associated with wide ranging structural and functional neural alterations that are likely to compromise numerous cognitive functions including goal setting. For example, MRI studies with VP neonates have shown a high prevalence of structural brain abnormalities including diffuse white matter pathology (punctate to cystic lesions, loss of white matter volume, thinning of the corpus callosum, and delayed myelination), as well as delayed development of the cortex, subcortical gray matter and cerebellar structures (Inder et al.,

2003; Maalouf et al., 1999). Quantitative MRI has demonstrated volumetric reductions in VP infants, children and adults in cortical, subcortical and cerebellar structures including the cerebellum, corpus callosum, basal ganglia, hippocampi, and midtemporal and parietooccipital regions (Inder, Warfield, Wang, Hüppi, & Volpe, 2005; Petersen et al., 2000; Shah et al., 2006). Diffusion imaging reveals delayed microstructural development of many major white tracts in VP neonates and children including the central and frontal white matter, corpus callosum (Counsell et al., 2003; Kaur, Powell, He, Pierson, & Parikh, 2014; Thompson et al., 2011), while functional imaging studies suggest alterations to thalamo-cortical networks (Smyser et al., 2010). However, the specific neural alterations associated with goal setting impairments are yet to be explored. While further research characterising this relationship in more detail is required, the current study contributes to the literature by demonstrating a link between the severity of brain abnormalities and goal setting abilities, particularly during late childhood.

Contrary to expectations, there was minimal evidence for a relationship between goal setting skills and neonatal medical risk or sex in the VP group. These results aligned with the view that the predictive value of neonatal risk factors on neurodevelopmental outcome reduces with age, possibly as a result of the increasing influence of social and environmental factors (Doyle et al., 2015; Miceli et al., 2000; Weisglas-Kuperus, Baerts, Smrkovsky, & Sauer, 1993).

For such a long-term follow-up study, our retention for both the VP and FT groups was excellent. However, the study had unequal sample sizes, and despite substantial effort the VP and FT groups were not matched on sociodemographic factors. Accordingly, the analyses for social risk were adjusted, which in general made little difference to the overall findings. Further research is needed to examine the developmental trajectory of goal setting skills, which ideally would span from the preschool period through to early adulthood. In addition, future research ought to examine the ramifications of VP goal setting impairments upon academic success and social skills during late childhood, given that impaired cognition is known to have a negative functional impact upon these domains (Alduncin, Huffman, Feldman, & Loe, 2014; Johnson, Wolke, Hennessy, & Marlow, 2011). Also, understanding the neural correlates associated with these difficulties using concurrent neuroimaging may assist

in understanding the underlying biological mechanisms and inform possible neurorecovery and neuroremediative strategies.

In summary, our findings extend current understanding of the extent and nature of goal setting impairments in VP children, and substantiate the capacity of neonatal brain abnormalities to predict later cognitive deficits, including executive functioning. Goal setting deficits are likely to have ramifications for academic success (Best, Miller, & Naglieri, 2011; Curtis et al., 2002), and subsequent vocational prospects, and as such these findings have implications for educators and parents of VP children in terms of ongoing surveillance, early detection and remediation strategies.

Chapter 4. Neonatal brain abnormalities and brain volumes associated with goal setting outcomes in very preterm 13 year olds

Chapter 4

4.1. Declaration for thesis chapter 4

Monash University

Declaration for Thesis chapter 4

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Data collection, generation of research questions, literature review, data analysis, results, interpretation, manuscript	65

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Catherine Willmott	Generation of research questions, data analysis, input into manuscript	7.5
Shannon Scratch	Data collection, input into manuscript	5 collectively
Leona Pascoe	Data collection, input into manuscript	
Kate Lee	Statistical consultation, input into manuscript	
Megan Spencer-Smith	Input into manuscript	
Jeanie Cheong	Input into manuscript	
Terrie Inder	Input into manuscript	
Lex Doyle	Input into manuscript	
Deanne Thompson	Generation of research questions, data analysis, input into manuscript	10
Peter Anderson	Generation of research questions, data analysis, input into manuscript	10

Candidate's signature: [redacted] **Date:** 3rd July 2018

Main supervisor's signature: [redacted] **Date:** 3rd July 2018

4.2. Overview

This chapter presents an empirical paper titled *"Neonatal brain abnormalities and brain volumes associated with goal setting outcomes in very preterm 13- year-olds",* submitted to Brain Imaging and Behavior. This paper investigated brain abnormalities and brain volumes during the neonatal period, in association with goal setting difficulties of very preterm children at 13 years of age. We identified specific neurological characteristics of very preterm birth that predispose these children to later associated goal setting difficulties. We also extended upon literature examining the predictive capabilities of neonatal magnetic resonance imaging, focusing on goal setting abilities of a VP sample.

4.3. Abstract

Objective: Executive dysfunction including goal setting deficits (i.e., planning, organisation skills, strategic reasoning) is documented in children born very preterm (VP; <30 weeks/<1250 grams), however the neurological basis for this impairment is unknown. This study sought to examine the relationship between brain abnormalities and brain volumes on neonatal magnetic resonance imaging (MRI) and goal setting abilities of VP 13-year-olds.

Method: Participants were 159 VP children in a prospective longitudinal study. Qualitative brain abnormality scores and quantitative brain volumes were derived from neonatal MRI brain scans (40 weeks' gestational age +/- 2 weeks). Goal setting at 13 years was assessed using the Delis-Kaplan Executive Function Systems Tower Test, the Rey Complex Figure, and the Behavioural Assessment of the Dysexecutive System for Children Zoo Map and Six Part Test. A composite score was generated denoting overall performance on these goal setting measures. Separate regression models examined the association of neonatal brain abnormality scores and brain volumes with goal setting performance.

Results: Higher neonatal global brain, white matter, deep gray matter and cerebellum abnormality scores were associated with poorer goal setting scores at 13 years. There were positive associations between total brain volume, cerebellum, thalamic and cortical gray matter volumes and goal setting performance. Associations largely persisted after controlling for potential confounders.

Conclusions: Neonatal brain abnormality and brain volumes are associated with goal setting outcome in VP 13-year-olds. Used in conjunction with other clinical indicators, neonatal MRI may help to identify VP children at risk for later executive dysfunction.

4.4. Introduction

Up to 60% of children born very preterm (VP; <32 weeks' gestation) exhibit cognitive deficits in late childhood (P. J. Anderson & Doyle, 2003). Of particular concern are impairments in executive function (EF; Burnett, Scratch, & Anderson, 2013), a set of cognitive abilities essential for reasoning, goal-directed and adaptive behaviour (P. J. Anderson, 2002; Lezak, Howieson, Bigler, & Tranel, 2012), including goal setting, cognitive flexibility, and attentional control abilities. Specifically, VP children experience deficits in complex attention (i.e., shifting, sustained, selective, and divided), impulse control, working memory, verbal fluency, and reasoning abilities compared with their full-term born peers (P. J. Anderson et al., 2011; P. J. Anderson & L. W. Doyle, for the Victorian Infant Collaborative Study Group., 2004; Bohm et al., 2004; Taylor, Hack, & Klein, 1998).

Goal setting, a key EF component, pertains to high level conceptual reasoning, the ability to organise a series of steps and formulate a strategy or establish a plan to work towards goal completion (P. J. Anderson, 2002). Goal setting competence is important for children to succeed in new and increasingly complex environments such as secondary school. Therefore, difficulties with reasoning, planning, organisation, or overreliance on previously learnt strategies are likely to be associated with poorer academic, social, emotional and/ or behavioural outcomes (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, et al., 2013; Alduncin, Huffman, Feldman, & Loe, 2014; P. J. Anderson, 2002; Breslau & Chilcoat, 2000). We have recently reported goal setting deficits in VP 13-year-olds compared with their full-term peers across a battery of measures, consistent with findings from earlier studies with younger children (P. J. Anderson & L. W. Doyle, for the Victorian Infant Collaborative Study Group., 2004; Haebich et al., 2017; J. M. Harvey et al., 1999; Loe et al., 2015; Marlow et al., 2007; Scott et al., 2012).

The neural network underpinning specific executive abilities, including goal setting, is diffuse, involving a wide network including the prefrontal cortex, parietal lobes, subcortical structures (i.e., basal ganglia, thalamus), and the cerebellum (Baker et al., 1996; Morris et al., 1993; Newman et al., 2003; O. A. van den Heuvel et al., 2003). Executive function deficits in VP children may be explained by the diffuse brain pathology commonly associated with VP birth (Ortinau & Neil, 2014). Very preterm infants are born during a period of rapid and dynamic brain development, and episodes of hypoxic-ischemia, infection, and inflammation are likely to compromise programmed brain maturational processes such as neuronal proliferation, migration and differentiation, as well as myelination (Adams-Chapman, 2009; Leviton & Gressens, 2007; Stiles & Jernigan, 2010). Common abnormalities

observed on neonatal brain magnetic resonance imaging (MRI) includes white matter lesions, loss of white matter, enlarged lateral ventricles, thinning of the corpus callosum, delayed myelination and cortical folding, and increased extracerebral space (P. J. Anderson et al., 2015; Counsell & Boardman, 2005; Inder et al., 2003; Thompson et al., 2014). In addition, volumetric MRI has demonstrated smaller brains of VP neonates, with selective cortical regions, basal ganglia, thalamus, corpus callosum, cerebellum and hippocampus being particularly vulnerable (Thompson, Inder, et al., 2012; Thompson et al., 2014; Thompson et al., 2008; Volpe, 2009a).

Neonatal brain abnormalities and reduced brain volumes based on qualitative review of MRI have been associated with later cognitive difficulties in young VP children. More severe neonatal white matter abnormalities have been associated with poorer neurodevelopmental and motor outcomes in VP infants (S. P. Miller et al., 2005; Woodward, Anderson, Austin, Howard, & Inder, 2006). In preschool and school-aged children, more severe neonatal global brain, white matter, deep gray matter and cerebellum abnormality scores have been related to poorer general cognitive ability, language, attention, memory and learning abilities (P. J. Anderson et al., 2017; Murray et al., 2014; Omizzolo et al., 2013; Woodward et al., 2012). Regarding brain volumes, reductions in neonatal cerebellum, basal ganglia, thalamus, and hippocampal volumes have been related to poorer language, reasoning ability, memory and learning abilities, as well as academic and motor difficulties in VP children (Loh et al., 2017; D. K. Shah et al., 2006; Thompson et al., 2008).

Few studies have examined neonatal MRI parameters in association with EF outcomes in VP children. In preschool and school-aged children, more severe white and gray matter abnormality scores and smaller deep gray matter volumes have been related to poorer working memory, inhibition, cognitive flexibility, problem solving and goal setting abilities of VP children, independent of other perinatal risk factors (Clark & Woodward, 2010; Edgin et al., 2008; Woodward et al., 2012). Recently, Loh et al. (2017) demonstrated a positive association between neonatal basal ganglia and thalamic volumes and poorer goal setting performances at 7 years. In the context of these preliminary goal setting findings in preschool and early school-age children, further examination of goal setting in late childhood is of interest given EF development is an ongoing process (P. J. Anderson, Anderson, & Lajoie, 1996). Goal setting abilities, in particular, are integral to development of independent thinking and self-management skills which children may increasingly rely on throughout late childhood as they encounter new and progressively more complex environments (e.g., secondary school; Haebich et al.,

2017; Luu, Ment, Allan, Schneider, & Vohr, 2011).

This study sought to examine the association between neonatal brain abnormalities and volumes, with goal setting abilities of VP children at 13 years of age. We hypothesised that more severe brain abnormality (specifically white matter, deep gray matter, and cerebellum), and decreased brain volumes (specifically white matter, corpus callosum, thalamus, basal ganglia, and cerebellum) at term-equivalent age would be associated with poorer goal setting performance in 13-year-old VP children. Understanding whether neonatal brain measurements are associated with later goal setting deficits in VP children would contribute to the growing literature examining the use of neonatal MRI as a diagnostic tool. Further, in clinical settings neonatal MRI may assist with the early identification of higher risk infants who warrant closer surveillance and who may benefit from early interventions (i.e., neuropsychological compensatory strategies).

4.5. Methods

4.5.1. Participants and procedure

Participants were part of the Victorian Infant Brain Study (VIBeS) cohort, a longitudinal study examining the development of children born VP (<30 weeks' gestation) and/or very low birth weight (<1250 g) in comparison to healthy control children born at term (≥ 37 to ≤ 41 weeks' gestation) and of normal birth weight (≥ 2500 g). Two hundred and twenty-seven VP participants without genetic or congenital abnormalities known to affect development were originally recruited between July 2001 and December 2003 at the Royal Women's Hospital, Melbourne. Three infants subsequently died, leaving 224 VP survivors. Perinatal characteristics were obtained by chart review, including birth weight, GA (both at birth and at scan), small for GA (defined as birth weight SD score > 2 standard deviations below mean weight for GA computed relative to the British growth reference data; Cole, Freeman, & Preece, 1998), multiple birth, received postnatal corticosteroids, bronchopulmonary dysplasia (BPD; defined as oxygen dependency at 36 weeks' GA), and proven sepsis or necrotising enterocolitis (NEC).

At term-equivalent age (target window - 38 to 42 weeks' gestation), MR images for the VP infants were acquired. 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).

Children were followed up at 2, 5, 7 and 13 years of age. Age was corrected for prematurity at all time points to avoid a known bias in cognitive test scores (Wilson-Ching et al., 2014). Neurosensory impairment (defined as either moderate or severe cerebral palsy, any deafness or any blindness) was diagnosed by a paediatrician at the 7-year follow up.

At the 13-year follow up, 224 VP children were eligible to participate in the current study. Eleven participants had withdrawn from the study and 34 were lost to follow up (uncontactable, n = 10; declined/failed to attend, n = 24), leaving a potential sample of 179 VP participants (80%). Of these, 16 were excluded because their neonatal MRI was conducted outside the target window for scanning (i.e., 38 to 42 weeks gestational age) and 4 were unable to complete goal setting tests due to significant intellectual or physical impairment, leaving a sample of 159 participants.

This study was approved by the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, and informed written consent was obtained from the parents at all time points.

4.5.2. Imaging

For the MRI brain scans, infants were fed, settled, and fitted with earmuffs and placed in a Vac Fix beanbag to reduce motion, before being scanned without sedation. Structural T_1 (0.8-1.6 mm coronal slices; repetition time 35 ms; echo time 9 ms; flip angle 45°; field of view 210x158 mm; matrix 256x192) and T_2-weighted (1.7-3.0 mm coronal slices; repetition time 4000 ms; echo time 60/160 ms; flip angle 90°; field of view 220x160 mm; matrix 256x192, interpolated 512x512) sequences were obtained with a 1.5 Tesla General Electric MRI scanner (Signa LX Echospeed System; General Electric, Milwaukee, WI).

