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**The effect of preterm birth on white matter
tracts and infant cognition**

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ABSTRACT

Preterm birth (defined as birth before 37 weeks) is a leading cause of neurocognitive impairment in childhood, including difficulties in social cognition and executive function. Microstructural divergence from typical brain development in the preterm brain can be quantified using diffusion magnetic resonance imaging (dMRI) tractography during the neonatal period. The relationship between dMRI tractography metrics and later cognitive difficulties remains inconclusive. A general measure of white matter microstructure (g_{WM}) offers a neural basis for cognitive processes in adults, however it remains unclear when g_{WM} is first detectable in the developmental trajectory. Eye-tracking is a technique which assesses eye-gaze behaviour in response to visual stimuli, which permits inference about underlying cognitive processes, such as social cognition and executive function in infancy.

The primary aims of this thesis were to test the hypotheses: dMRI tractography reveals significant differences in tract-average fractional anisotropy (FA) and mean diffusivity (MD) between preterm and term infants, and variance in tract-average FA and MD is shared across major tracts. Secondly, infants born preterm have altered social cognition and executive function compared to term born peers, assessed by eye-tracking and finally, neonatal MRI g_{WM} is associated with cognitive function in infancy.

Preterm (birth weight $\leq 1500\text{g}$) and term infants (born ≥ 37 weeks' post-menstrual age [PMA]) were recruited and underwent a MRI scan at term equivalent age (between 38 - 42 weeks' PMA) and an eye-tracking assessment six to nine months later. Preterm infants were assessed at two years using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). dMRI tractography metrics were generated using probabilistic neighbourhood tractography (PNT) in eight pre-defined tracts-of-interest. Principal component analyses (PCA) were used to determine the correlations between the eight tracts-of-interest for four tract-averaged water diffusion parameters. dMRI metrics were compared to the eye-tracking performance and two year outcome data.

Quantitative microstructural changes were identifiable within the preterm brain when compared to infants born at term. PCA revealed a single variable that accounts for nearly 50% of shared variance between tracts-of-interest, and all tracts showed positive loadings. Eye-tracking revealed group-wise differences in infant social cognition, attributable to preterm birth, but executive functions inferred from eye-tracking did not differ between groups. dMRI tractography metrics within the neonatal period did not relate to later outcome measures.

This thesis shows that variance in dMRI parameters is substantially shared across white matter tracts of the developing brain and suggests that anatomical foundations of later intelligence are present by term equivalent age. Social cognition is altered by preterm birth, however social cognitive ability in infancy is independent of g_{WM} .

LAY SUMMARY

Being born early (preterm) is a leading cause of developmental problems in childhood, such as social difficulties. Using an imaging technique, such as magnetic resonance imaging (MRI), it is possible to see differences between the preterm and term (born \geq 37 weeks) brain at around their due date. However, there are advanced MRI methods, termed diffusion MRI, that go beyond the simple picture of the brain. These techniques can show a representation of each white matter tract (or highway) in a three-dimensional manner and give more detailed information about these differences at a microstructural level. Diffusion MRI, despite being able to show a detailed representation of each white matter tract, is not definitive in its prediction of developmental problems in childhood in preterm infants. Diffusion MRI has been useful in showing how different shared structural properties of white matter tracts underpin brain functions in adults, but this requires to be explored in infants. Eye-tracking is a technique which assesses and records where subjects look on a screen in response to images or animations. From looking patterns, judgements can be made about development in areas such as social development or problem solving and memory, especially in the case of infants.

This thesis was undertaken to answer the questions: (i) Can diffusion MRI accurately identify microstructural changes within the brain of infants that are born prematurely, and is there any evidence of shared structural properties in white matter tracts detectable in early infancy? (ii) Do preterm infants perform differently in eye-tracking assessments examining areas of learning and development when compared to term infants? (iii) Is there any evidence gained from diffusion MRI of different shared structural properties of white matter tracts within the brain in early life that indicates how well the same child might later learn?

Preterm infants (with a birth weight of \leq 1500g) and term infants were recruited and had an MRI scan at around their due date and an eye-tracking assessment six to nine months later. Preterm infants were assessed at two years using a commonly used assessment which tests different areas of development. Diffusion MRI results were analysed and compared to the eye-tracking scores (assessed using where, how long

and how quickly an infant looked at pre-designed images and animations) and the scores from the follow-up assessment.

This study demonstrates differences in brain connectivity between the preterm and term brain using diffusion MRI. Even by their due date, the white matter tracts in infants' brains showed shared structural properties about 50% of the time, however this did not relate to their later eye-tracking assessment or assessment at two years. Using the eye-tracking assessment, preterm infants performed differently in their social development but not in other areas. The preterm brain has shown to be susceptible to damage secondary to early exposure to life outside the womb and these may explain the differences seen in assessments of social development in early infancy. The long-term implications of damage to the preterm brain is worthy of further study and whether widespread or more targeted brain damage is more important in predicting later difficulties in learning.

DECLARATION

Except where the appropriate acknowledgement has been made, the studies undertaken in this thesis were undertaken solely by the author. No part of the work described in this thesis has been previously accepted for, or is currently being submitted in candidature for another degree. The publications included in this thesis are the work of the author unless where otherwise indicated. First or co-author publications can be found in Chapters One, Six and Seven of this thesis, with published papers in their original format in Appendix IV. The specific contribution of the author to each published manuscript can be found within each chapter where relevant.

Chapter 1

I acknowledge the work of Dr James Boardman as a co-author of ‘Modifiable risk factors for preterm brain injury.’

Chapter 5

I acknowledge the help of Drs Chinthika Piyasena, Rozalia Pataky and Sarah Sparrow in the recruitment, and clinical supervision of infants during MRI scanning. I acknowledge the help of nursing staff and radiographers during MRI scanning.

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Chapter 6

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Chapters 7 and 8

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I acknowledge the work of Dr Mark Bastin in generating the values for the habituation score analysis.

Emma J Telford

DEDICATION

This thesis is dedicated to the memory of my dear late grandmother, Marjorie Moore, for whom education was so important.

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PUBLICATIONS, PRESENTATIONS AND POSTERS

Please note that during my PhD I got married, therefore publications and posters are in both my married name of Telford and my maiden name of Moore.

First author publications:

1. **Telford EJ**, Cox SR, Fletcher-Watson S, Anblagan D, Sparrow S, Pataky R, Quigley A, Semple SI, Bastin ME, Boardman JP. A latent measure explains substantial variance in white matter microstructure across the newborn human brain. *Brain Structure and Function*, 2017, *in press*.
2. **Telford EJ**, Fletcher-Watson S, Gillespie-Smith K, Pataky R, Sparrow S, Murray IC, O'Hare A, Boardman JP. Preterm birth is associated with atypical social orienting in infancy detected using eye tracking. *Journal of Child Psychology and Psychiatry*, 2016, *57* (7), 861 - 868, doi:10.1111/jcpp.12546.
3. **Moore EJ** and Boardman JP. Modifiable risk factors for preterm brain injury. *Paediatrics and Child Health*, 2014, *24* (9), 401-406, doi:10.1016/j.paed.2014.02.004.

Other publications:

1. Anblagan D, Bastin ME, Sparrow S, Piyasena C, Pataky R, **Moore EJ**, Wilkinson AG, Clayden JD, Semple SI, Boardman JP. Tract shape modeling detects changes associated with preterm birth and neuroprotective treatment effects. *Neuroimage-Clinical*, 2015, *8*, 51-58, doi:10.1016/j.nicl.2015.03.021.
2. Sparrow S, Manning JR, Cartier J, Anblagan D, Bastin ME, Piyasena C, Pataky R, **Moore EJ**, Semple S, Wilkinson AG, Evans M, Drake AJ, Boardman JP. Epigenomic profiling of preterm infants reveals DNA methylation differences at sites associated with neural function. *Translational Psychiatry*, 2016, *6*, e716, doi:10.1038/tp.2015.210.
3. Serag A, Blesa M, **Moore EJ**, Pataky R, Sparrow S, Wilkinson AG, MacNaught G, Scott SI, Boardman JP. Accurate Learning with Few Atlases

- (ALFA): An algorithm for MRI neonatal brain extraction and comparison with 11 publicly available methods. *Scientific Reports*, 2016, 6, doi:10.1038/srep23470.
4. Blesa M, Serag A, Wilkinson AG, Anblagan D, **Telford EJ**, Pataky R, Sparrow S, MacNaught G, Semple SI, Bastin ME, Boardman JP. Parcellation of the healthy neonatal brain into 107 regions using atlas propagation through intermediate time points in childhood. *Frontiers in Neuroscience*, 2016, 10, 220, doi:10.3389/fnins.2016.00220.
 5. Anblagan D, Pataky R, Evans MJ, **Telford EJ**, Serag S, Sparrow S, Piyasena C, Semple SI, Wilkinson AG, Bastin ME, Boardman JP. Association between preterm brain injury and exposure to chorioamnionitis during fetal life. *Scientific Reports*, 2016, 6, doi:10.1038/srep37932.
 6. Serag A, Wilkinson AG, **Telford EJ**, Pataky R, Sparrow SA, Anblagan D, Macnaught G, Semple S, Boardman JP. SEGMA: an automated SEGmentation Approach for human brain MRI using sliding window and random forests. *Frontiers in Neuroinformatics*, 2017, 11, 2, doi:10.3389/fninf.2017.00002.
 7. Blesa Cábez M, Serag A, Anblagan D, Quigley A, **Moore E**, Pataky R, Semple S, Bastin M, Boardman JP. A modular framework for neonatal connectome construction optimized with anatomically - constrained tractography and linear fascicle evaluation. *Human Brain Mapping*, 2017, *submitted*.

Oral presentations

1. Moore et al. Preterm Birth is Associated with Atypical Social Cognition in Infancy. March 2015 Neonatal Society Spring Meeting. Presented by Emma Moore.
2. Invited lecture to The Association of Paediatric Chartered Physiotherapists. First Annual Infant Mental Health Study Day, Edinburgh 2014.

3. Telford et al. Neonatal white matter integrity exhibits a clear general factor. Neonatal Society Summer meeting, Cambridge 2016. Presented by Dr James Boardman.

Poster Presentations:

1. Telford et al. Diffusion Metrics in callosal fibres in the neonatal period predicts attention to complex visual stimuli in infancy. Pediatric Academic Societies Meeting, Baltimore, USA May 2016. Presented by Dr James Boardman.
2. Telford et al. Preterm Birth is Associated with Atypical Social Cognition in Infancy. Edinburgh University Neuroscience Day 2016. Presented by Emma Telford.
3. Moore et al. Preterm Birth is Associated with Atypical Social Cognition in Infancy (preliminary findings). Enhancing the Study of Early Autism. Toulouse, France, September 2014. Presented by Emma Moore.

Prizes:

1. Poster section prize winner at Edinburgh University Neuroscience Day 2016.
2. Joint winner of best presentation by a trainee at Neonatal Society, London 2015.
3. Stipend awarded to cover travel expenses and accommodation for the Enhancing the Study of Early Autism conference in Toulouse (2014). Award based on the academic merit of the abstract.

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ABBREVIATIONS

ε	Eigenvector
λ	Eigenvalue
λ_{rad}	Radial diffusivity
λ_{ax}	Axial diffusivity
ACC / SMA	Anterior cingulate cortex / supplementary motor area
ADC	Apparent diffusion coefficient
ADHD	Attention-deficit / hyperactivity disorder
AN	Antenatal
ASD	Autism spectrum disorder
AOI	Area of Interest
BE	Base excess
BiPAP	Bilevel positive airway pressure
BMI	Body Mass Index
BPD	Bronchopulmonary Dysplasia
BSID-II	Bayley Scales of Infant and Toddler Development, Second Edition
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CAP	Caffeine for Apnoea of Prematurity
CCG	Cingulum cingulate gyri
CGA	Corrected Gestational Age
CI	Confidence Interval

CoNS	Coagulase Negative Staphylococcus
CP	Cerebral Palsy
CPAP	Continuous positive airway pressure support
CPC	Cerebro-ponto-cerebellar
CRIC	Clinical Research Imaging Centre
CST	Corticospinal tract
CTC	Cerebello-thalamo-cortical
DLPFC	Dorsolateral prefrontal cortex
dMPFC	Dorsomedial prefrontal cortex
dMRI	Diffusion Magnetic Resonance Imaging
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
ERP	Event-related potentials
ELBW	Extremely Low Birth Weight
FA	Fractional Anisotropy
FEF	Frontal eye fields
FFA	Fusiform face area
fMRI	Functional magnetic resonance imaging
GA	Gestational age
GMH	Germinal matrix haemorrhage
<i>g_{WM}</i>	General measure of white matter microstructure

HFNC	High flow nasal cannulae
HIE	Hypoxic-ischaemic encephalopathy
HPI	Haemorrhagic parenchymal infarction
IBQ-R	Infant Behaviour Questionnaire Revised
ILF	Inferior longitudinal fasciculus
INS / VFC	Insula /ventral frontal cortex
IQ	Intelligence Quotient
IQR	Inter-quartile range
ISI	Inter-stimulus interval
ITSEA	Infant Toddler Social and Emotional Assessment
IUGR	Intra-uterine growth retardation
IVH	Intraventricular Haemorrhage
LBW	Low Birth Weight
LC	Locus coeruleus
LOS	Late-onset sepsis
LT	Looking time
MD / $\langle D \rangle$	Mean Diffusivity
MDI	Mental Developmental Index
MgSO ₄	Antenatal Magnesium Sulphate
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging

NC	Low flow nasal cannulae
NEC	Necrotising enterocolitis
NHS	National Health Service
OR	Odds ratio
OR-VERP	Orientation-reversal event-related potential
PCA	Principal component analysis
PDI	Psychomotor Developmental Index
PET	Positron emission tomography
PFC	Pre-frontal cortex
PMA	Postmenstrual Age
PN	Postnatal
Pre-OL	Pre-oligodendrocyte
PNT	Probabilistic Neighbourhood Tractography
PVL	Periventricular leukomalacia
RCOG	Royal College of Obstetricians and Gynaecologists
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
RR	Relative Risk
SC	Superior colliculus
sd	Standard deviation
SDQ	Strengths and Difficulties Questionnaire