4.5.3. Brain abnormalities

Neonatal T_1 and T_2 brain scans were reviewed for cerebral abnormality by an experienced neonatal neurologist using the rating system described by Kidokoro et al. (2013). The scoring system gives an overall rating of white matter (WM) abnormality, cortical gray matter (CGM) abnormality, deep gray matter (DGM) abnormality, cerebellum abnormality and global brain abnormality. The WM abnormality scale (range 0 to 17) is the sum of 6 subscales assessing the presence and severity of cystic lesions, signal abnormality, myelination delay, thinning of the corpus callosum, lateral ventricle

dilation, and volume reduction. The CGM abnormality scale (range 0 to 9) is the sum of 3 subscales assessing signal abnormality, delayed gyral maturation and increased extracerebral space. The DGM and cerebellum abnormality scale (range 0 to 7) have 2 subscales assessing signal abnormality and volume reduction. The global brain abnormality scale (range 0 to 40) is generated by summing the WM, CGM, DGM, and cerebellum scales. Higher scores across all abnormality scales reflect greater severity. This rating system has excellent interrater and intrarater reliabilities (intraclass correlation coefficient > .90; Kidokoro et al., 2013).

4.5.4. Brain volumes

Volumes of WM, CGM, cerebellum, total brain tissue and intracranial cavity were derived from the Morphologically Adaptive Neonatal Tissue Segmentation (MANTiS) technique, applied to T_2 structural images at term equivalent age (Beare et al., 2016). Basal ganglia and thalamus volumes were obtained from the combined T_2- and proton density-weighted images (Thompson, Ahmadzai, et al., 2012) using the Pediatric Subcortical Segmentation Technique (Loh et al., 2016), as previously described (Loh et al., 2017). Hippocampi were manually traced with 3D slicer 2.5 software (http://slicer.org/) by a single operator on the combined raw T_2- and proton density–weighted images, as previously described (Thompson, Ahmadzai, et al., 2012). The corpus callosum area was traced on the mid-sagittal slice of the structural T_1 scan that had been manually aligned along the anterior–posterior commissure line, as previously described (Thompson et al., 2011). Poorer brain growth is reflected by smaller volumes (R. W. Cooke, 2010).

4.5.5. Goal setting

A composite score of goal setting was generated in order to provide a global measure of this ability (i.e., includes core components of goal setting assessed across multiple measures), as well as to reduce measurement error and the number of analyses conducted. The goal setting composite was generated for each participant using scores from the following measures:

From the *Delis-Kaplan Executive Function Systems* (D-KEFS; Delis, Kaplan, & Kramer, 2001) the Tower Test was administered to estimate spatial planning, rule learning, inhibition of impulsive and perseverative responding, and the ability to establish and maintain instructional set. The total

achievement score was used, which represents the number of correct towers assembled within specific time limits.

The *Rey Complex Figure Test* (RCFT) involves reproducing a geometric line drawing (Anderson, Anderson, & Garth, 2001). The Copy accuracy and organisational strategy scores were used to estimate spatial planning and planning strategy. Copy Accuracy was judged using the 18 item accuracy criteria established by Osterrieth (1944). Organisational strategy was based on the RCFT Organizational Strategy score (Anderson, Anderson, & Garth, 2001), which classifies drawings into 7 categories according to set criteria from 1 = unrecognizable/substitution to 7 = excellent organization.

From the *Behavioural Assessment of the Dysexecutive System for Children* (BADS-C; Emslie, Wilson, Burden, Nimmo-Smith, & Wilson, 2003) the Zoo Map and Six Part Test were used. Zoo Map captures the ability to plan and execute a specific eight-location sequence in accordance with several rules. The total score was used, which is calculated from the number of correct locations visited, including deductions for rule breaks. The Six Part Test examines planning, task scheduling and performance monitoring skills by asking participants to complete 6 simple tasks in 5 minutes following several rules. The total score was used, which accounts for effective strategy/pattern as well as point deductions for rule breaks.

To generate the goal setting composite, the DKEFS Tower Test total achievement score, the RCFT Copy Accuracy score and Organizational Strategy score, and the BADS-C Zoo Map 1 and Six Part Test total scores raw scores were converted into *z* scores (based on the mean (M) and standard deviation (*SD*)) of the study's full-term control group (*n* = 61). We have previously reported on the goal setting skills of this full-term control sample (see Haebich et al., 2017). Individual *z* scores were then averaged in order to calculate a composite goal setting *z* score for each participant. For 5 participants with a missing value for up to 2 of the 5 goal setting tests (equipment failure, *n* = 2; could not complete due to reduced comprehension/intellectual disability/misunderstanding, *n* = 3), their missing values were replaced with the average of their non-missing *z* score values. Lower *z* scores are indicative of poorer goal setting ability. The internal consistency of this composite score was reasonable (Cronbach alpha = .67, range = .54 to .71).

4.6. Statistical analysis

Data from the neonatal period and 13-year follow-up were analysed in Stata 14.2 (StataCorp, College Station, Texas).

A standardised version of each quantitative brain volume variable was calculated, due to differences in measurement scales across these variables (i.e., corpus callosum measured in cm^2 versus other volumes in cm^3), to enable comparisons to be made between the regression coefficients.

Separate primary, secondary and tertiary linear regression models were conducted to examine the relationship between each individual qualitative and quantitative brain variable and goal setting outcome. Models were fitted using generalised estimating equations reported with robust standard errors to allow for clustering of multiples within a family (i.e., twins/triplets). Primary analyses covaried for sex and age at scan. All quantitative brain volume analyses additionally covaried for intracranial brain volume (ICV). To ensure the independent contribution of neonatal MRI brain volumes and abnormalities, secondary analyses additionally covaried for perinatal factors known to affect cognitive outcomes, namely birth weight, GA, small for GA, BPD, sepsis or NEC (Duvall et al., 2014; Young et al., 2016). Tertiary analyses further excluded children with significant neurosensory impairment or an IQ less than or equal to 70 (n = 12), to ensure that associations were not due to a small number of significantly impaired VP children.

Given the large number of predictors considered in this analysis, findings are interpreted based on the pattern of the results (direction and magnitude of differences across measures) rather than focussing on the p-values.

4.7. Results

The final sample consisted of 159 VP participants (75% of eligible children) with a composite goal setting z score and neonatal MRI data. See Table 4.1 for characteristics of the VP participants. The baseline characteristics were similar between VP participants and VP non-participants across the available neonatal and sociodemographic variables (data not shown). Neonatal and sociodemographic characteristics were largely representative of VP cohorts born in Australia (Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013).

Table 4.1. Sample characteristics

	VP (N = 159)^
Neonatal Characteristics	
Gestational age (weeks), M (SD)	27.5 (1.9)
Birth weight (grams), M (SD)	973.1 (222.8)
Small for gestational age, n (%)	15 (7.9)
Male sex, n (%)	82 (51.6)
Multiple birth, n (%)	75 (47.2)
Postnatal corticosteroids, n (%)	12 (7.6)
Necrotising enterocolitis, n (%)	7 (4.4)
Bronchopulmonary dysplasia, n (%)	53 (33.3)
Any sepsis, n (%)	51 (32.1)
Grade 3/4 intraventricular haemorrhage, n (%)	7 (4.4)
Cystic periventricular leukomalacia, n (%)	3 (1.9)
Sociodemographic Characteristics at 13 years	
Higher social risk[a], n (%)	87 (54.7)
Maternal age at birth (years), M (SD)	30.5 (5.5)
Intact family, n (%)	105 (66)
Primary caregiver with tertiary education, n (%)	56 (35.2)
Recipient of allied health services since 7 year follow-up (OT, psychology, physio, ST), n (%)	50 (31.5)
General Outcomes at 13	
Corrected age at testing (years), M (SD)	13.3 (0.4)
FSIQ[b], M (SD)	100 (18.3)

Note. ^Some sample sizes are less than the total sample due to missing data (maternal age at birth [*n* = 158], Intact family [*n* = 151], tertiary education [*n* = 142], social risk [*n* = 151], allied health service [*n* = 146]). N = total sample size; n = sample size; *%* = percentage; M = mean; SD = standard deviation; ST = speech therapy; yo = years old; OT = occupational therapy; CI = confidence interval; FSIQ = full scale intelligence quotient; [a]Social Risk - cumulative scale of 0 to 12 taking into account family structure, employment status, occupation, educational level, language spoken, and maternal age at birth. Higher scores reflect greater level of social risk (G. Roberts et al., 2008); [b]based on performance on the Kaufman Brief Intelligence Test, Second Edition (A. S. Kaufman & Kaufman, 2004).

4.7.1. Neonatal brain abnormalities and goal setting

Neonatal brain abnormality scores are presented in Appendix 8.1. There was a consistent pattern of greater severity in neonatal brain abnormality scores associated with poorer goal setting ability in VP children at 13 years of age (see Figure 4.1.). In particular, there was evidence that higher global brain, WM, DGM and cerebellum abnormality scores were associated with significantly poorer goal setting ability, with these associations largely persisting after adjustment for perinatal risk factors and strengthened after excluding children with IQ under 70 and/or significant neurosensory impairment. The association between CGM abnormality and poorer goal setting scores was weaker.

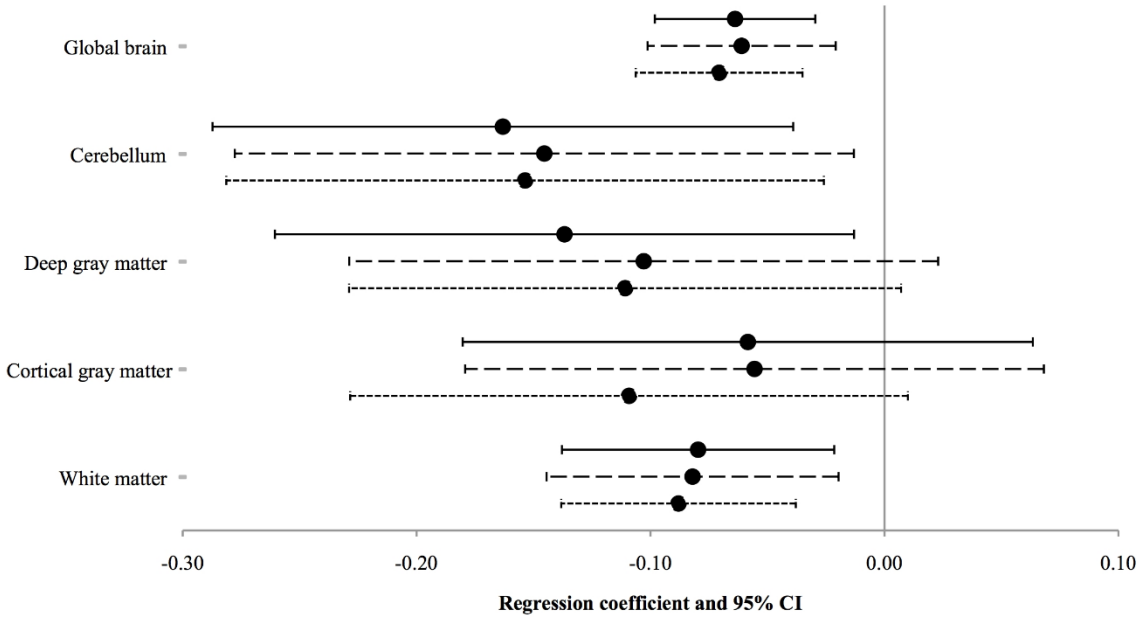

Figure 4.1. Regression coefficients and 95% confidence intervals (CI) for the association between neonatal brain abnormalities and goal setting ability in VP children at 13 years of age. Regression coefficients represent the change in goal setting ability per unit increase in severity of brain abnormality score. The solid line represents the results from the primary analysis adjusted for sex, age at scan and intracranial volume (n = 159), the dashed line represents the results from the secondary analysis adjusting for sex, age at scan, intracranial volume, birth weight, gestational age, small for gestational age, necrotising enterocolitis, sepsis and bronchopulmonary dysplasia (n = 159), and the dotted line represents the results from the tertiary analysis which additionally exclude those with IQ <70 and/or neurosensory impairment (n = 138).

4.7.2. Neonatal brain volumes and goal setting

Neonatal brain volumes are presented in Appendix 8.2. There was evidence for positive associations between neonatal brain volumes and goal setting performance at 13 years of age (see Figure 4.2.). Greater total brain volume was associated with better goal setting performance, although the association weakened after excluding children with IQ under 70 and/or significant neurosensory impairment. Greater cerebellum, thalamus and cortical gray matter volumes were associated with better goal setting performances, across primary and secondary analyses, and persisted after adjustment for perinatal risk factors. Unstandardised coefficients for associations between goal setting and neonatal brain volumes are presented in Appendix 8.3.

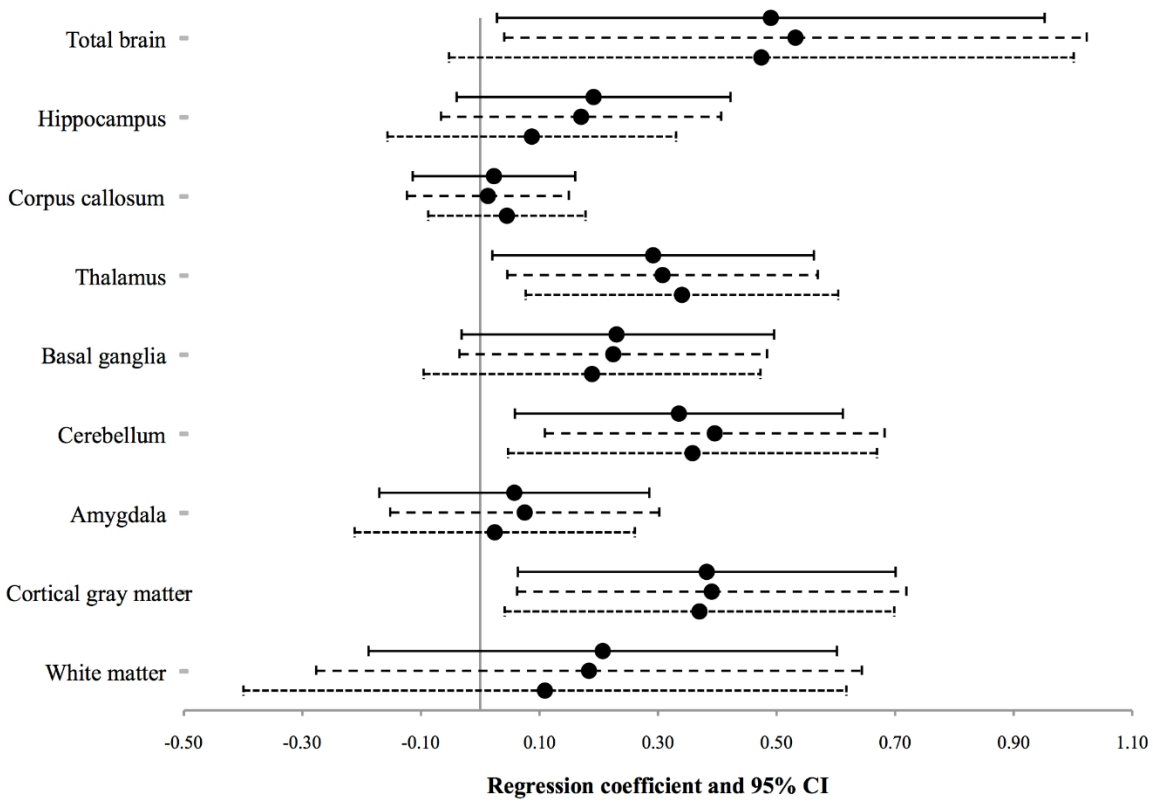

Figure 4.2. Regression coefficients and 95% confidence intervals (CI) for the association between neonatal brain volumes and goal setting ability in VP children at 13 years of age using standardised values. Regression coefficients represent the change in goal setting ability per unit increase in brain volume. All volumes were measured in cm^3, with the exception of the corpus callosum, which was measure in cm^2. The solid line represents the results from the primary analysis adjusted for sex, age at

scan and intracranial volume (n = 159), the dashed line represents the results from the secondary analysis adjusting for sex, age at scan, intracranial volume, birth weight, gestational age, small for gestational age, necrotising enterocolitis, sepsis and bronchopulmonary dysplasia (n = 159), and the dotted line represents the results from the tertiary analysis which additionally exclude those with IQ <70 and/or neurosensory impairment (n = 138).