SIMD	Scottish Index of Multiple Deprivation
SPL	Social preferential looking
sMRI	Structural Magnetic Resonance Imaging
STS / STG	Superior temporal sulcus/gyrus
SVD	Spontaneous vaginal delivery
TD	Typically developing
TEA	Term equivalent age
TFF	Time to first fixate
TPJ	Temporoparietal junction
TPN	Total parenteral nutrition
VLBW	Very Low Birth Weight
vMPFC / OFC	Ventromedial prefrontal cortex/orbitofrontal cortex

CHAPTER 1 : PREMATURITY

Preterm birth is a significant public health problem. Brain injury associated with preterm birth is a leading cause of adverse neurocognitive outcomes in childhood and beyond (Blencowe et al., 2013, Johnson and Marlow, 2011). Despite the large numbers of infants born preterm, the ability to reliably identify those infants at highest risk of developing an adverse neurological outcome is relatively limited. Consequentially, preterm infants are often diagnosed after the potentially optimal period of intervention. This thesis explores the role of magnetic resonance imaging (MRI) as an early tool to detect high-risk preterm infants in the neonatal period and in later infancy using eye-tracking. Furthermore, the predictive value of MRI scanning will be explored by examining the relationship between early imaging and later cognitive outcomes.

This chapter will discuss the modifiable risk factors associated with preterm brain injury including the vulnerability of white matter within the spectrum of preterm brain injury. A formatted published review (Moore and Boardman, 2014) with added citations, co-authored by Emma Telford (née Moore) and Dr James Boardman, is included in this chapter in Section 1.3, reproduced with permission from Elsevier. Within this review paper, Emma Telford wrote a first draft and was involved in the editing process. The publication in its original format can be viewed in Appendix IV. Parts of Sections 1.1.2, 1.3.2, 1.3.3.1, 1.3.3.2, 1.5.1, 1.5.2 and 1.5.2.1 were also submitted as part of the first year review process for this degree. This chapter will finally discuss quantitative MRI and analysis techniques with reference to preterm brain injury.

1.1 Introduction

1.1.1 Definition of prematurity

Preterm birth is defined as birth before 37 completed weeks' postmenstrual age (PMA) (Blencowe et al., 2012) and can be further defined by either birth weight or gestational age for the purposes of comparing outcomes. Common definitions are summarised in Table 1.1 (Wardlaw et al., 2004, World Health Organisation, 2016b, Blencowe et al., 2013).

Table 1.1 Definitions of prematurity by weight and gestational age

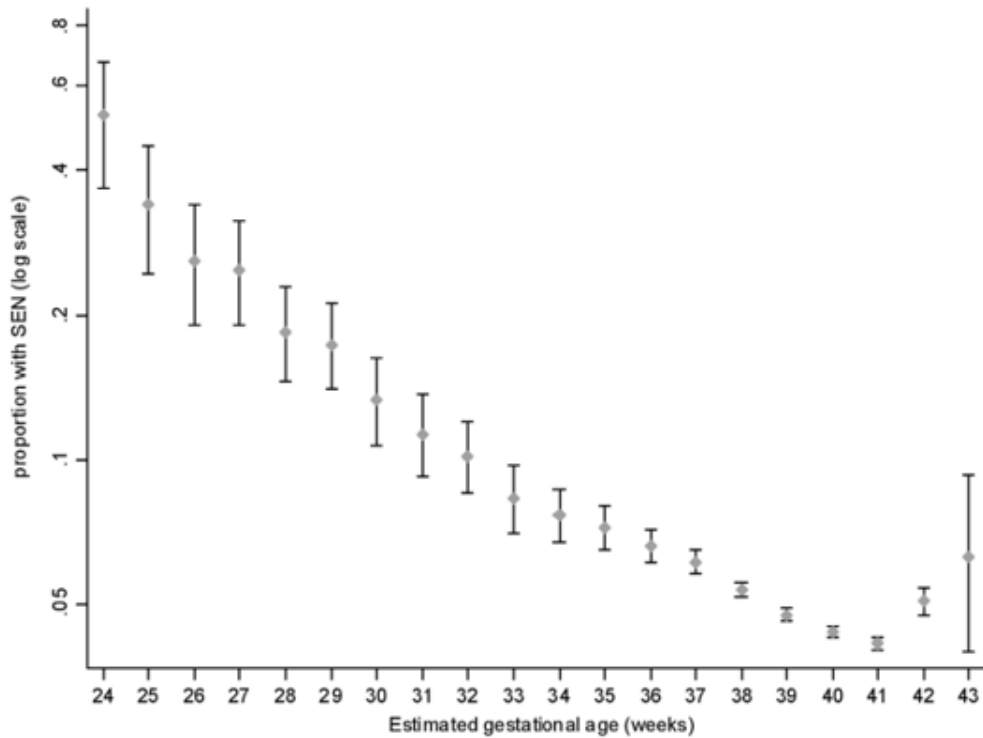
Gestational age category	Definition
Moderate or late preterm	Birth 32 ⁺⁰ - 36 ⁺⁶ weeks' PMA
Very preterm	Birth at 28 ⁺⁰ - 31 ⁺⁶ weeks' PMA
Extremely preterm	Birth under 28 ⁺⁰ weeks' PMA
Weight category	Definition of birth weight (BW)
Low birth weight (LBW)	1500 - 2499g
Very low birth weight (VLBW)	Under 1500g
Extremely low birth weight (ELBW)	Under 1000g

1.1.2 Cognitive outcome after preterm birth

The survival rate of preterm infants has significantly increased, however the burden of disability amongst survivors of preterm birth remains a significant problem (Blencowe et al., 2013). A proportional relationship exists between the degree of prematurity and the likelihood of adverse neurological outcomes (Moore et al., 2012), with the most frequent occurrence in infants born before 28 weeks' post menstrual age or with birth weights of < 1000 g (Colvin et al., 2004). At school age up to 50% of infants born before 28 weeks' PMA require some degree of educational support (Bhutta et al., 2002), but long-term cognitive risk exists across the spectrum of gestational age (Quigley et al., 2012, MacKay et al., 2010). Mackay et al. (2010) undertook a population-based study linking health records to educational outcomes in Scotland. Infants born at the earliest gestation conferred the greatest risk, however an increased risk of special educational needs (SEN) persisted until 39 weeks' PMA (see Figure 1.1) (MacKay et al., 2010).

Figure 1.1 Rate of special educational needs at school age as a logarithmic scale, shown against the gestation at birth

Reproduced from PLoS Medicine^a (MacKay et al., 2010).



Two large clinical studies have been undertaken in the UK in the last two decades examining the outcomes associated with extreme prematurity (described in detail in Section 1.3.2), termed EPICure 1 and 2 (Costeloe et al., 2012). Although these studies generated invaluable insight into the outcomes of preterm birth, limitations exist in their potential clinical utility. Studies with long follow-up periods and local data are often used as a basis to counsel parents of preterm infants about the long-term implications of prematurity, however outcome definitions are broad and often do not encompass subtle deficits. Therefore, a more accurate method for risk stratification and early prognostication has the potential to reduce parental anxiety and pressure on National Health Service resources (Allen et al., 2004).

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1.1.3 Early identification and optimising outcome

The early identification of infants at risk of cognitive impairment would also benefit the individual infant. Appropriate referrals would be made which could allow the application of targeted interventions with the aim of improving outcomes (Johnson and Marlow, 2011). The plasticity of the developing brain in early life is influenced by several external factors (Kolb and Gibb, 2011), and recent research has shown successful adaptation or improvement following brain injury in early life (Stiles et al., 2005). Whilst brain injury associated with prematurity is unique (Bennet et al., 2013), it is certainly plausible that interventions applied earlier within the developmental trajectory are likely to be most effective. To date, various interventions have been attempted in the preterm cohort, however whilst some show improvement in cognitive outcomes during the pre-school period, these do not persist to school-age (Spittle et al., 2015).

This next section will describe a brief overview of the developing brain, before defining and exploring risk factors associated with preterm brain injury.

1.2 Overview of the developing brain

Brain maturation involves complex changes throughout foetal life, beginning at conception and extending into the postnatal period (Stiles and Jernigan, 2010), requiring the connection and myelination of white matter tracts (Dubois et al., 2014). With increasing gestation, the cell-rich cortex increases in volume secondary to neuronal and glial cell proliferation and synapse formation (Saleem, 2013, Stiles and Jernigan, 2010). Gyration and sulcation begin early in embryonic life in a predefined sequence with subsequent rapid progression. All primary sulci develop as early as 8 - 14 weeks' PMA with formation of tertiary sulci continuing into the postnatal period (Stiles and Jernigan, 2010, Chi et al., 1977). Many neurons found within the critically important cortical subplate will form part of the cortex or undergo apoptosis during the third trimester (Stiles and Jernigan, 2010).

Within the central nervous system, white matter is an important component and is made up of myelinated axons (Feldman et al., 2010). Axons which stem from neuronal

cell bodies allow synaptic transmission and are surrounded by myelin (which has a high lipid profile). The axons collectively form bundles and these are grouped together into tracts (Feldman et al., 2010). Cells migrate from subventricular or ventricular zones or germinal matrix to form the basis of white matter tracts (Volpe, 2008). There is a high water content (Dubois et al., 2014) with little myelination until around term equivalent age (Kinney et al., 1988). Myelination begins in the third trimester in the brainstem with very slow progress during the foetal period with a later increase in speed during infancy until adolescence (Dubois et al., 2014), occurring in a "caudorostral" direction (Baumann and Pham-Dinh, 2001). White matter tracts are mainly described based upon their connectivity. Two fibre types are of particular importance: commissural and projection fibres. Commissural fibres are inter-hemispheric and projection fibres link the cortex and the following structures: thalamus, brainstem and spinal cord (Dubois et al., 2014). The cerebellum develops from four weeks' PMA until term and beyond, with exponential growth between 24 and 40 weeks' PMA (Volpe, 2009b, ten Donkelaar et al., 2003). Neurons similarly originate in and migrate from the germinal matrix (Volpe, 2008) (see Section 1.3.3.3).

1.3 Published review: Modifiable risk factors for preterm brain injury

Developments in perinatal care have contributed to the increase in survival of very preterm infants, with a more recent focus on optimising neurological outcome. Emerging evidence has contributed to changes in service provision and clinical guidelines and recommendations within the UK and beyond which have impacted on the preterm brain and subsequent injury. This section includes the published review entitled "Modifiable risk factors for preterm brain injury" with added citations. Reproduced with permission from Elsevier. The original images in Figure 1.3 were also reproduced with permission from Elsevier and John Wiley and Sons.

1.3.1 Abstract

The prevalence of preterm birth is increasing globally and it is a leading cause of neurodevelopmental impairment in childhood. Preterm brain injury consists predominantly of: white matter disease, which may be diffuse or cystic and is usually

accompanied by grey matter alterations; and haemorrhagic lesions (germinal matrix haemorrhage - intraventricular haemorrhage).

The evidence base for neuroprotective strategies has grown in recent years. Antenatal interventions include the use of corticosteroids and magnesium sulphate, and organisation of maternity services so that early postnatal transfer is avoided. Postnatal interventions associated with improved neurological outcome include delayed cord clamping of the umbilical cord, respiratory management strategies that reduce the incidence of pneumothorax and bronchopulmonary dysplasia, avoidance of hypotension and hypocarbia, feeding practices that promote human milk intake, caffeine therapy, avoidance of early relatively high dose postnatal dexamethasone, and minimising the incidence of postnatal sepsis. In this review, we describe the predominant forms of preterm brain injury in the current era and consider the evidence base for clinical practices designed to reduce brain injury and adverse outcome after preterm birth.

Keywords: brain; magnetic resonance image; neonatal; neonate; preterm; white matter

1.3.2 Introduction

Fifteen million children are born at less than 37 weeks' of gestation around the world each year (Blencowe et al., 2012, Blencowe et al., 2013) and this number is rising (World Health Organisation, 2016b). The rate of preterm birth ranges from 5 to 18% by country (Blencowe et al., 2012); in the United Kingdom the figure is 7 - 8% of all deliveries (Information Services Division Scotland, 2012, Office for National Statistics, 2015). Globally, preterm birth is a leading cause of death, and among survivors the rates of disability are high (Blencowe et al., 2013). The most informative UK data about the survival and later health of extremely premature infants comes from the EPICure studies: EPICure 1 collected data on all deliveries in the UK and Ireland between 20 and 25⁺⁶ weeks' gestation over a 10 month period in 1995, and the EPICure 2 study collected perinatal data for babies born between 22 and 26⁺⁶ weeks in England during 2006. Overall, rates of survival to hospital discharge increased from 40% in 1995 to 53% in 2006, but the risk of disability is high: 14% of the 2006 cohort had

cerebral palsy when assessed at 3 years and developmental quotients were lower than those of the general population (Moore et al., 2012, Costeloe et al., 2012). These data are consistent with observations from other countries, which report that 5 - 10% of all very low birth weight (VLBW, less than 1500 g) infants develop cerebral palsy (CP) and 25 - 50% develop cognitive, behavioural, attentional, and / or social difficulties (Marret et al., 2013, Delobel-Ayoub et al., 2009, Roberts et al., 2009, Hack et al., 2002, Hack et al., 2009, Saigal et al., 2003). Here, we will review the common forms of preterm brain injury and consider the factors that promote resilience to injury and improve long-term outcome.