4.8. Discussion

The current study demonstrates that better goal setting ability at 13 years of age in VP children is negatively associated with less severe brain abnormality and is positively associated with diffuse WM abnormalities (Khwaja & Volpe, 2008). Given the high prevalence of WM abnormalities reported in VP cohorts on MRI, where up to 71% have mild to severe WM abnormality (Inder et al., 2003), and the role of WM in goal setting proficiency (Tullberg et al., 2004), the association between neonatal WM abnormality and later goal setting outcome is not surprising. In contrast, the evidence that neonatal WM volumes were associated with later goal setting outcomes was weak, suggesting that features of WM pathology and maturation are more important in the development of goal setting abilities than quantitative volume.

To the best of our knowledge, our study is the first to specifically examine the relationship between neonatal cerebellum pathology and goal setting abilities in VP children. Increasing severity of neonatal cerebellum abnormalities and decreasing cerebellar volumes were associated with poorer goal setting in late childhood. DGM abnormalities were similarly associated with later goal setting performance, and there was evidence that thalamic volume was positively related goal setting but the evidence was weaker for basal ganglia volume. In our cohort, the prevalence of DGM and cerebellum lesions was low, and abnormality in these structures mostly referred to delayed maturation and reduced volume inferred from linear measures of cerebellum diameter and 2D measures of DGM. While our findings provide initial evidence that early growth of the cerebellum and DGM structures is predictive of later goal setting ability, further research is needed to confirm these findings.

We previously reported no association between neonatal basal ganglia volume and goal setting at 7 years in VP children (Loh et al. (2017), consistent with the current study, however this earlier study also noted no association between thalamic volume and later functioning, which is contrary to what we found at 13 years. Given the procedure for estimating thalamic volumes were identical at 7 and 13

years, this discrepancy in findings may reflect the different age at assessment (i.e., 7 versus 13 years) or different outcomes measures.

DGM and cerebellum abnormalities and volume reductions are well documented in the VP population (Limperopoulos et al., 2007; Volpe, 2009b), and neuroimaging research indicates that both DGM (Monchi, Petrides, Strafella, Worsley, & Doyon, 2006; Owen, McMillan, Laird, & Bullmore, 2005) and cerebellum regions are integral for planning ability, an important component of goal setting (Baker et al., 1996; J. B. Rowe, Owen, Johnsrude, & Passingham, 2001). Fronto-striatal-cerebellar circuits connect DGM and cerebellum regions with the prefrontal cortex, facilitating communication (Krienen & Buckner, 2009; Schmahmann, 1996) and mediating EF abilities (Elliott, 2003). Thus, we speculate that the early disruption to DGM and cerebellum development, as observed in VP infants, may interfere with the development of fronto-striatal-cerebellar networks, leading to compromised goal setting abilities. Further neuroimaging research exploring the neuroanatomical networks underpinning fronto-striatal-cerebellar circuits of DGM and cerebellum is needed, to better understand the neural circuitry underlying goal setting impairments.

In our study CGM abnormality in VP infants presented as delayed cortical folding and enlarged extra-cerebral space, with limited evidence of cortical lesions. There was little evidence that this pattern of abnormality was related to goal setting in late childhood, consistent with previous research that has examined the association of CGM abnormality with children's attention, general intelligence, academics, motor function and behaviour (P. J. Anderson et al., 2017; Murray et al., 2014). Delayed gyral maturation and increased extracerebral space in VP children may resolve across development (Huppi et al., 1998), and based on research to date, probably reflects developmental delay rather than irreversible cortical abnormalities (P. J. Anderson et al., 2017). In contrast, greater neonatal CGM volumes were related to better goal setting outcomes at 13 years, demonstrating the value of assessing both cortical abnormality and volume. CGM volumes in VP neonates have been consistently shown to be reduced (Inder et al., 1999; Peterson et al., 2003) due to disrupted cortical development during the last trimester (i.e., neural differentiation; M. S. van der Knaap et al., 1996), which generally reflects atypical brain maturation and has been associated with poorer neurodevelopmental outcomes (J. L. Y. Cheong et al., 2016; Peterson, Vohr, Staib, & et al., 2000). This may be a result of altered connections between the prefrontal cortex and other cortical regions such as association cortex (P. J. Anderson, 2002; V. A. Anderson, Anderson, Jacobs, & Spencer-Smith, 2008). Goal setting or other

executive abilities have not previously been examined in relation to neonatal CGM volumes to the best of our knowledge. We have shown that neonatal volumetric quantification is positively associated with goal setting outcomes in late childhood. Further research is required to validate or refute the findings of the current study.

Associations were not found between neonatal amygdala, and hippocampi volumes and goal setting in our VP 13-year-olds. While these structures have connections with the prefrontal regions (Unterrainer & Owen, 2006) important for EF such as goal setting, the primary role of these brain structures is memory, learning, affect and mood functions (Schoenberg, Marsh, & Lerner, 2011). There was also little evidence for an association between neonatal corpus callosum volumes and goal setting ability at 13 years, which was somewhat surprising given 1) the integral role of this structure in interhemispheric connections between regions integral to EF (Just, Cherkassky, Keller, Kana, & Minshew, 2007; L. J. van der Knaap & van der Ham, 2011), 2) the considerable research demonstrating that the corpus callosum is compromised in VP infants (Thompson et al., 2011), and 3) the literature demonstrating an association between corpus callosum volume and a range of cognitive and motor outcomes (Caldu et al., 2006; Peterson et al., 2000; Rademaker et al., 2004; Thompson, Inder, et al., 2012) including goal setting (Woodward et al., 2011). Possibly explaining our unexpected finding is that in VP neonates, volumetric reductions are more common in the posterior portion of the corpus callosum body, adjacent to commonly injured periventricular regions, which connect brain regions responsible for sensory processing, motor coordination, hearing, language and vision rather than higher level cognition (C. Nosarti et al., 2004; Thompson et al., 2011). In contrast, anterior and mid-body corpus callosum regions, more likely to be involved in goal setting skills, appear to be relatively preserved in VP neonates (Thompson et al., 2011). There is also some suggestion that corpus callosum development ‘catches up’ from infancy to early childhood in VP children (Thompson et al., 2015), which may help to explain the lack of association with goal setting outcomes in late childhood we observed.

Overall, the findings of this study were fairly robust, with the majority of associations remaining unaltered after adjusting for perinatal risk factors and excluding children with low IQ and/or significant neurosensory impairment. Consistent with previous research examining VP neonatal MRI parameters in relation to EF outcomes during childhood, associations were not solely explained by medical complications or severe neurodevelopmental impairments, thus indicating the general vulnerability of

VP children towards goal setting deficits (Clark & Woodward, 2010; Edgin et al., 2008; Woodward et al., 2012).

For such a long-term follow up study, the retention of our sample was excellent. Unfortunately despite our best efforts, neonatal MRI brain abnormality and volume data was not available for all participants with a composite goal setting score at 13 years. Also, while a composite goal setting measure based on 5 outcome measures provided a general assessment of VP goal setting ability at 13 years, results may have differed if an alternate selection of goal setting measure were used. The range of brain structures assessed by qualitative and quantitative measures was a unique feature of our study, enabling comprehensive examination of the structural pathology related to goal setting. It is worth noting, however, that given the longitudinal nature of this study, our neonatal brain scans were acquired across 2001 to 2003, and considerable advancements in MRI acquisition and analysis techniques have occurred since this time. Although our study provides important information about neonate MRI scans, further research is needed to examine the trajectory of neonatal brain structures in relation to goal setting outcomes, ideally spanning across early childhood, into adolescence as well as early adulthood, when goal setting is especially relevant to academic and vocational pursuits. Additional research examining the microstructural organisation and connectivity within neural networks relevant to goal setting skills is warranted, to better understand the neurophysiological mechanisms and neural substrates underlying impairment in this group during late childhood.

In summary, our findings indicate that neonatal brain abnormalities and volume reductions identified on neonatal MRI relate to goal setting impairments in VP 13-year-olds, contributing to the accumulating evidence of the predictive capabilities of neonatal MRI. Compromised goal setting is likely to have negative implications upon academic success (Best et al., 2011; W. J. Curtis et al., 2002), and vocational prospects subsequently in late adolescence and adulthood. As such, these findings are relevant to educators and parents of VP children who have experienced early brain abnormality, denoting that these children are most in need of ongoing follow-up, and may require early intervention, compensatory strategies and remediation.

Chapter 5. Resting-state connectivity and goal setting outcomes of very preterm and full-term born children at 13 years of age

Chapter 5

5.1. Declaration for thesis chapter 5

Monash University

Declaration for Thesis chapter 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Data collection, generation of research questions, literature review, pre-processing, data analysis, results, interpretation, manuscript	65

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Deanne Thompson	Generation of research questions, data analysis, input into manuscript	12.5
Catherine Willmott	Generation of research questions, data analysis, input into manuscript	7.5
Chiara Nosarti	Input into manuscript	2.5
Jian Chen	Neuroimaging preprocessing and analysis consultation, input into manuscript	5 collectively
Megan Spencer-Smith	Input into manuscript	
Terrie Inder	Input into manuscript	
Lex Doyle	Input into manuscript	
Peter Anderson	Generation of research questions, data analysis, input into manuscript	7.5

Candidate's signature: [redacted] **Date:** 3rd July 2018

Main supervisor's signature: [redacted] **Date:** 3rd July 2018

5.2. Overview

This chapter presents an empirical paper titled *"Resting-state connectivity and goal setting outcomes of very preterm and full-term born children at 13 years of age".* This completed chapter is in manuscript form and is yet to be submitted. This chapter investigated resting state connectivity networks thought to be associated with goal setting in both children born very preterm and full-term during late childhood, also examining network associations with goal setting skills during this developmental period. We characterised the nature of functional connectivity differences between very preterm and full-term groups, and described the relationship these differences may have in contributing to goal setting skills of both groups. We also extended the literature utilising resting state functional magnetic resonance imaging in very preterm samples, and demonstrated the utility of this novel neuroimaging technique for investigating prematurity as a brain network disorder related to performance deficits on neuropsychological assessment.

5.3. Abstract

Using resting state functional magnetic resonance imaging (rs-fMRI), this study aimed to examine differences between children born very preterm (VP; <30 weeks' gestation) and full-term (FT) in networks thought to be involved in goal setting, including left and right frontoparietal (lFPN, rFPN), executive control (ECN) and default mode (DMN) networks, and to examine network associations with goal setting skills in late childhood. Participants comprised 101 VP and 39 FT children from a prospective longitudinal study. Goal setting performance, represented by a composite score across several goal setting measures, and resting state neuroimaging data were acquired at 13-years of age. Separate regression models examined resting state network (RSN) group differences, and associations with goal setting outcome by birth group (VP vs FT). Results showed that VP children exhibited reduced functional connectivity compared with FT children within the rFPN, DMN and ECN, and particularly in frontal, temporal and occipital clusters, and within the lFPN, in frontal, temporal and insular clusters. VP children demonstrated greater functional connectivity than FT children in alternate frontal regions, including the frontal pole and pars triangularis. In both groups lFPN, rFPN, ECN and DMN connectivity was largely unrelated to goal setting performance. Our study supports the utility of rs-fMRI for understanding prematurity as a brain network disorder, and highlights the currently limited understanding of neural connectivity in relation to late childhood goal setting skills and deficits.

5.4. Introduction

During late childhood, children born very preterm (VP; <32 weeks gestation) demonstrate poorer goal setting abilities than their full-term (FT; >37 weeks gestation) peers (Aarnoudse-Moens et al., 2012; W. J. Curtis et al., 2002; Taylor, Minich, Bangert, et al., 2004). Their deficits include impaired conceptual reasoning, planning and organisational ability, and strategic problem solving, as well as parent reported planning and organisation difficulties in everyday life (Haebich et al., 2017). Goal setting skills are particularly important in late childhood, contributing to the development of independence and self-management skills in new and increasingly complex environments, and facilitating academic, personal and social growth (Burnett et al., 2013; Luu et al., 2011). Therefore, impaired goal setting abilities in preterm children may partly explain later academic and behaviour problems, low self-esteem and high rates of psychiatric disorders (R. W. Cooke, 2004; de Jong, Verhoeven, & van Baar, 2012; C. Nosarti et al., 2012).

Structural brain pathologies and alterations observed on neonatal magnetic resonance imaging (MRI) in VP samples have been associated with goal setting deficits during late childhood, specifically neonatal abnormalities of the cerebellum, deep gray matter, white matter and total brain (e.g., signal abnormality, cystic lesions, ventricle dilation), as well as reductions in neonatal cerebellum, thalamus, and cortical gray matter volumes (Haebich et al., 2017). The link between compromised brain regions and goal setting deficits may be explained by the diffuse neural network that underpins executive functions, such as goal setting (i.e., prefrontal cortex, subcortical structures, parietal lobes, cerebellum; Baker et al., 1996; Morris, Ahmed, Syed, & Toone, 1993; Newman, Carpenter, Varma, & Just, 2003; van den Heuvel et al., 2003). While some of the structural brain pathologies associated with VP goal setting impairments during late childhood are known, the role of specific functional connectivity networks in relation to such goal setting deficits of VP children remains poorly characterised.