1.3.3 Types of preterm brain injury

1.3.3.1 White matter disease of prematurity

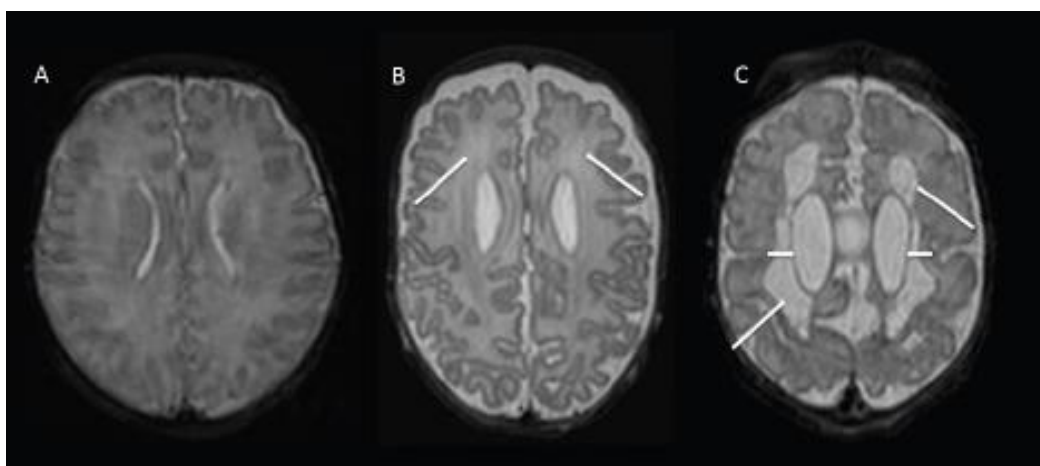
Over the past 15 years there has been a paradigm shift in understanding of the importance of white matter disease of prematurity (Volpe et al., 2011), with greater appreciation of diffuse white matter disease as well as the focal cystic form of periventricular leukomalacia (PVL) (Figure 1.2). The focal form represents the classic description of coagulation necrosis of all cellular elements leading to cystic degeneration in a periventricular distribution (Volpe et al., 2011). This pattern of injury is strongly associated with cerebral palsy (usually spastic diplegia), cerebral visual impairment, and cognitive impairment (Back and Miller, 2014, Munck et al., 2009, Resch et al., 2000). The prevalence of cystic PVL has declined over the past twenty years (Volpe, 2009a), and now affects 2 - 5% of VLBW children (Larroque et al., 2003, Miller et al., 2003, Woodward et al., 2006).

Diffuse white matter disease is characterized by loss of premyelinating oligodendrocytes (pre-OLs) and subsequent hypomyelination with astrogliosis and microgliosis (Volpe et al., 2011). The neuropathological description has come from experimental models and the post-mortem study of human tissue (Volpe, 2008, Volpe et al., 2011). It is thought that the diffuse abnormality in signal intensity on magnetic resonance imaging (MRI) commonly seen among preterm infants at term equivalent age (Boardman et al., 2006) (and quantifiable using diffusion tensor imaging, DTI) (Pandit et al., 2013a) may be an image marker of diffuse white matter disease

(Boardman et al., 2010) (Figure 1.2). MRI evidence of diffuse white matter disease is seen in around one half to two thirds of preterm infants at term equivalent age, and because this is similar to the prevalence of later cognitive impairment, this pattern of injury is now a focus of research attention as a neural substrate for impairment (Boardman et al., 2006, Boardman et al., 2010). The pathogenesis of white matter disease of prematurity centres on the vulnerability of the pre-OL and involves two upstream processes - cerebral ischaemia and systemic infection / inflammation (Volpe et al., 2011, Volpe, 2009a) which activate three downstream mechanisms to converge on pre-OL injury: microglial activation, glutamate mediated excitotoxicity, and release of reactive oxygen and nitrogen species (see review by Volpe in further reading list) (Volpe, 2009a).

Figure 1.2 T2 weighted axial images at the level of the lateral ventricles

From (a) a healthy infant born at 39⁺¹ weeks with images acquired on day 16 after birth; (b) an infant born at 25⁺⁰ weeks with image acquisition at 42⁺⁴ weeks' PMA and (c) an infant born at 26⁺⁰ weeks, with images acquired at 39⁺³ weeks PMA. Figure (b) shows features that are common among preterm infants at term equivalent age including enlargement of the ventricular system and extracerebral space and diffuse excessive high signal intensity in the white matter (arrows) compared with (a). Figure (c) shows areas of cystic periventricular leucomalacia (long arrows) distinct from the lateral ventricles (short arrows).



1.3.3.2 Punctate white matter lesions

These are small areas of increased signal intensity on T1 weighted MRI (Benders et al., 2014), usually situated in the corona radiata, the posterior periventricular white matter, and the optic radiation (Bassi et al., 2011, Dyet et al., 2006, Cornette et al., 2002). They occur in around one quarter of very preterm infants and are seen more frequently in the preterm period than at term equivalent age (Dyet et al., 2006), which suggests a transitory course. The aetiology is uncertain (Rutherford et al., 2010, Cornette et al., 2002). Although they are not known to predict poor outcome (Dyet et al., 2006), they are associated with altered DTI measures (Counsell et al., 2003), and further follow-up studies are required to assess their clinical significance. Evidence from experimental, pathological and neuroimaging studies shows that white matter disease is not limited to the pre-OL population but that injury to the white matter also affects neurons and is associated with structural alterations in cortical grey matter, the deep grey matter nuclei, the brainstem and the cerebellum (Volpe, 2009a, Volpe, 2009b, Volpe et al., 2011). These observations suggest that preterm brain injury disturbs the connectivity of developing neural systems (Ball et al., 2013).

1.3.3.3 Haemorrhagic lesions

Germinal matrix - intraventricular haemorrhage (GMH-IVH): GMH-IVH describes the spectrum of haemorrhagic lesions that originate with a bleed in the subependymal germinal matrix (Inder and Volpe, 2000), a structure that lies over the head of the caudate nucleus predominantly (Takashima et al., 1986), but also in the periventricular zone (Volpe, 2008). It is most prominent between 24 and 34 weeks' gestation, with almost complete regression by term (Raets et al., 2013, Scott et al., 2011). It is populated with neuroblasts and glioblasts and contains a capillary bed that is supported by stromal tissue (Ballabh et al., 2004, Dummula et al., 2010). Haemorrhage at this site can be limited to the germinal matrix ('grade 1' according to the Papile classification), or extend into the lateral ventricle without causing distension (uncomplicated GMH-IVH / Papile grade 2), or extend into the ventricle leading to enlargement (complicated GMH-IVH / Papile grade 3) (Papile et al., 1978). If GMH-IVH leads to a progressive enlargement of the ventricles over time so that the ventricular index exceeds 97th centile for gestation, then the term post-haemorrhagic