Neural network connectivity in VP samples has been examined during infancy and early childhood using resting-state functional MRI (rs-fMRI), which indirectly assesses neural activity by measuring blood oxygen level dependent (BOLD) signal within the brain at rest (Smitha et al., 2017). Fluctuations in BOLD signal that are spatially and temporally coherent

within widely distributed brain regions constitute a resting state network (RSN) and reflect neural connectivity (Smyser et al., 2013). Studies have reported VP infants demonstrate less mature basal ganglia, visual and thalamo-cortical networks than FT infants before term equivalent age (Smyser et al., 2010; Smyser et al., 2016). However, other studies have reported comparable RSNs in VP and FT infants (Doria et al., 2010; Imai et al., 2014; Smyser et al., 2016). Throughout early development, marked changes in network connectivity strength occur (Smyser et al., 2010), and with the exception of one study (Damaraju et al., 2010), RSNs connectivity strength and activation patterns appear to be relatively similar in young VP and FT children (Lee et al., 2013; Padilla et al., 2014). Differences in functional connectivity between preterm children and FT controls have been shown to emerge again between 9 and 13 years, with increased parietal and occipital connectivity in the posterior default mode network (DMN) demonstrated in VP children (Degnan et al., 2015). Differences in functional connectivity have also been reported in adulthood, with the striatal salience network being preferentially affected in VP samples (White et al., 2014). Alternative processes of network maturation in VP children may occur as a result of prematurity-specific pathology related to disrupted synaptic pruning and myelination (Fair et al., 2008; Fair et al., 2009; Fair et al., 2007; Supekar et al., 2009). Further investigation of VP RSNs compared with their FT peers during late childhood is required to better understand the impact prematurity has upon the maturation of higher level neural networks, and whether RSN alterations underlie the higher rates of VP goal setting deficits (P. J. Anderson et al., 2015).

It has been proposed that reduced connectivity strength in executive networks may explain the well documented executive function deficits of VP children (He & Parikh, 2015). To the best of our knowledge, only one study has compared RSNs associated with executive deficits between VP and FT groups. In a small sample of 16 year old children, Lubsen et al. (2011) demonstrated that altered RSN connectivity in VP children was associated with poorer executive functioning performance (Lubsen et al., 2011).

Resting state networks underlying goal setting abilities during late childhood may include the frontoparietal network (FPN), executive control network (ECN) and default mode network (DMN). For example, altered DMN, ECN, and FPN connectivity has been previously related to executive function deficits in other pediatric populations including attention deficit

hyperactivity disorder and epilepsy (H. Lin et al., 2015; Widjaja et al., 2013). The FPN, ECN and DMN are established in FT and VP samples by early childhood (de Bie et al., 2012). The FPN is likely to involved in planning and strategic reasoning; core components of goal setting (Boghi et al., 2006; Coricelli & Nagel, 2009; Fincham et al., 2002). The ECN is more active for externally directed attention (Corbetta & Shulman, 2002; Seeley et al., 2007), and the DMN is more active for internally directed attention (Buckner, Andrews-Hanna, & Schacter, 2008; Leech & Sharp, 2014). Since attentional resources are integral to goal setting proficiency (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010), the ECN and DMN networks are also of interest.

This study aimed to compare the FPN, ECN and DMN between VP and FT 13-year-old children, and we hypothesised that FPN, ECN, and DMN connectivity strength within networks would differ between the groups. The second aim of this study was to examine the association between the FPN, ECN, and DMN functional connectivity and goal setting ability in VP and FT 13-year-old-children, and determine whether these associations differed between groups. We hypothesised that FPN, ECN and DMN functional connectivity would be associated with goal setting ability in both VP and FT 13-year-olds, but that connectivity strength would differ between the birth groups.

5.5. Methods

5.5.1. Participants

Participants were part of the Victorian Infant Brain Study (VIBeS) cohort, a longitudinal study examining the development of children born VP (<30 weeks' gestation) and/or very low birth weight (<1250 g) compared with healthy children born FT (≥ 37 to ≤ 41 weeks' gestation) and of normal birth weight (≥ 2500 g). Two hundred and twenty-seven VP participants fitting eligibility criteria and without genetic or congenital abnormalities known to affect development were originally recruited between July 2001 and December 2003 at the Royal Women's Hospital, Melbourne. Three infants subsequently died, leaving 224 survivors.

5.5.2. Procedure

Participants were followed-up at 2, 5, 7 and 13 years of age. Age was corrected for prematurity at all time points to avoid a known bias in cognitive test scores (Wilson-Ching et

al., 2014). At the 7-year follow up, neurosensory impairment (defined as either moderate or severe cerebral palsy, any deafness, or any blindness) was diagnosed by a pediatrician. At the 13-year follow up, a neuropsychological assessment was performed, and MRI brain scans were acquired at the MRI Centre at Melbourne's Royal Children's Hospital using a research dedicated 3 Tesla Trio Siemens machine with a 32-channel head coil. This study was approved by the Human Research and Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, and informed written consent was obtained from the parents at all time points.

At the 13-year follow up, 179 (80%) of the 224 eligible children in the VP cohort agreed to participate. Eleven participants did not consent, and 34 were lost to follow-up (uncontactable, n = 10; declined/failed to attend, n = 24). An optional MRI brain scan was completed by 141 VP participants (declined, n = 7; orthodontic appliances, n = 16; overseas/interstate, n = 6; failed practice MRI, n = 5; too impaired, n = 3; MRI facility unavailable, n = 1).

Of the 77 eligible FT children, 61 (79%) participated, with 11 having withdrawn and 5 lost to follow up (uncontactable, n = 4; overseas, n = 1). Forty-seven of these participants completed the optional MRI brain scan (declined, n = 7; orthodontic appliances, n = 5; overseas/interstate, n = 1; failed practice MRI, n = 1).

5.5.3. Goal setting measures

The Delis-Kaplan Executive Function Systems (D-KEFS; Delis, Kaplan, & Kramer, 2001) Tower Test was administered to estimate spatial planning, rule learning, inhibition of impulsive and perseverative responding, and the ability to establish and maintain instructional set. The total achievement score was used, which represents the number of correct towers assembled within specific time limits.

The Rey Complex Figure Test (RCFT) involves reproducing a geometric line drawing and was administered to estimate spatial planning and organisational strategy (Anderson, Anderson, & Garth, 2001). Copy Accuracy, assesses spatial planning, and was scored using the 18 item accuracy criteria established by Osterrieth (1944). Organisational strategy was scored using the RCFT Organizational Strategy score (Anderson, Anderson, & Garth, 2001).

From the Behavioural Assessment of the Dysexecutive System for Children (BADS-C; Emslie, Wilson, Burden, Nimmo-Smith, & Wilson, 2003), the Zoo Map and Six Part Test were administered. Zoo Map 1 captures the ability to plan and execute a specific eight-location sequence in accordance with several rules. The total score was used, which is calculated from the number of correct locations visited, including deductions for rule breaks. The Six Part Test examines planning, task scheduling and performance monitoring skills by asking participants to complete 6 simple tasks in 5 minutes following several rules. The total score was used, which accounts for effective strategy/pattern as well as point deductions for rule breaks.

For each participant *z* scores were calculated for each goal setting measure, summed together and then averaged to generate a composite score. A composite measure was used to provide a robust measure of goal setting (i.e., core components of goal setting assessed across multiple measures), as well as to reduce measurement error and limit the number of analyses. One participant had missing values for 2 of the 5 tests (due to administration error), and their missing values were replaced with the average of their non-missing *z* score values. One participant had an extreme outlier on 1 of the 5 goal setting tests, which was replaced with the average of their non-missing *z* score values. Lower composite z scores are indicative of poorer goal setting ability. The internal consistency of the goal setting composite was reasonable (Cronbach alpha = .67, range = .54 to .71).

5.5.4. Neonatal characteristics

During the neonatal period, neonatal characteristics were obtained by chart review, including birth weight, gestational age (GA) at birth and at scan, small for GA (defined as birth weight standard deviation (SD) score > 2 SDs below mean weight for GA computed relative to the British growth reference data; Cole, Freeman, & Preece, 1998), multiple birth, bronchopulmonary dysplasia (BPD; defined as oxygen dependency at 36 weeks' GA), proven sepsis or necrotising enterocolitis (NEC), and administration of postnatal corticosteroids.

5.5.5. MRI acquisition

Prior to the MRI brain scans, children completed a familiarisation session with a mock MRI. Children were eligible to have a MRI scan if they completed a standardised practice scanning protocol without excessive head or body movement.

The VIBeS 13-year follow-up MRI acquisition protocol involved an approximately 50-minute scanning session, from which T_1 and rs-fMRI sequences were utilised for the current study. Neuroanatomical data were acquired with T_1 - weighted multi-echo Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence with echo planar image (EPI) navigated prospective motion compensation. Acquisition parameters were as follows: repetition time (TR) = 2530ms, echo time (TE) 1= 1.77, TE 2= 3.51, TE 3= 5.32, TE 4= 7.2ms, flip angle= 7°, field of view (FOV) = 230 x 209mm, matrix= 256 x 230 (interpolated 256 x 256), voxel size= .9mm^3 isotropic voxels.

Resting-state functional connectivity images were acquired via a BOLD contrast sensitive sequence using a multiband EPI sequence with the following acquisition parameters: multiband acceleration factor = 3, TR = 1500ms, TE = 33ms, flip angle = 85°, FOV = 255 x 255mm, matrix = 104 x 104, voxel size= 2.5mm^3 isotropic. During this sequence participants were instructed to focus on the cross while lying still, staying awake, and thinking of nothing in particular. For the first 22 participants (16%; VP, *n* = 20; FT, *n* = 2) the images were obtained using a single 12-minute sequence. For the remainder (*n* = 118), rs-fMRI acquisition was broken up into 3 separate sequences of 4 minutes each to improve compliance and scan quality (84%; VP, *n* = 81; FT, *n* = 37). Additional matching reference images with phase-encode direction reversal were also obtained to correct magnetic susceptibility-induced distortions, as well as a gradient echo field map to estimate field inhomogeneity in the BOLD images.

5.5.6. Pre-processing

Prior to beginning preprocessing, the following steps were taken to prepare rs-fMRI data. Firstly, data were qualitatively assessed to exclude participants whose T_1 and rs-fMRI scans were of insufficient quality for further analysis (i.e., incomplete datasets, or other imaging artifact). Datasets deemed to be incomplete if their volume total was less than 441. Significant head motion was defined as absolute mean motion exceeding 0.40mm and/or an absolute

maximum motion exceeding 3.00mm. Incomplete datasets and those with significant head motion were removed. Resting-state data acquired over three sequences were merged into one file.

The first step of data preprocessing involved using the CONN toolbox from the SPM12 software package (Gabrieli Lab McGovern Institute for Brain Research, 2014) in MATLAB Statistics Toolbox Release R2016b (MATLAB version 8.5.1., 2016) to analyze and correct for motion artifact, as well as the TOPUP tool to estimate and correct for susceptibility induced distortions within the data set.

Using the CONN pipeline, functional volumes were subjected to time shift correction (TR 2.53) and then each participant's functional image was registered linearly to their T_1 structural image and converted to the MNI152 adult brain atlas space (A. C. Evans et al., 2001). Next, the spatial volumes of the functional images were smoothed with full width at half maximum (FWHM) Gaussian kernel of 8mm. T_1 structural images were segmented into cerebrospinal fluid (CSF), white and gray matter, in order to mask out the effect of the CSF and white matter from the fMRI image. This denoising process was achieved by regressing out the signal from the CSF and white matter to preserve the gray matter BOLD signal only. The final step, was applying temporal filtering of low frequency signal whereby the residual time series were band pass filtered (0.008 - 0.09 Hz).

5.6. Statistical analysis

5.6.1. Sample characteristics

Sample characteristics were analyzed using Stata 14.2 (StataCorp, 2015). Categorical data were compared using chi-squared tests to compare the maximum likelihood of odd ratios, continuous data were examined using two-sample *t*-tests, and binary data were compared using tests of proportions.

5.6.2. Analysis of rs-fMRI data

For first-level analysis in CONN, the independent components analysis (ICA) was specified to generate 15 group-level components using temporal concatenation of fMRI data from all subjects, a commonly applied clustering/splitting method (Beckmann et al., 2005; Damoiseaux et al., 2006; Smith et al., 2009). Network components were compared with

healthy adult brain networks previously identified by Smith et al. (2009).

For second-level results, group contrast analysis was run to examine between-group differences in ICA RSNs of interest, including the FPN (separated into left and right networks; lFPN, rFPN), DMN, and ECN, chosen a priori due to their functional relevance to goal setting abilities (Palacios et al., 2013; Smith et al., 2009), adjusting for sex and demeaned age at MRI as potential confounders.

Using CONN, primary and secondary regression analyses were run to examine the relationship between lFPN, rFPN, ECN and DMN connectivity strength and goal setting ability, using the goal setting composite, separately for each group. Primary models included sex and demeaned age at MRI as potential confounders, with secondary models additionally excluding children with significant neurosensory impairment or an FSIQ less than or equal to 70 (FT, n = 1; VP, n = 11), to ensure that group differences and/or associations were not due to a small number of significantly impaired children.

Additional analyses examined a possible group interaction for the goal setting composite association with the rFPN, lFPN, ECN and DMN separately, to determine whether the association between goal setting ability and RSN connectivity differed between groups.

All analyses were corrected for multiple voxel-wise comparisons using the false discovery rate (FDR) correction procedure, with a critical value of less than or equal to .05 used to evaluate statistical significance.

5.7. Results

Resting state MRI data were unavailable or removed for 40 of 141 VP participants (intellectual disability, n = 1; refusal/fell asleep, n = 6; insufficient rs-fMRI data, n = 3; excess motion, n = 30), and 8 of 47 FT participants (insufficient rs-fMRI data, n = 1; excess motion, n = 7). We were strict on motion artefact in order to restrict our analyses to a high-quality data set, resulting in a final sample consisted of 101 VP (75%) and 39 FT (83%) participants with sufficient rs-fMRI and goal setting data.

5.7.1. Sample characteristics

Sample characteristics are presented in Table 5.1. The VP and FT groups differed on neonatal characteristic variables as expected (i.e., birth weight, GA, BPD, sepsis, postnatal corticosteroids, and brain injuries). Participants from both groups were of a similar age at both neuropsychological testing and MRI. Very preterm participants demonstrated poorer full-scale IQ (FSIQ) scores and goal setting ability.

Table 5.1. Sample characteristics

	Very preterm (n = 101)	Full-term (n = 39)	Group comparison statistics		
				[95% CI]	*P*-value
Neonatal Characteristics					
Gestational age (weeks), M (SD)	27.5 (1.9)	39.0 (1.4)			
Gestational age <28 weeks	54 (53.5)	0			
Birth weight (g), M (SD)	986 (233)	3322 (563)			
Birth weight <1000g	51 (50)	0			
Small for gestational age	6 (6)	0			
Male sex[b]	52 (51)	17 (44)	.8[†]	[.4, 1.5]	.42
Multiple birth	54 (53)	3 (8)			
Postnatal corticosteroids	5 (5)	0			
Necrotising enterocolitis	3 (3)	0			
Bronchopulmonary dysplasia	31 (31)	0			
Any sepsis	27 (27)	0			
Grade 3/4 intraventricular haemorrhage	4 (4)	0			
Cystic periventricular leukomalacia	2 (2)	0			
Moderate/severe white matter injury at TEA[a]	10 (10)	0			<.001
Sociodemographic characteristics at 13 years					
Maternal age at birth (years), M (SD)[c]	30.7 (5.6)	30.4 (4.3)	-.3	[-2.3, 1.7]	.78

Intact family[a]	65 (67)	29 (76)			.036
Primary caregiver with tertiary education[b]	38 (43)	21(58)	.1	[-.0, .3]	.11
Higher social risk score at 13 years[b d]	53 (55)	15 (39)	.1	[-.3, -.0]	.11
Recipient of allied health services since 7 years[Δ b]	29 (31)	6 (17)	.9	[-.3, .0]	.09
General outcomes at 13 years					
Corrected age at testing (years), M (SD)[c]	13.2 (.5)	13.2 (.5)	.0	[-.1, .2]	.73
Corrected age at MRI (years), M (SD)[c]	13.2 (.4)	13.3 (.5)	.0	[-.1, .2]	.78
FSIQ, M (SD)[c e]	102.4 (16.7)	110.5 (12.7)	8.2	[2.3, 14.0]	.006
Goal setting z score[c]	-.41 (.71)	-.00 (.58)	.41	[.16, .66]	.0017

Data are n (%), unless otherwise specified. *Note.* n = sample size; *%* = percentage; M = mean; SD = standard deviation; [†] = odds ratio; TEA = Term equivalent age (37 to 42 weeks' gestational age); [Δ] = including speech therapy, psychology, occupational therapy, physiotherapy; CI = confidence interval; FSIQ = full scale intelligence quotient; [a] = chi square statistic for categorical data; [b] = proportional difference; [c] = mean difference; [d] = Social Risk - cumulative scale of 0 to 12 taking into account family structure, employment status, occupation, educational level, language spoken, and maternal age at birth. Higher scores reflect greater level of social risk (G. Roberts et al., 2008); [e] = based on performance on the Kaufman Brief Intelligence Test, Second Edition (A. S. Kaufman & Kaufman, 2004).

Some sample sizes are less than the total sample due to missing data (social risk, family risk, [VP = 97, FT = 38], recipient of allied health services since 7 year old [VP = 93, FT = 36], primary caregiver with tertiary education [VP = 89, FT = 36], maternal age at birth [FT = 36, VP = 89], moderate/severe white matter injury at TEA [FT = 20]).

5.7.2. Resting state network identification

The group ICA estimated 15 components, of which 10 networks reflected functionally relevant RSNs based on a mean spatial correlation between group-level networks and the reference atlas of $r = 0.43$ (range, $r = 0.17$ to $r = 0.70$; Smith et al., 2009), including the visual-medial, visual-occipital, the visual-lateral, auditory, sensorimotor, executive control, default mode, left frontoparietal, right frontoparietal and the cerebellum networks. These 10 networks corresponded to previously defined rs-fMRI network representations (Smith et al., 2009). The 5 remaining network maps were discarded as they were deemed to represent artefact (i.e., head motion, physiological noise, cerebrospinal fluid) or complex network amalgamations.

Whole group ICA networks of interest to this study include the lFPN, rFPN, ECN and DMN (presented in Figure 5.1.).

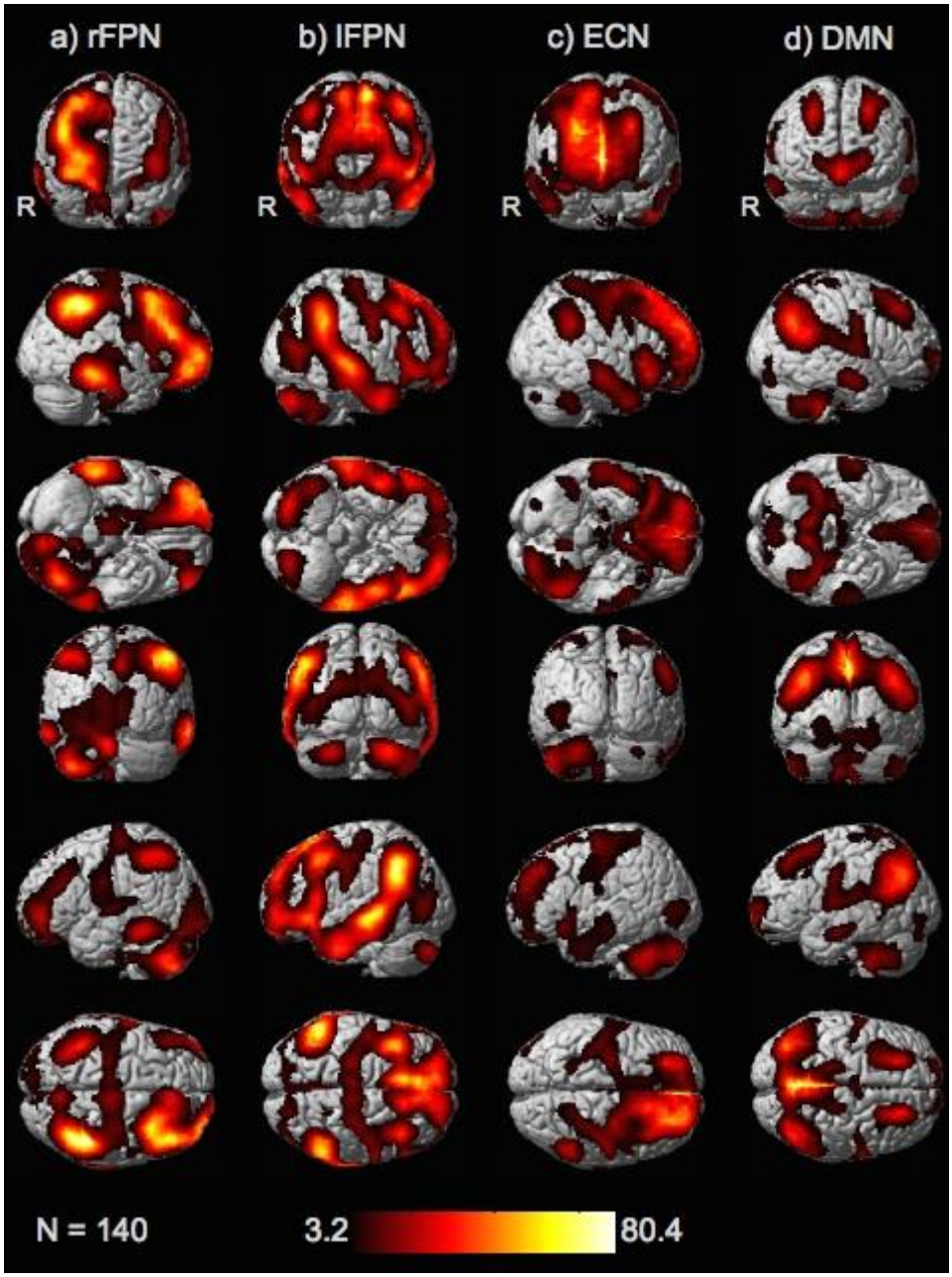

Figure 5.1. Resting-state networks identified by group-level independent components analysis. Component labels: a) right frontoparietal network (rFPN); b) left frontoparietal network (lFPN); c) executive control network (ECN) and d) default mode network (DMN). R = Right. Images are z statistics overlaid on the high resolution Montreal Neurological Institute reference brain. Connectivity networks are thresholded at $p < .05$. Connectivity z scores range from 3.2 to 80.4, as displayed in red-to-yellow color bar.

5.7.3. Group differences in resting state network connectivity

Group differences in RSNs are shown in Table 5.2. Very preterm participants demonstrated greater RSN connectivity strength within a cluster of the lFPN in comparison to FT participants (see Figure 5.2.a). The VP group demonstrated several clusters of weaker RSN connectivity strength within the rFPN, lFPN, ECN, and DMN, in comparison to the FT group (see Figure 5.2.b through 5.2.e).

Table 5.2. Characteristics of group differences in clusters of resting state network connectivity

	Cluster	Regions	Voxel size (% atlas region)	Coordinate x	Coordinate y	Coordinate z	*P*-value
FT>VP							
	rFPN	Right posterior middle temporal gyrus, right inferior posterior temporal gyrus, right anterior middle temporal gyrus	512	+62	-18	-22	.03*
	lFPN	Left temporal pole, left frontal orbital cortex, left insular cortex, left frontal operculum cortex, left anterior middle temporal gyrus	317	+46	+18	-10	.002**
	ECN 1	Right temporal pole, right anterior middle temporal gyrus, right posterior middle temporal gyrus, right temporooccipital middle temporal gyrus, left frontal pole, left pars triangularis inferior frontal gyrus, left frontal operculum, left middle frontal gyrus, right anterior superior temporal gyrus, right hippocampus	319	+50	-34	-08	.014*
	ECN 2	Left frontal pole, left pars triangularis inferior frontal gyrus, left frontal operculum cortex, left middle frontal gyrus	305	-34	+36	+06	.014*
	ECN 3	Right temporal pole, right anterior middle temporal gyrus, right anterior superior temporal gyrus	229	+56	+08	-24	.031*
	DMN	Precuneous cortex, left intracalcarine cortex, left supracalcarine cortex, right intracalcarine cortex, right supracalcarine cortex, right cuneal cortex, left lingual gyrus, right lingual gyrus	618	+10	-58	+12	< .001
VP>FT							
	lFPN 1	Right frontal pole, right par triangularis inferior frontal gyrus, right frontal orbital cortex	526	+46	+40	-08	.002**
	lFPN 2	Left frontal pole, left pars triangularis inferior frontal gyrus	330	-48	+40	-02	.013*

Note. FT = full-term; VP = very preterm; rFPN = right frontoparietal network; lFPN = left frontoparietal network; ECN = executive control network; DMN = default mode network. FT sample size = 39; VP sample size = 101.

All associations were independent of the covariates age at MRI and sex, and were corrected for multiple comparisons using the false discovery rate correction procedure.

* < .05; ** < .01.

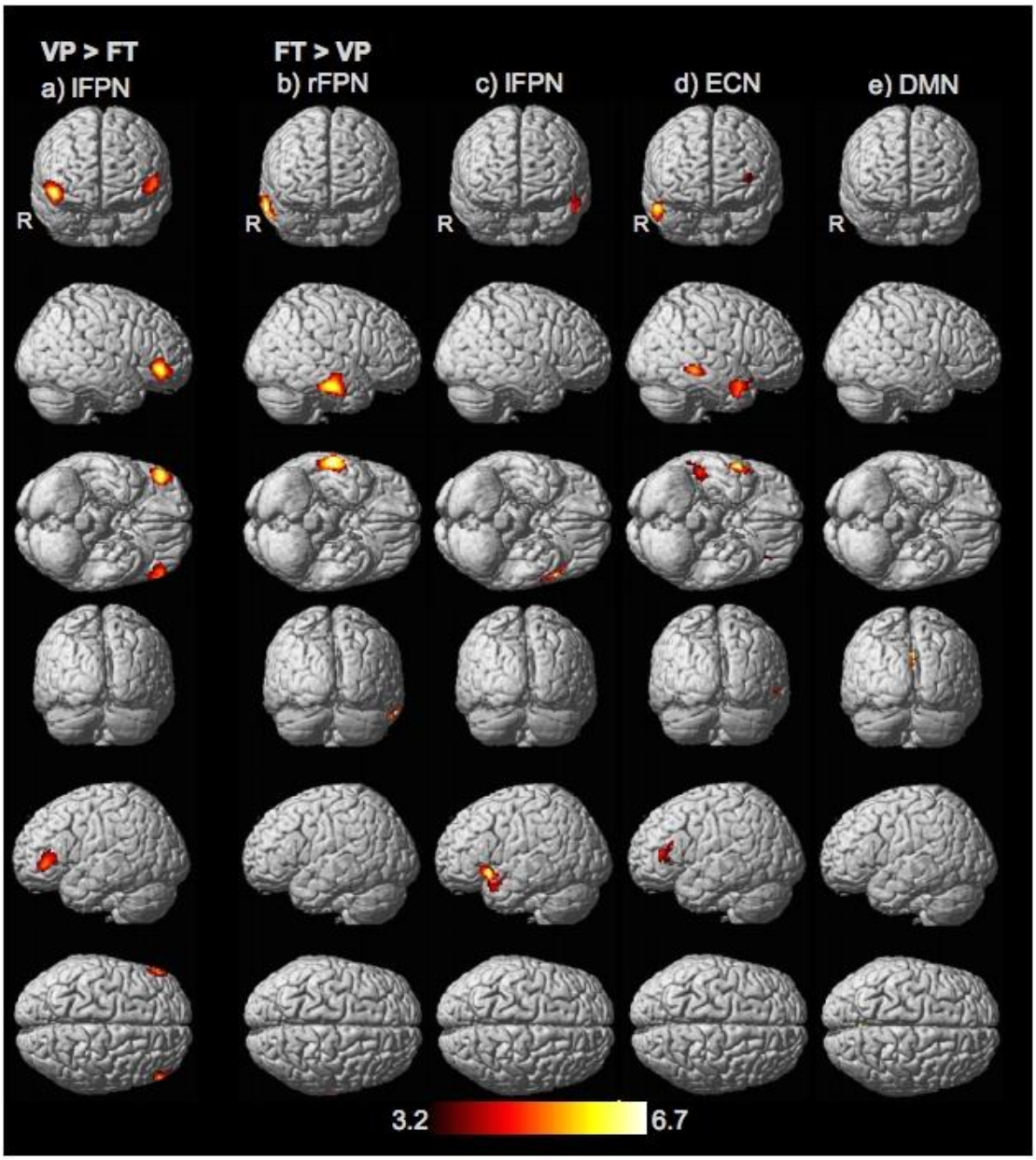

Figure 5.2. Greater very preterm (VP) sample (n = 101) than full-term (FT) sample (n = 39) connectivity was observed in the a) left frontoparietal network (lFPN). Clusters of weaker resting-state network connectivity in the VP sample compared with the FT sample included the b) right frontoparietal network (rFPN); c) left frontoparietal network; d) executive control network (ECN); and e) default mode network (DMN). Connectivity networks are thresholded at $p < .05$. Connectivity z scores range from 3.2 to 6.7, as displayed in red-to-yellow color bar.

5.7.4. Within group resting state network connectivity associated with goal setting ability

For both the VP and FT groups, few significant associations between goal setting performance and functional connectivity in rFPN, lFPN, ECN and DMN were observed. In the VP group greater goal setting ability was positively associated with increased connectivity within a cluster of the DMN (Figure 5.3). This DMN cluster consisted 237 voxels in total, covering regions of the cuneal cortex and supracalcarine cortex bilaterally (coordinates: *x* = +00, *y* = -68, *z* = +20; *p* = .029). This association was no longer significant after excluding children with neurosensory impairment or FSIQ<70 (n = 11). There were no associations between goal setting ability and any of the resting state networks for the FT group.