ventricular dilatation is used (Levene and Starte, 1981). Venous drainage of the deep white matter converges on the terminal vein, which runs through the germinal matrix (Inder and Volpe, 2000, Takashima et al., 1986). If haemorrhage in the germinal matrix disrupts venous return through the terminal vein, this can lead to obstruction of the medullary veins of the deep white matter leading to venous infarction of parenchymal tissue with or without a haemorrhagic component (Gould et al., 1987, Takashima et al., 1986, Volpe, 2008). Typically this occurs in a characteristic distribution, which can be visualized on ultrasound as a ‘wedge-shape’ adjacent to the lateral ventricle in the coronal plane (Dudink et al., 2008). Although the term grade 4 IVH has been applied to this lesion in the past, it is important to recognize that this is not an extension of an IVH, but rather the consequence of venous infarction (Volpe, 2008), and the term haemorrhagic parenchymal infarction (HPI) is a more suitable description if imaging or post-mortem examination confirms haemorrhage in the affected area. Most GMH-IVH occurs in the first 72 hours after birth (Dummula et al., 2010, Partridge et al., 1983) and is strongly associated with younger gestational age (Wells and Ment, 1995). There is evidence of a decline in the prevalence of GMH-IVH over the past two decades (Heuchan et al., 2002, Raets et al., 2013, Batton et al., 1994). Uncomplicated GMH-IVH is not usually associated with significant impairment (Radic et al., 2015), however the risk of neurodevelopmental impairment increases to around 50% if ventricular dilatation develops and is around 80% if a shunt is required (Volpe, 2008). Outcome following HPI is determined by site and size of the lesion (Rademaker et al., 1994): frontal lesions anterior to the trigone may not lead to significant motor impairment, whereas lesions posterior to the trigone are associated with hemiplegic cerebral palsy. HPIs that degenerate into porencephalic cysts are associated with seizures and cognitive impairment as well as motor impairment (Blackman et al., 1991).

1.3.3.4 Cerebellar haemorrhage

MRI allows improved visualisation of the posterior fossa compared with conventional ultrasound approaches through the anterior fontanelle, and this has led to greater appreciation of the prevalence of cerebellar haemorrhage (Wezel-Meijler and de Vries, 2014, Benders et al., 2014) as a complication of preterm birth. It is seen in 10 - 15%

of preterm infants (Miller et al., 2005, Limperopoulos et al., 2005a) and is specifically associated with motor and cognitive deficits (Limperopoulos et al., 2007).

1.3.4 Modifiable risk factors for preterm brain injury

1.3.4.1 Antenatal and intra-partum factors

- Place of delivery: delivery of preterm infants in centres that deliver a high volume of neonatal intensive care activity is associated with improved outcomes (Marlow et al., 2014). This has been one of the leading drivers for the reorganization of neonatal care into managed clinical networks (MCNs) in the UK (The National Audit Office study team, 2007). In the MCN model groups of hospitals work collaboratively to deliver different levels of specialist care, ensuring that intensive care is delivered in centres with the greatest experience, and that transfer back to the local hospital for ongoing care after the period of intensive care is over is facilitated. One of the outcomes that is improved by avoiding early postnatal transfer of VLBWs is IVH (Mohamed and Aly, 2010). The National Audit Office and the National Institute for Health and Clinical Excellence suggest that maternity and neonatal services should work together to ensure that in utero transfer takes place before delivery if it is safe for the mother so that acute postnatal transfer of infants of low gestational ages can be avoided (The National Audit Office Study Team, 2007, Fenton et al., 2008).
- Antenatal corticosteroids: antenatal corticosteroids given to women at risk of threatened preterm labour are associated with reductions in neonatal death, respiratory distress syndrome (RDS) and IVH, and are safe for the mother (Roberts and Dalziel, 2006). A Cochrane review of 21 studies (3885 women and 4269 infants) found that antenatal steroids reduced the risk of death by 31% (95% CI 19 - 42%), of IVH by 46% (95% CI 31 - 67%), and of RDS by 44% (95% CI 31 - 57%) (Roberts and Dalziel, 2006). Other neonatal benefits include reductions in necrotizing enterocolitis, need for respiratory support, and early-onset infection (Carlo et al., 2011, Roberts and Dalziel, 2006). Therefore the Royal College of Obstetricians and Gynaecologists (RCOG)

recommend that all women who present with threatened preterm labour between 24⁺⁰ and 34⁺⁶ weeks' should receive antenatal corticosteroids (National Institute for Health and Care Excellence, 2015). There are likely survival benefits to the neonate born at 23 weeks who has been exposed to antenatal steroids, so if following discussion with obstetric colleagues and parents, a decision has been made to offer intensive care to a baby born at this gestation then our practice is to counsel in favour of giving the mother corticosteroids prior to delivery.

- Antenatal magnesium sulphate (MgSO₄): a number of case-control studies describe an association between exposure to antenatal MgSO₄, given for maternal reasons, and a reduction in the risk of cerebral palsy (Nelson and Grether, 1995, Matsuda et al., 2000, Boyle et al., 2000). The apparent neuroprotective effects seen in the early observational studies have been tested in randomized controlled trials where antenatal MgSO₄ versus placebo is given for the purpose of fetal neuroprotection (Rouse et al., 2008, Crowther et al., 2003). There is unequivocal evidence of benefit when given to mothers who are at risk of preterm labour at less than 30 weeks' gestation. An updated Cochrane systematic review included five trials (6145 babies) and showed that 63 mothers (95% CI 43 - 155) need to be treated with MgSO₄ for one baby to avoid cerebral palsy (Doyle et al., 2009). Based on these figures, and with no evidence of long-term harm to mother or infant, several countries have developed clinical practice guidelines that endorse or support the use of antenatal MgSO₄ for fetal neuroprotection in women who are at risk of preterm delivery. A Scientific Impact Paper (No.29) from the RCOG (Peebles and Kenyon, 2011) concludes that if clinicians plan to use antenatal MgSO₄ for fetal neuroprotection then they should base local guidelines on the National Clinical Practice Guideline published by the University of Adelaide in 2010 (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel, 2010). This recommends use of antenatal MgSO₄ in women at risk of early preterm (GA less than 30 weeks), imminent birth (early preterm birth is planned or definitely expected within 2 hours). The guideline recommends an intravenous 4 g loading dose over 20 - 30 minutes followed by

a 1 g / hour maintenance infusion to continue for 24 hours or until birth, whichever occurs soonest. Trials and follow-up studies are ongoing to determine whether antenatal MgSO₄ is protective at later gestations and whether it confers benefit for long-term cognitive function.

- Placental transfusion: increasing the volume of placental transfusion to the newborn by delayed clamping of the umbilical cord is associated with a number of health benefits to the preterm neonate. A recently updated Cochrane review of fifteen studies (738 infants aged between 24 and 36 weeks' gestation at birth) found that delayed cord clamping was associated with a significant risk reduction for all grades of IVH with RR 0.59 (95% CI 0.41 - 0.85), as well as reducing the number of transfusions required for anaemia (RR 0.61, 95% CI 0.46 - 0.81) and the risk of necrotizing enterocolitis (RR 0.62, 95% CI 0.43 - 0.90), when compared with immediate clamping of the cord (Rabe et al., 2012). Although there is a slight increase in the peak bilirubin in infants who have experienced delayed cord clamping (mean difference 15.01 micromol / litre, 95% CI 5.62 - 24.40), it is unlikely that this will lead to harm in settings where accurate and regular surveillance of hyperbilirubinaemia is carried out, and where there is access to effective phototherapy if levels exceed gestational age appropriate thresholds.

1.3.4.2 Neonatal factors

- General neonatal care: survival rates after birth at young gestational ages have improved between 1996 and 2006 (Costeloe et al., 2012). During this time period there have been changes to the way services are organized, and a number of evidence based practice changes have occurred or become embedded over this time period: more widespread use of antenatal steroids; occlusive wrapping to prevent hypothermia immediately after birth, earlier and more frequent use of surfactant replacement treatment, and a reduction in the use of postnatal dexamethasone to wean babies from mechanical ventilation (National Institute for Health and Care Excellence, 2015, Vohra et al., 2004, Bahadue and Soll, 2012, Doyle et al., 2014). It is plausible that some of these

measures have also had a positive effect on the rates of preterm brain injury, since some are known to be associated with specific adverse outcomes: lack of antenatal steroids, postnatal transfer and respiratory distress syndrome (especially if complicated by pneumothorax) are all associated with GMH-IVH (Roberts and Dalziel, 2006, Mohamed and Aly, 2010, Kadri et al., 2006, Pishva et al., 2012) and relatively high dose dexamethasone early in the postnatal period, is associated with cerebral palsy (Doyle et al., 2014). Other general measures are important for protecting the preterm brain including ventilation strategies that minimize risk of pneumothorax and bronchopulmonary dysplasia (Pishva et al., 2012, Teberg et al., 1991), and the avoidance of hypoglycaemia, hypothermia, hypotension and hypocarbia (Rozance and Hay, 2006, McCall et al., 2008, Osborn and Evans, 2004, Wheeler et al., 2011, Leviton et al., 2010).

- Feeding: the benefits of breast feeding term infants are unequivocal and underpin the World Health Organisation recommendation that all infants should be exclusively breast fed from birth until 6 months (World Health Organisation, 2016a). Optimal enteral feeding of the VLBW infant is challenging because unmodified human milk does not meet the VLBW infant's requirements for protein, energy, sodium, calcium, phosphorus and magnesium, trace elements and vitamins (Corvaglia, 2015, Embleton, 2007, Kashyap et al., 1990, Atkinson et al., 1983, Finch, 2014, Greer, 2001). The physician has a number of options to help deliver nutrient requirements including human milk (mother's own preterm milk; donor milk; fortified human milk; and human milk formulas), and term and preterm infant formulas. The advantages of using human milk include reduced risk of necrotizing enterocolitis, improving gastrointestinal tolerance, and possible long-term modulating effects on cardiovascular, metabolic health and immune modulation (Quigley and McGuire, 2014, Singhal et al., 2001, Oddy, 2012, Matson et al., 2009). There is also evidence that human milk feeds are neuroprotective for preterm infants. In early seminal studies, preterm infants fed with maternal expressed breast milk had higher developmental quotients at 18 months and higher IQs at 7 years compared to infants fed on other diets

(Vohr et al., 2006, Lucas et al., 1998), and in sophisticated MRI studies of adolescents born preterm white matter volume in males correlates positively with neonatal human milk exposure (Isaacs et al., 2010). Many questions remain about the optimal timing of introducing enteral feeds, the pace of increase, the role of fortification, the macronutrient components of early parenteral nutrition, and the role of donor milk in supporting the preterm infant and optimising brain outcomes (Wackernagel, 2016, Adamkin and Radmacher, 2014), but the evidence of neurodevelopmental benefit for infants fed human milk is compelling, and mothers should be made aware of this during postnatal counseling after preterm delivery.

- Caffeine: caffeine is widely used for the treatment of apnoea of prematurity and because it reduces the rate of bronchopulmonary dysplasia (BPD) in VLBW infants. The CAP (Caffeine for Apnoea of Prematurity) study, which randomly assigned 2006 infants with birth weights of 500 - 1250 g during the first 10 days after birth to receive either caffeine or placebo, found a reduction in BPD in the intervention group, but also showed that the intervention group were less likely to have cerebral palsy (OR 0.58, 95% CI 0.39 - 0.87) or cognitive delay (OR 0.81, 95% CI 0.66 - 0.99) at 18 - 21 months, and improvements in some aspects motor function and visual perception were sustained at 5 years (Schmidt et al., 2007, Schmidt et al., 2012). In the original CAP trial, caffeine was continued to a median age of 34 weeks' postmenstrual age, so it seems prudent to continue caffeine therapy until this age if the neuroprotective effects are to be realized.
- Minimise exposure to infection / inflammation: perinatal infection, including chorioamnionitis and early-onset (less than 72 hours after birth) and late-onset (more than 72 hours after birth) sepsis are risk factors for white matter disease, and are closely associated with neurodevelopmental impairment (Kim et al., 2015, Anblagan et al., 2016, Shane and Stoll, 2014). In a meta-analysis by Wu and colleagues, clinical chorioamnionitis was associated with cerebral palsy (RR 1.9, 95% CI 1.4 - 2.5) and cystic PVL (RR 3.0, 95% CI 2.2 - 4.0) in preterm infants (Wu and Colford, 2000). Postnatal sepsis is very common

among VLBWs, with rates of early-onset sepsis around 2 - 5% and late-onset around 20 - 40% (Hornik et al., 2012, Klinger et al., 2010, Stoll et al., 2010, Shah et al., 2015, Mitha et al., 2013). The National Institute of Child Health and Human Development Neonatal Research Network in the United States assigned 6093 ELBW infants to one of five groups: uninfected; clinical evidence of sepsis; blood culture positive sepsis; sepsis and necrotizing enterocolitis; and meningitis with or without sepsis (Stoll et al., 2004). When compared with uninfected infants those in the four sepsis groups had significantly increased odds of neurodevelopmental impairments including cerebral palsy (range of significant ORs 1.4 - 1.7), low Bayley Scales of Infant Development II scores on the mental development index (ORs 1.3 - 1.6) and psychomotor development index (ORs 1.5 - 2.4), and vision impairment (ORs, 1.3 - 2.2). Data from the Epipage study group show that the effects of neonatal sepsis exposures are cumulative for cerebral palsy and persist to 5 years of age (Mitha et al., 2013). Although the mechanistic link between perinatal inflammation or sepsis and cerebral injury is a subject of ongoing research and may yield new treatment strategies, there is little doubt that prevention is vitally important.