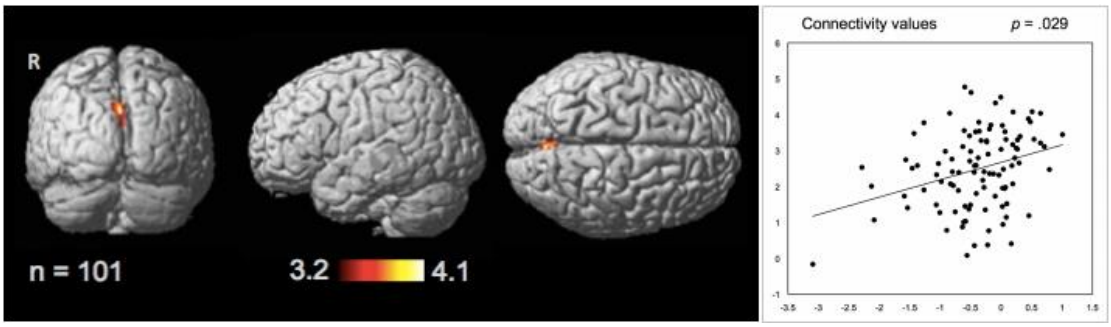

Figure 5.3. Cluster of increased default mode network connectivity positively associated with greater goal setting abilities in very preterm (VP) children. Connectivity networks are thresholded at p < .05. Connectivity z scores range from 0 to 3.6, as displayed in red-to-yellow colour bar. Scatter plot with y axis showing individual mean values for connectivity within default mode network cluster in relation to goal setting composite z score within the VP group on the x axis.

5.7.5. Between group differences in the association between resting state network connectivity and goal setting ability

There was little evidence of group differences between the VP and FT groups in connectivity associated with goal setting ability across the rFPN, lFPN, ECN and DMN.

5.8. Discussion

In the current study, VP children exhibited weaker functional connectivity within small clusters of frontoparietal, executive control and default mode networks compared with FT children, but also showed greater connectivity in a separate cluster of the lFPN. We did not find evidence to indicate that ECN, DMN or FPN were related to late childhood goal setting skills.

During late childhood, children born ≤ 32 weeks gestation have been reported to demonstrate reduced insular cortex connectivity within the FPN and reduced connectivity of prefrontal regions within the ECN in comparison with their FT peers (Degnan et al., 2015). In support of these findings, we provided evidence for several small clusters of reduced frontal and temporal connectivity within the ECN, lFPN and rFPN in VP children compared with FT controls, involving bilateral temporal, temporoccipital and frontal gryi, frontal and temporal poles, the frontal orbital cortex, frontal operculum, insular cortex and pars triangularis. This altered FPN and ECN connectivity we observed in late childhood is disparate with studies that report similar connectivity in children born VP and FT earlier in childhood (Lee et al., 2013; Padilla et al., 2014). One explanation for this discrepancy is statistical power, with our considerably larger sample providing more power to detect subtle differences. Within the FPN and ECN, frontal and temporal brain regions are comprised of rich white matter connections that facilitate communication, signal transduction and support neural connectivity (Barnea-Goraly et al., 2005). Considering that white matter abnormalities, particularly those that are moderate to severe in nature, are associated with altered RSN connectivity of VP infants (He & Parikh, 2015; Smyser et al., 2013), it is possible that such pathology has contributed to aberrant FPN and ECN neural connectivity in our VP sample. There is a growing interest in investigating how the structural architecture of the human brain may constrain its own function (Gu et al., 2015) and previous studies have shown that the functional specialisation of a region could be accurately predicted using structural connectivity data (Saygin et al., 2012). Structural connectivity abnormalities in VP children may result in neural reorganisation and lead to alterations in functional network connectivity (Damoiseaux & Greicius, 2009; Schafer et al., 2009). Given that moderate to severe neonatal white matter and gray matter

abnormalities (e.g., cystic lesions, signal abnormality) have previously been reported in the current VP sample (J. Cheong et al., 2009; Kidokoro et al., 2014; Thompson et al., 2008), we speculate that such pathology may have contributed to disrupted neural organisation and communication, and therefore reduced ECN and FPN connectivity in this sample at 13 years. Having said that, the relationship between brain structure and functional connectivity is not strictly one-to-one (Smyser et al., 2016), given that functional connectivity may occur between regions (Friston, Frith, Liddle, & Frackowiak, 1993; Uddin et al., 2008; Vincent et al., 2007). Accordingly, structural deficits may not solely account for group FPN and ECN connectivity differences in our study.

Interestingly, VP children demonstrated small clusters of greater connectivity strength within the lFPN including the frontal pole, pars triangularis, frontal gyri, and frontal orbital cortex in comparison with FT children. Connectivity clusters were not strongly lateralised however, appearing to be stronger in the right hemisphere, which perhaps indicates a more bilateral representation of the lFPN in VP children. Compensatory mechanisms and network reorganisation have been suggested to be linked with increased connectivity in neurologically compromised populations (Bettus et al., 2009). Increased VP lFPN connectivity might also be explained by disrupted synaptic pruning in association with prematurity. Synaptic pruning is essential for eliminating unwanted neural connections to make way for superior connections, and without this process, weaker brain connections may remain (Paolicelli et al., 2011; Zhan et al., 2014). Failed synaptic pruning has been suggested to contribute to greater gray matter volumes of VP adults in comparison with their FT peers (C. Nosarti et al., 2014), as well as altered brain connectivity in networks associated with executive function of VP children during late childhood (Degnan et al., 2015). Failed synaptic pruning in the context of prematurity may contribute to increased FPN connectivity as demonstrated in our findings. Having said that, these findings ought to be interpreted with caution, given the relatively weak correlation the largely bilateral lFPN network demonstrated with the reference atlas (r^2 = 0.19), which might be improved with the use of an age appropriate template in future studies.

Previous research has documented *increased* DMN connectivity in posterior regions, including the posterior cingulate and precuneus, in late preterm born children compared with

FT controls during late childhood (Degnan et al., 2015). We found evidence for *reduced* DMN connectivity in a cluster of posterior VP brain regions, involving the precuneus, cuneus, lingual gyrus and calcarine cortex compared with FT controls. At term-equivalent age, anterior-posterior DMN connectivity exhibited by FT infants is reported to be absent in VP infants (Smyser et al., 2010). Typical anterior and posterior DMN connectivity is supported by white matter pathways within the cingulum tract (Hagmann et al., 2008). Brain injured VP infants however demonstrate microstructural white matter abnormalities within the DMN-cingula (Cui et al., 2017), which reportedly contributes to reduced intra-hemispheric connectivity in preterm infants (Smyser et al., 2013). Accordingly, we postulate that adverse microstructural alterations within regions comprising the DMN during infancy persist throughout a preterm child's development (Caldinelli et al., 2017), and may contribute to altered DMN functional connectivity patterns at 13 years of age. Alternatively, inconsistency between our findings and those of Degnan et al. (2015) may be attributed to methodological differences such as the gestational age of the children, sample size (11 preterm vs. 101 VP participants; 14 vs. 39 FT controls) and analytic approach (seed-based vs. ICA).

While better goal setting performance was associated with increased DMN connectivity, this result was no longer significant after excluding children with significant neurosensory impairment or a FSIQ less than or equal to 70. Accordingly, we did not find any evidence for an association between the FPN, ECN and DMN and goal setting ability in either VP or FT children at 13 years, contrary to our expectations. Our findings contrast with preliminary research documenting the ECN to be related to executive function performance in FT and VP 16-year-olds, with poorer executive function performance of VP children related to altered connectivity within the ECN (Lubsen et al., 2011). The lack of association in our study conflicts with the plethora of extant literature linking executive dysfunction with altered resting state connectivity in neurologically compromised child and adult populations (e.g., temporal lobe epilepsy, traumatic brain injury, attention deficit hyperactivity disorder, spinocerebellar ataxia, Parkinson's disease and normal aging; Bonnelle et al., 2011; Damoiseaux et al., 2008; H. Lin et al., 2015; Lucas-Jimenez et al., 2016; Palacios et al., 2013; Palacios et al., 2017; Pereira et al., 2017; Widjaja et al., 2013). More specifically, our results contrast with evidence

of an association between impaired goal setting performance and reduced frontostriatal functional connectivity (i.e., in adults with obsessive-compulsive disorder; Vaghi et al., 2017). Additionally, we had expected that FPN, ECN and DMN connectivity would be associated with goal setting skills, given that these networks are thought to be functionally relevant and pertinent to higher level cognition such as goal setting (Boghi et al., 2006; Coricelli & Nagel, 2009; Fincham et al., 2002; McCabe et al., 2010; Ramnani & Owen, 2004). It is possible that immaturity of FPN connectivity during late childhood weakened our results in both groups, given that FPN connectivity development is ongoing between childhood and adolescence (Wendelken et al., 2017). It is also possible that alternative RSNs to those selected actually underlie goal setting skills, such as the salience network which via cortico-striatal-thalamic connectivity loops (Seeley et al., 2007; Yeo et al., 2011) supports cognitive control during executive function task performance (Peters, Dunlop, & Downar, 2016). Beyond the scope of the current study however, future research could explore additional RSNs underlying goal setting, with the additional use of fMRI to examine network activation during completion of goal setting tasks.

Several additional factors may explain our failure to detect an association between goal setting performance and RSN connectivity in the FPN, ECN, and DMN in either the VP or FT group. Firstly, while the composite goal setting measure provided a general assessment of goal setting ability at 13 years, a different selection of more ecologically valid goal setting measures may have improved the sensitivity for detecting results in both groups, including immersive (e.g., The Jansari assessment of Executive Functions for Children; Gilboa et al., 2017) or functional measures (e.g., Party Planning Task; Shanahan, McAllister, & Curtin, 2011). Alternatively, the inclusion of ecologically valid measures as part of the composite goal setting measure may contribute to the contrasting findings we documented, in comparison to previous research utilising only traditional cognitive measures. Additionally, while the spatial correlation between the reference atlas and the DMN was strong (r^2 = .67), correlations for the ECN, rFPN and lFPN were weak (r^2 = .23, and r^2 = .37, r^2 = .19, respectively). Higher spatial correlations may have provided greater certainty for examining RSNs, and might have enhanced our ability to find associations between RSN connectivity strength and goal setting

performance (Bajic, Craig, Mongerson, Borsook, & Becerra, 2017). Alternatively, a significantly larger sample size (i.e., using pooled participant cohorts) may be necessary to demonstrate a link between RSN connectivity and goal setting ability. Moreover, though resting state connectivity networks of typically developed 12-year-olds are shown to be consistent with those of young adults (Jolles, van Buchem, Crone, & Rombouts, 2011), it is possible that associations between RSN connectivity and goal setting outcome become more apparent with increasing age, as shown in extant VP rs-fMRI research (Gozzo et al., 2009; Myers et al., 2010).

For such a long-term follow-up study, the retention of our sample was excellent and our total sample size was particularly large for a rs-fMRI study, especially in the context of sample sizes of previous rs-fMRI studies of typically developing adults and children (Smyser et al., 2016). Having said that, our sample sizes were unequal and despite substantial effort the VP and FT groups were not equally matched on sociodemographic factors.

This study has a number of other limitations. It is possible that despite rigorous motion-correction procedures, in-scanner head motion may have affected rs-fMRI data (van Dijk, Sabuncu, & Buckner, 2012). We also had to discard the MRI datasets for many participants, due to significant levels of movement artifact. Additionally, use of an adult brain template to identify RSN components may have limited our investigation due to the misclassification of brain tissue due to incorrect white and gray matter tissue distribution and age-related structural differences, as well as the misalignment of MRI image with a common reference space/template (Richards, Sanchez, Phillips-Meek, & Xie, 2016; Sanchez, Richards, & Almli, 2012). Given that distinct structural differences in white and gray matter volumes of VP children are documented through childhood, adolescence and adulthood (de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012; C. Nosarti et al., 2014), although unavailable for the current study, use of an age-appropriate template may have enhanced the identification of RSNs (Damaraju et al., 2014). Lastly, the present findings await validation in independent datasets, and we acknowledge our inability to infer causality given a cross-sectional observational study design. Future directions may include using diffusion weighted

imaging in conjunction with connectivity in order to identify the characteristics of the structural connections underlying the group differences we observed in RSNs.

In conclusion, our study identified differences in neural connectivity between VP and FT children during late childhood. This supports the utility of rs-fMRI for investigating the impact of prematurity, and the view that prematurity is a brain network disorder with an enduring impact upon neural architecture (H. Lin et al., 2015; Smyser et al., 2016). We did not find strong evidence that higher level RSNs were associated with late childhood goal setting skills in VP or FT children, highlighting that more research is needed to better understand neural connectivity in relation to goal setting skills in late childhood, including the neural mechanisms underlying goal setting deficits in VP children.

Chapter 6. General discussion

Chapter 6

6.1. Summary of findings

The findings of this dissertation yield new insights regarding the relationship between goal setting difficulties and the neuropathology associated with prematurity. At 13 years of age, VP children demonstrated poorer and more inefficient goal setting abilities than their FT peers. Within the VP group, poor goal setting performances during late childhood were related to moderate/severe brain abnormalities documented during the neonatal period. More specifically, white matter, deep gray matter and cerebellum abnormalities on neonatal magnetic resonance imaging (MRI), and volume reductions of the total brain, cerebellum, thalami, and cortical gray matter, were related to poorer goal setting exhibited by VP children during late childhood. In addition to structural findings during the neonatal period, VP and FT functional connectivity networks were examined during late childhood. Very preterm children demonstrated small clusters of reduced functional connectivity within frontoparietal, default mode, and executive control networks, encompassing frontal, temporal, insular and occipital cortices. Very preterm children also demonstrated a cluster of increased functional connectivity in comparison to FT children within the frontoparietal network, incorporating the frontal pole and pars triangularis. In both groups frontoparietal, default mode, and executive control network connectivity was largely unrelated to goal setting performance.

6.2. Very preterm goal setting difficulties during late childhood

This dissertation both supports and extends a limited body of literature indicating VP children demonstrate poorer goal setting in comparison to their FT born peers during late childhood (Aarnoudse-Moens et al., 2012; W. J. Curtis et al., 2002; Taylor, Minich, Bangert, et al., 2004). Goal setting difficulties during late childhood appear to be yet another adverse outcome which preterm children may experience as part of the long-term neurodevelopmental sequelae of premature birth, highlighting the vulnerability of this population throughout development. In considering our findings together with previous research, evidence demonstrating poorer preterm goal setting performances appears to be accumulating. Furthermore, in conjunction with well documented information processing, cognitive flexibility,

and attentional control difficulties documented across preterm samples (Burnett et al., 2013; Mulder et al., 2009), evidence for goal setting difficulties appears to contribute to mounting evidence for global executive dysfunction during late childhood. Indeed, it is these four domains that comprise the Executive Control System (ECS) framework that guided the current dissertation (P. J. Anderson, 2002).

Within the ECS framework, attentional control, information processing, cognitive flexibility and goal setting are interrelated higher level cognitive skills, but also interdependent (P. J. Anderson, 2002). Accordingly, VP goal setting difficulties are just as likely to be negatively implicated by attentional control, information processing and cognitive flexibility deficits. Conversely, it is possible that goal setting difficulties experienced by VP children are negatively affecting attentional control, information processing and cognitive flexibility skills. For example, VP goal setting deficits may result in a disorganised approach to the holding and the manipulation of information in mind, or dysfluent processing of incoming information, consequently impeding cognitive flexibility and information processing. Additionally, planning inefficiency may contribute to an erratic approach to self-monitoring by VP children, negatively affecting attentional control. Altogether, we have contributed to the understanding of goal setting difficulties experienced by VP children during late childhood by establishing the nature of these deficits, in the context of the ECS framework.

This study demonstrated a pattern of goal setting difficulties and inefficiency across multiple novel and ecological measures, as well as on parent report, representing convergent evidence for VP goal setting difficulties during late childhood. Since ecological measures and behavioural reports are purported to have high concordance with cognitive difficulties observed in real life functioning, our findings imply that the GS difficulties experienced are having functional implications (Aarnoudse-Moens et al., 2012; Burgess, Alderman, Evans, Emslie, & Wilson, 1998; W. J. Curtis et al., 2002; Taylor, Minich, Bangert, et al., 2004). This is particularly worrisome during late childhood, with poorer goal setting difficulties having a potentially detrimental impact upon areas of functioning that are reliant on planning and organisation skills, including academic achievement, school and social functioning, as well as future behavioural and emotional development (Burgess et al., 1998). Planning skills and

organisational abilities (i.e., of oneself/ones materials) are critical for determining the steps and processes required to accomplish short and long term goals, such as studying for tests, completing assignments, taking on leadership roles, undertaking new extracurricular activities, as well as participating in social events. Feelings of success that are derived from goal achievement are additionally associated with life satisfaction, self-confidence and mood (Macleod, Coates, & Hetherton, 2008). Recognition of goal setting difficulties experienced during late childhood is critical, to prevent them from becoming entrenched and persisting throughout adolescence and adulthood (Burnett et al., 2013). Should late childhood goal setting difficulties endure, they may negatively impact a child's ability to achieve their full cognitive and academic potential throughout the late high school years, which is concerning given the bearing high school achievement has upon vocational prospects, as well as consequent employment, job performance and financial security (Benz, Yovanoff, & Doren, 1997; Hunter, 1986; Kuncel, Hezlett, & Ones, 2004). Accordingly, intervention aimed at alleviating goal setting difficulties during late childhood is beneficial for VP children experiencing such difficulties, with the intention to prevent future negative ramifications.

Neuropsychological intervention may assist in preventing enduring consequences. While early developmental interventions with preterm infants do not appear to result in long-term improvements in cognitive outcomes during the school years (A. Spittle, Orton, Anderson, Boyd, & Doyle, 2015), there is some evidence to suggest that cognitive training programs (i.e., 'Cogmed') may be of benefit, with some findings demonstrating generalisable improvements in everyday functioning in children and adults (Spencer-Smith & Klingberg, 2015). Computerised working memory training in preterm samples indicates improvements in working memory skills of VLBW preschool children at 5 weeks and ELBW adolescents at 6 months, generalising to improvements in memory skills in both age groups (Hermansen Grunewaldt, Skranes, Brubakk, & Lahaugen, 2015; Lohaugen et al., 2011). Given that working memory proficiency likely contributes to successful goal setting abilities, it is possible that working memory training may result in corresponding improvements in goal setting skills or minimise the impact of the difficulties experienced (Friedman et al., 2006; Grunewaldt et al., 2014; Lohaugen et al., 2011; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000;

Taylor & Clark, 2016). Having said that, it is notable that recent evidence indicates negligible improvements in the academic skills of primary school aged children in association with computerised working memory training intervention (P. J. Anderson et al., 2018; Roberts et al., 2016). In cohorts of early primary school aged children with low working memory abilities and EP/ELBW children, computerised working memory training interventions were not recommended, based on the lack of lasting benefit (e.g., not maintained at 2 years), reduced classroom time associated with completing them, as well as the substantial costs that they impose (P. J. Anderson et al., 2018; Roberts et al., 2016).

Environmental modifications in children's home and school environments may also assist with alleviating goal setting difficulties (Catroppa & Anderson, 2010). For planning difficulties, Dawson and Guare (2010) suggest the provision of a plan or schedule, breaking long-term projects into subtasks, assigning a deadline to each subtask, and asking questions that prompt children to think about how to plan (e.g., asking "what do you do first?"). Organisational difficulties can be helped with the implementation of systematic organisation techniques (Dawson & Guare, 2010). For example, a home organisational checklist delineating the steps required to organise oneself for school or a social activity, or colour-coding school materials may be helpful. Compensatory strategies and supports may also alleviate the impact of planning and organisation difficulties and inefficiencies. Teaching children how to effectively use a paper or electronic diary may help them achieve their plans, organise their time and plan ahead (Ponsford et al., 2013). Further, they may benefit from parent or teacher assistance in identifying and breaking down the steps required to begin, work through, and accomplish a goal or plan (Ponsford et al., 2013). Neuropsychological intervention would be complemented by additional allied health supports such as speech therapy, occupational therapy, and physiotherapy, which may assist in facilitating corresponding cognitive development (e.g., Spittle, Orton, Anderson, Boyd, & Doyle, 2012). Not all preterm children will develop goal setting difficulties during late childhood, thus determining which children are in greatest need of intervention services early on will be beneficial.

6.3. Neurological predictors of preterm goal setting difficulties

The current dissertation contributes to preterm literature by identifying early brain characteristics associated with goal setting deficits during late childhood. Our findings provide further support for the benefit of routine neonatal MRI brains scans to identify vulnerability for future impairment in preterm children (Glass et al., 2015). Our results extend the documented association between reduced neonatal basal ganglia and thalamic volumes and poorer goal setting performances within this cohort at 7 years (Loh et al., 2017). Our findings also extend limited literature examining general executive function outcomes in VP children in association with neonatal MRI parameters (Clark & Woodward, 2010; Edgin et al., 2008; Woodward et al., 2012). The link we documented between numerous widely distributed, compromised brain structures and goal setting difficulties supports the widely held view that a broad neural network supports executive functions, including cortical, subcortical and cerebellar regions (Baker et al., 1996; Morris et al., 1993; Newman et al., 2003; O. A. van den Heuvel et al., 2003). Our findings also highlight the predictive utility of neonatal MRI brain metrics for informing which preterm children ought to be monitored since they are at risk for later neurodevelopmental impairments due to compromised brain structure. While neonatal MRI alone is not specific enough to identify children at risk for later executive function deficits, this finding contributes to future research that aims to identify the range of early factors that predict executive functioning difficulties in VP groups. Regardless, such information is highly informative to caregivers, healthcare providers and educators of preterm children, given that it denotes vulnerability and provides scope for prompt intervention during early childhood that may lessen or prevent the impact of goal setting impairments later on (Taylor & Clark, 2016).

While perinatal medical complications (e.g., bronchopulmonary dysplasia, sepsis) and sex are historically related to poorer executive function outcomes in preterm cohorts, they were not highly predictive of later goal setting functioning (Bohm et al., 2004; C. E. Curtis & D'Esposito, 2003; Duvall et al., 2014; Marlow et al., 2007; Orchinik et al., 2011; Urben et al., 2017). The reduced predictive value of neonatal risk factors with increased age is a possible explanation for the null association in our findings, and it is possible that similar to previous research, social and environmental factors exert a greater influence upon the vulnerabilities of

preterm goal setting difficulties in late childhood (Aarnoudse-Moens, Weisglas-Kuperus, et al., 2009; Doyle et al., 2015; Miceli et al., 2000; Weisglas-Kuperus, Baerts, Smrkovsky, & Sauer, 1993). While male sex has been linked with poorer executive function outcomes in preterm samples (Aarnoudse-Moens et al., 2012; Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, et al., 2013), it was not associated with poorer goal setting performances of VP children during late childhood in our study. Thus, female and male VP children appear to be at equal risk for late childhood goal setting difficulties, which has implications for ongoing monitoring for impairments and later follow-up.

6.4. Resting state network connectivity and preterm goal setting difficulties

The current dissertation provides preliminary evidence for altered functional connectivity in VP children across networks thought to underlie goal setting skills, involving frontoparietal, default mode and executive control networks, adding to literature documenting altered preterm network connectivity during infancy (Smyser et al., 2010; Smyser et al., 2016), early childhood (Damaraju et al., 2010), and adolescence (Degnan et al., 2015). We consolidate evidence for altered default mode network connectivity exhibited by preterm children during late childhood (Degnan et al., 2015), and provide preliminary evidence for altered frontoparietal and executive control networks. Our findings further signify that pathophysiological mechanisms of prematurity impact brain connectivity, and may endure, given their presence during late childhood. The potential for persistence of connectivity alterations would be unsurprising in the context of neural connectivity differences documented in preterm adults (White et al., 2014), although more research is needed. Differences in network connectivity may alternatively be indicative of developmental lag in neural connectivity networks in comparison to FT children (Gozzo et al., 2009), and further longitudinal follow-up studies will enable us to determine whether connectivity changes resolve or persist. The differences we observed in network connectivity between VP and FT children may be indicative of neural reorganisation and brain plasticity having occurred in response to structural deficits incurred in association with prematurity (Widjaja et al., 2013). Regardless, our findings provide some suggestion that prematurity affects the development of

interconnected neural networks. Having said that, the clusters of altered brain connectivity identified were small and may in fact indicate that neural networks between VP and FT children during late childhood are relatively similar. Given this uncertainty, what our findings most clearly indicate is just how little is known about the neural connectivity networks of preterm children during late childhood, highlighting the need for further research to comprehensively examine preterm functional connectivity networks.

Despite neural network differences between VP and FT children, there was a lack of association between the frontoparietal, default mode and executive control networks and late childhood goal setting skills in both FT and VP children, contrasting with a documented association between executive function scores and altered executive control network connectivity in preterm 16-year-olds (Lubsen et al., 2011). Further, our null finding contrasted with evidence for an association between impaired goal setting performance and reduced frontostriatal functional connectivity (i.e., in adults with obsessive-compulsive disorder; Vaghi et al., 2017), and a plethora of literature associating these networks with higher level cognition, including goal setting (Boghi et al., 2006; Coricelli & Nagel, 2009; Fincham et al., 2002; McCabe et al., 2010; Ramnani & Owen, 2004). Our results may indicate that alternate neural networks underlie goal setting skills during late childhood, such as the salience network which via cortico-striatal-thalamic connectivity loops (Seeley et al., 2007; Yeo et al., 2011) supports cognitive control during executive function task performance (Peters et al., 2016). Further, our results may signify that the selected neural networks are underdeveloped during late childhood in terms of their subservience to goal setting skills, given that executive neural networks may become increasingly refined and specialised across the course of adolescence (Fair et al., 2007; Sherman et al., 2014; Taylor & Clark, 2016). Our null findings serve as a preliminary step to advancing current knowledge about functional connectivity networks underpinning goal setting skills in late childhood, highlighting our limited understanding and the scope for clarification in future studies.

6.5. Future research

Though our findings contribute to an improved understanding of preterm goal setting

difficulties and their relationship with brain integrity, they also raise several questions, and additional research is required to address these research gaps.

The contribution of alternate cognitive domains to goal setting difficulties experienced by preterm children during late childhood needs to be further disentangled. Executive functions comprise numerous higher level, multidimensional and interrelated cognitive skills. Attentional control, working memory, and information processing speed are shown to be mediated by or be highly correlated with executive functions (Friedman et al., 2007; Gathercole, Pickering, Knight, & Stegmann, 2004; McCabe et al., 2010; Mulder et al., 2011), including goal setting (P. J. Anderson, 2002). When completing organisation tasks, attention, working memory and information processing skills are integral for determining the required steps towards goal completion, holding the steps in mind, and completing the steps in a timely and efficient manner. Attention, working memory and information processing speed deficits are prominently and widely documented within preterm samples, and are evident during late childhood (Mulder et al., 2009). It possible that the goal setting deficits we documented are in fact secondary to more primary attention, working memory, or processing speed deficits that mediate goal setting skills, akin to findings in alternate executive function domains (Mulder et al., 2011). While exploration of the influence of lower cognitive domains upon goal setting skills of preterm children was beyond the scope of the current dissertation, it is a topic that warrants further investigation. Consideration of other cognitive domains is especially important when designing interventions aimed at alleviating goal setting difficulties. For example, cognitive training intervention programs targeting domains such as working memory and inhibitory control demonstrate improvements that generalised to improvements in new learning and memory skills (Grunewaldt, Lohaugen, Austeng, Brubakk, & Skranes, 2013; Hermansen Grunewaldt et al., 2015; Lohaugen et al., 2011; Taylor & Clark, 2016).

It is difficult to ascertain the degree of functional goal setting difficulties experienced by preterm children from our assessment, which might have been improved with a greater selection of goal setting measures. In addition to the ecological measures we used, more ecologically valid functional measures of planning and executive functions may have yielded further insight into goal setting skills in the preterm population. The Multiple Errands Task (T.

Shallice & Burgess, 1991) for example, is an assessment of executive functions involving performing multiple simple tasks within a shopping environment (e.g., hospital gift shop). It has been proposed that this task may be more sensitive than traditional neuropsychological tests in revealing executive deficits and predicting their presence in everyday settings (Alderman, Burgess, Knight, & Henman, 2003; Cuberos-Urbano et al., 2013). Constraints of these more ecologically valid functional tests however (e.g., time consuming, requiring sound physical mobility, suitable to only high functioning individuals, difficulties controlling test environment) made them unsuitable to the assessment of goal setting within the current research (Alderman et al., 2003; Knight, Alderman, & Burgess, 2002). Further, these ecologically valid functional tests are more experimental in nature, lacking well established validity and the appropriate normative data necessary for inclusion in the current study. Virtual reality tasks are an increasingly popular alternative for addressing limitations of functional tasks. Virtual reality tasks are praised for their ability to precisely control test environment and stimuli, combining the control of neuropsychological tests using a real-world simulation (Pedroli, Pallavicini, Serino, & Cipresso, 2016). In general, virtual reality tasks are most appropriate for relatively well-functioning individuals (Bohil, Alicea, & Biocca, 2011), but they may have utility in preterm populations whose cognitive deficits are subtle (Tideman, 2000). While child adaptations of adult executive function virtual reality tasks are in the early stages of development (e.g., Virtual Reality Classroom, Jansari assessment of Executive Functions for Children, Virtual Reality Stroop task), they show promise for future research studies, including the assessment of preterm goal setting skills (Parsons, Carlew, Magtoto, & Stonecipher, 2017).

A social risk index score was used in this study to adjust for the potential influence of sociodemographic factors (e.g., family structure, language spoken at home, education of primary caregiver, occupation of the primary income earner, employment status of primary income earner, and maternal age at birth) upon goal setting abilities, given the known association between executive functions and sociodemographic characteristics (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, Oosterlaan, et al., 2013; G. Roberts et al., 2008; Robson & Pederson, 1997). Future research may involve more specific investigation of the

relationship between particular sociodemographic characteristics and goal setting, given that VP groups are known to differ from their FT born counterparts in terms of parental income and education (Aarnoudse-Moens, Weisglas-Kuperus, et al., 2009; Omizzolo et al., 2013). Additionally, proximal sociodemographic factors that may contribute to executive functions, such as neighbourhood and opportunities for hobbies and sports, and family resources, should be considered in further research, given that they may exert an additional positive influence upon executive functions (Aarnoudse-Moens et al., 2013; Diamond & Lee, 2011).

Beyond neonatal brain injury, the risk factors associated with VP goal setting deficits during late childhood remain largely unidentified and warrant future research. Family functioning, parenting style, parent mental health, resources and opportunities have also previously been linked with preterm executive function outcomes (Gueron-Sela, Atzaba-Poria, Meiri, & Marks, 2015; Taylor & Clark, 2016), and are additional potential predictors of VP goal setting difficulties. The identification of the factors that relate to goal setting deficits in late childhood would help to determine which preterm children are at greatest risk for later difficulties, and flag which children would benefit most from intervention services.

Whilst not examined in the current study, preterm goal setting deficits during late childhood may have negative ramifications upon academic achievement. In typically developed populations, executive function difficulties (e.g., working memory, inhibitory control) are associated with poorer academic achievement in math, science, and reading during across early to late childhood (Biederman et al., 2004; Bull, Espy, & Wiebe, 2008; Gathercole et al., 2004). Preterm children with cognitive impairments (i.e., working memory deficits) are at high risk for learning impairments and academic underachievement in late childhood (Johnson et al., 2011; Mulder, Pitchford, & Marlow, 2010). Goal setting difficulties such as poor planning, disorganisation, strategy development difficulties, overreliance on previously learned strategies, as well as poor reasoning (P. J. Anderson, 2002) are similarly likely to hinder the academic progress of preterm children during late childhood. For example, disorganisation may result in poorly formulated essay structure, and poor reasoning is likely to make it difficult to complete complex arithmetic problems. More broadly, planning and organisation deficits may result in difficulties completing and handing in assignments on time, or assigning

appropriate time to study for exams. The relationship between goal setting difficulties in preterm populations and academic outcomes warrants further investigation, given that it may assist in designing environmental modifications for improving school performance.

The impact of psychiatric diagnoses or mood upon goal setting difficulties in preterm children is another consideration for future research. Changes in mood state have a known secondary impact upon cognition and have the potential to confound executive test performance (Gioia & Isquith, 2004), particularly in populations with higher rates of internalising and externalising disorders. For example, children aged between 9 to 17 years with attention deficit hyperactivity disorder experience comparatively greater executive dysfunction than their typically developed counterparts on tests of organisation, cognitive flexibility and response inhibition (P. D. Harvey, 2012). Anxiety may also impair goal-directed attention skills, due to distraction from the task at hand with the reallocation of attention to the anxiety (Derakshan & Eysenck, 2009). Very preterm children are at increased risk of persistent psychiatric disorders, especially anxiety and depressive disorders (Treyvaud et al., 2013). At previous follow-up of the current VP sample at 7 years of age, higher rates of psychiatric diagnoses were documented, including anxiety disorders, ADHD, and autism spectrum disorder (Seidman et al., 2005). Accordingly, is possible that premorbid psychiatric diagnoses or anxiety experienced by preterm children may have dampened their performance on goal setting tasks, particularly given the complexity of these tasks which may have led to feelings of being overwhelmed.

While the aims of this dissertation focused on characterising goal setting deficits and determining their neurological basis, an important research question warranting further investigation involves understanding the trajectory of goal setting skills exhibited by preterm children. It would have been interesting to examine this trajectory but unfortunately goal setting was not assessed in the current VP cohort at 7 years of age, rendering us unable to address this research question. When considering our findings relative to previous literature examining planning, organisation and strategy formulation skills of preterm children through early to late childhood, a coherent picture of goal setting deficits throughout the early to late childhood is apparent, although longitudinal analysis is required to determine whether goal

setting difficulties are persistent (i.e., impaired throughout early childhood to adolescence), or whether they demonstrate maturational lag (i.e., initial developmental delay but age-appropriate skills demonstrated during adolescence). While there is a dearth of longitudinal research specifically examining executive function domains in preterm cohorts, there is some indication that set switching, verbal fluency and working memory deficits may be ongoing (Gilboa et al., 2017; Lalonde, Henry, Drouin-Germain, Nolin, & Beauchamp, 2013; Parsons, Bowerly, Buckwalter, & Rizzo, 2007). Our cross sectional results provide the grounds for examining goal setting skills over time by the way of longitudinal research. Following children across the early to late years of development may help to understand when goal setting deficits manifest, how they develop, or when they plateau along the development continuum (Aarnoudse-Moens et al., 2012; Taylor, Minich, Klein, et al., 2004). Longitudinal assessment of goal setting outcomes would be complemented by serial neuroimaging of preterm children throughout late childhood and adolescence to evaluate changes in brain maturation in association with goal setting outcomes across development.

The structural brain changes, connectivity and brain microstructure underlying clusters of altered network connectivity that we documented remains unclear, and is a topic of interest that might be addressed using multimodal neuroimaging applications. In multimodal neuroimaging, quantitative neuroimaging techniques (e.g., cortical morphometry, shape analysis, diffusion weighted imaging and tractography) are applied in conjunction with functional imaging (e.g., resting state connectivity, task-based) to describe structural brain characteristics as they relate to network connectivity. These techniques permit the concurrent examination of reductions in structural and functional connectivity as well as anatomical variations in order to better understand altered pathophysiology of neurological compromise in prematurity (Michael et al., 2010; Smyser et al., 2016). Combining multimodal neuroimaging to determine structural and functional alterations in association with cognitive outcomes would be beneficial (Baldoli et al., 2015; Chiara Nosarti et al., 2009; Schafer et al., 2009; Weinstein et al., 2016). For example, combining resting state connectivity with diffusion tensor imaging, Cui et al. (2017) demonstrated reduced fractional anisotropy (indicating loss or disorganisation of axons or myelin) and elevated radial diffusivity (corresponding to

possible reduced myelin integrity) of the cingula within the default mode network of brain injured preterm infants. Structural alterations were additionally associated with impaired cognitive functioning, suggesting that microstructural white matter tract abnormalities within the default mode network are important to neurocognitive functioning (Cui et al., 2017). Multimodal examination of altered executive control, frontoparietal and default mode network connectivity in conjunction with structural abnormalities of preterm children during late childhood would help to better understand the neurological underpinnings of these alterations, and may additionally be examined in relation to goal setting difficulties.

6.6 Strengths and Limitations

The current dissertation involved the most comprehensive examination of goal setting skills of preterm children during late childhood to date, including multiple novel and ecological measures of goal setting skills, in association with both neonatal and 13 year neuroimaging data. Prognostic indicators for identifying late childhood goal setting difficulties in preterm samples were also determined. As well, this dissertation initiated research into the neural substrates and neurophysiological mechanisms related to preterm goal setting difficulties in late childhood. The findings of this study extend previous research findings while also identifying aspects of the preterm goal setting literature that warrant further examination. As part of the world's largest prospective longitudinal neuroimaging and neurodevelopmental study of VP and FT children, this dissertation boasted data from numerous developmental time points which allowed us to examine associations over time using numerous demographic, physiological, cognitive and neuroimaging variables. Strong retention rates of this study also contributed to large sample sizes, particularly in our resting state functional magnetic resonance imaging (rs-fMRI) study, allowing us greater certainty that our findings are robust and representative of the VP population.

Despite its numerous strengths, this study also features several limitations. Our VP and FT samples were not matched in terms of sociodemographic factors and sample size. Despite this, the retention rates of our cohort were excellent considering the long-term nature of the study. Given that this dissertation was conducted as part of a larger study with an established

neuropsychological assessment battery, time constraints prohibited us from including a lengthier, functional measure (e.g., Multiple Errands Tests; Knight et al., 2002) of goal setting. Despite this, our study boasts the use of multiple novel and ecologically valid measures of goal setting to assess and interpret ability/impairment. A composite goal setting score was generated to denote overall performance across five measures assessing aspects of goal setting. A composite score has value in increasing power and has the added benefit of equally representation, however it is possible that an alternate method of reducing the data (e.g., principal components analysis or a latent variable approach) may have more strongly represented the goal setting performance by retaining more variance during the variance reduction process (Bryant & Yarnold, 1995).

Regarding neonatal MRI scans, given that there have been substantial advances in MRI technology since this cohort was born (between 2001 and 2003), replication of this study in the current era is required (P. J. Anderson et al., 2017). Modern MRI scanning provides higher resolution scans, featuring improved image quality that enables more precise characterisation of brain structure and function. Given that the Kidokoro et al. (2013) MRI scoring system we applied to assess brain abnormalities during the neonatal period requires the expertise of an experienced neonatal neurologist trained in this method as well as newborn MRI facilities, replication of our findings may be difficult. In spite of this, the MRI scoring system itself has clinical applications and does not require advanced computer analysis. Since the neonatal volumetric MRI technique (e.g., MANTiS) we used is largely a research application and not yet routinely used in clinical settings, the use of this technique for the prediction of long-term VP outcomes may not always be practical. Recognition for the utility of advanced MRI techniques outside of research settings is increasing however, and therefore may become available to clinicians in the future.

Regarding rs-fMRI, a number of cases were rejected for use in our rs-fMRI analyses due to excess motion artefact. While this restricted our data to a high quality dataset, it resulted in a reduction in sample size and possibly power. A limitation in the interpretation of rs-fMRI connectivity data in this study is that rs-fMRI data provides an indirect rather than direct measure of neuronal activity. Having said that, the spatial sensitivity and specificity of

independent components analysis of rs-fMRI data is relatively high and it is a widely used and accepted analytic technique (Beckmann et al., 2005). Additionally, while the interpretation of RSN processes remains challenging, particularly given the relatively young nature of rs-fMRI within the functional neuroimaging field, it is an emerging technique that yields interesting insights into spontaneous connectivity patterns within the brain, and how they may alter at the group level (Cole, Smith, & Beckmann, 2010).

Another challenge to the associations documented between both neonatal and 13-year MRI parameters and goal setting outcome may be the ECS framework that guided this study. While the ECS posits goal setting to be interrelated and interdependent with information processing, cognitive flexibility, and influenced by attentional control, it is possible that goal setting may have a weaker relationship with these alternate executive domains than the model presently suggests (P. J. Anderson, 2002). Accordingly, limitations inherent to the ECS framework might have contributed to a lack of association documented between neuroimaging parameters and goal setting outcomes in this study. Having said that, the ECS is a the first developmental framework to consider the importance of goal setting as a discrete function and thus was considered the best framework to guide this study.

6.7. Conclusion

Our findings further characterise the brain-behaviour relationship in association with premature birth, broadening our understanding of the negative implications upon long term neurodevelopment. Our findings establish that VP children demonstrate significantly poorer goal setting skills than their FT peers during late childhood, confirming that goal setting difficulties are yet another executive function deficit related to premature birth. Goal setting deficits are particularly concerning during late childhood, given their importance for everyday functioning during this developmental period. We have yielded evidence to suggest that neonatal MRI is useful for the identification of early structural subcortical and cortical brain abnormalities which can assist in predicting which preterm children may be most at risk for later goal setting deficits. This finding confirms the ongoing ramifications that the neuropathology of premature birth has upon neurodevelopment, given that the functional

effects of early brain abnormality extend into late childhood. While VP children demonstrate minor alterations in neural connectivity networks during late childhood, these do not appear to contribute to goal setting difficulties during this developmental period.

In summary, this dissertation extends and highlights the implications of premature birth upon EF, brain structure and functional connectivity. Premature birth can result in long-term impairments with potentially deleterious ramifications upon development higher-level cognitive skills such as goal setting and thus, everyday functioning. Thus, understanding the neurophysiological factors associated with these outcomes is critical for providing essential knowledge to inform diagnosis and management, including enhancing early detection and intervention for those at high risk.

Chapter 7. References

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Chapter 8. Appendix

Chapter 8.

8.1. Summary of neonatal brain abnormality scores

	VP (N = 159)
	M (SD)
Global brain	5.36 (3.14)
Cerebellum	.94 (.90)
Cortical gray matter	.67 (1.06)
Deep gray matter	.84 (.96)
White matter	2.91 (1.84)

Note. M = mean; SD = standard deviation; N = total sample size.

8.2. Summary of neonatal brain volumes

Volumes, cm^3	VP (N = 159)^ M (SD)
Brain total	359.00 (48.48)
Corpus callosum area‡	96.52 (26.48)
Hippocampus	2.25 (.31)
Cerebellum	24.63 (3.62)
Thalamus	6.96 (.88)
Amygdala	1.32 (.20)
Cortical gray matter	154.15 (24.02)
White matter	146.27 (18.88)
Basal ganglia	7.04 (0.88)

Note. ^Some volumes sample sizes are less than the total sample due to missing data on independent variables: (basal ganglia and thalamus [n = 158], total brain, cerebellum, amygdala, white matter and cortical gray matter [n = 157], hippocampus [n = 135], corpus callosum [n = 153]. M = mean; SD = standard deviation; ‡ = mm^2; N = total sample number; n = sample number.

8.3. Relationship between neonatal brain volumes and goal setting ability

Volumes, cm^3	Primary[a] (N = 159)^			Secondary[b] (N = 159)^			Tertiary[c] (n = 138)^		
	b	[95% CI]	*p*	*b*	[95% CI]	*p*	*b*	[95% CI]	*p*
Brain total	.01	[.00, .01]	.038*	.01	[.00, .01]	.034*	.01	[-.00, .01]	.07
Corpus callosum area‡	.00	[-.00, .01]	.74	.00	[-.00, .00]	.85	.00	[-.00, .01]	.50
Hippocampus	.44	[-.09, .97]	.10	.39	[-.15, .94]	.15	.20	[-.36, .76]	.48
Cerebellum	.06	[.01, .11]	.018*	.07	[.02, .12]	.007**	.06	[.01, .12]	.024*
Thalamus	.22	[.02, .42]	.035*	.23	[.03, .42]	.021*	.25	[.06, .45]	.011*
Amygdala	.21	[-.63, 1.05]	.62	.28	[-.56, 1.11]	.51	.09	[-.78, .96]	.83
Cortical gray matter	.01	[.00, .02]	.019*	.01	[.00, .02]	.020*	.01	[.00, .02]	.027*
White matter	.01	[-.01, .02]	.30	.01	[-.01, .02]	.43	.00	[-.01, .02]	.67
Basal ganglia	.00	[-.00, .00]	.08	.00	[-.00, .00]	.09	.00	[-.00, .00]	.19

Note. N = total sample number; n = sample number; CI = confidence interval. ‡ = mm^2; [a] = covarying for sex, age at MRI, and intracranial volume; [b] = covarying for sex, age at MRI, intracranial volume, birth weight, gestational age, small for gestational age, necrotising enterocolitis, sepsis and bronchopulmonary dysplasia; [c] = covarying for sex, age at MRI, intracranial volume, birth weight, gestational age, small for gestational age, necrotising enterocolitis, sepsis and bronchopulmonary dysplasia, and excluding children with IQ <70 and/or significant neurosensory impairment.

^Some volume sample sizes are less than the total sample due to missing data on independent variables: (basal ganglia and thalamus [primary, n = 158], total brain, cerebellum, amygdala, white matter and cortical gray matter [primary, n = 157; secondary, n = 137], hippocampus [primary, n = 135; secondary, n = 117], corpus callosum [primary, n = 152; secondary, n = 133]. Missing value: intracranial volume covariates [n = 1].

* $p < .05$; ** $p < .01$.