- Intra-partum antibiotic prophylaxis is effective at reducing early-onset infection with Group B streptococcus in women whose infants are known to be at risk, and local systems should be in place to ensure eligible women are identified and offered this treatment in labour (Ohlsson and Shah, 2013, Royal College of Obstetrics and Gynaecologists, 2013). Quality improvement initiatives can be highly effective at reducing the prevalence of late-onset sepsis among VLBWs. A detailed description of the care bundles and practices that are effective is beyond the scope of this review, but in summary the following strategies should be considered: systematic collection of high quality sepsis data and benchmarking; rigorous attention to hand hygiene including the use of gloves for handling VLBWs; care bundles for central and peripheral line insertion and maintenance; chlorhexidine solution for skin antisepsis; promotion of human milk feeds; bathing protocols; implement strategies for preventing ventilator (including nasal CPAP) associated pneumonia; use

antifungal prophylaxis; improve antibiotic stewardship; avoid over-crowding and provide staff with education and feedback (Shane and Stoll, 2014, Polin et al., 2012, Sinha et al., 2015, Edraki et al., 2014, Kaier et al., 2014, Tablan et al., 2004, Kaufman et al., 2001, Saiman, 2002).

- Minimise respiratory morbidity: bronchopulmonary dysplasia is an independent predictor of poor neurodevelopmental outcome (Ball et al., 2010, Hansen et al., 2004), and in a primate model of premature birth, prolonged exposure to ventilation is associated with adverse cerebral outcomes including reduced oligodendroglia number, volume loss and white matter injury (Loeliger et al., 2006). We have shown that brain volumes are reduced in preterm infants with an oxygen requirement that persists beyond 28 days and that white matter microstructure is altered in preterm infants with bronchopulmonary dysplasia (Figure 1.3) (Ball et al., 2010, Boardman et al., 2007). The mechanistic link between lung and brain injury is uncertain (Albertine, 2012), and could include factors related to nutrition, inflammation, or fluctuating hyperoxia (Loeliger et al., 2006); but the associations described suggest that interventions designed to improve respiratory outcomes should also be assessed for neuroprotective effects.

1.3.5 Future direction

Advances in perinatal medicine have improved the survival of VLBWs, and understanding about how to protect the preterm brain has increased. It is important that evidence based strategies are translated into clinical practice. Basic research in to the neurobiology of preterm brain injury has led to the development of new therapeutic strategies (Aversa et al., 2011, Xiong et al., 2011, Jin et al., 2015). Some of these are already at the stage of clinical trial, including melatonin, erythropoietin, IGF-1, optimal management of the umbilical cord at birth, nutrition, tissue perfusion, and transfusion practice (Biran et al., 2014, Clinical Trials Register, 2016, March et al., 2013, Duley and Batey, 2013, Bianchi et al., 2014). It is likely that technical advances in the acute assessment of the cerebral perfusion, and quantitative high resolution MRI and DTI will play significant roles in assessing the effect of interventions on the

developing brain and so expedite the translation of new neuroprotective strategies to the cotside.

1.3.6 Role of the funding source

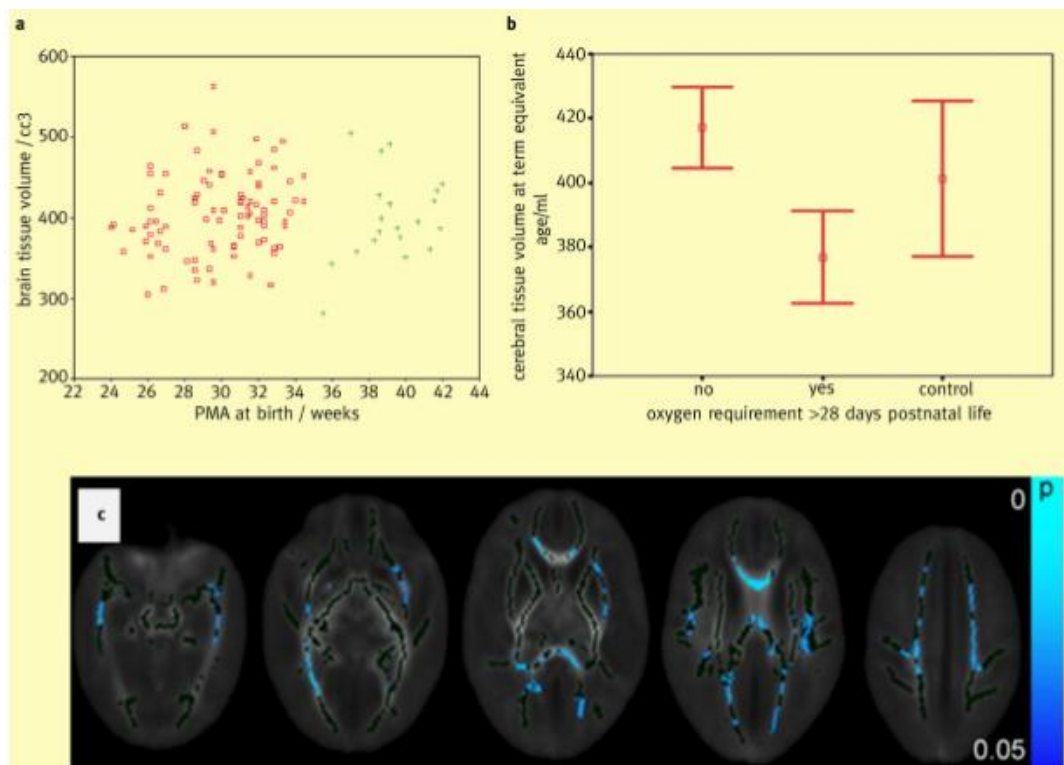
The authors are grateful for the grant support from Theirworld for Dr Moore's PhD fellowship (www.theirworld.org).

1.3.7 Conclusion in the context of the current thesis

This review paper has identified the spectrum of white matter injury in the context of preterm brain injury, highlighted several clinical factors which may impact on the neurocognitive outcome associated with prematurity and has reaffirmed the potential of MRI imaging as an image marker of diffuse white matter disease. However, despite the improvements in clinical care, the prevalence of preterm brain injury remains high and role of quantitative DTI imaging remains less conclusively explored. The next sections will focus on the diffuse pattern of disease and the role of DTI in the assessment of preterm brain injury.

Figure 1.3 Association between respiratory morbidity and cerebral development.

Whole brain volume is preserved in the majority of preterm infants at term equivalent age, and does not differ significantly from brain volumes of healthy controls (a). However preterm infants with prolonged need for supplemental oxygen have lower brain volume than preterm infants without this complication (b). In a two group comparison of preterm neonates with and without BPD, there were significant alterations in white matter microstructure associated with BPD. Areas of blue show regions at the centre of white matter tracts where fractional anisotropy, a measure of tract integrity, is reduced with BPD (c). Figures (a) and (b) are from Boardman et al. *Ann Neurol* 2007, reproduced with permission from John Wiley and Sons. Figure (c) is from Ball et al. *Neuroimage* 2010.



1.4 Pathogenesis of diffuse preterm brain injury

The pathogenesis of preterm brain injury and the importance of white matter vulnerability is briefly discussed above in Section 1.3.3. Due to the relatively low prevalence, cystic PVL will not be dealt with further in this thesis. The diffuse pattern

of preterm brain injury will now be examined in more detail. As previously described, diffuse white matter injury is not localised to the pre-OL population and damage is more widespread. The combination of pre-OL loss, and the resultant inflammatory process with associated axonal and neuronal disease (Back and Miller, 2014, Volpe, 2009a) has been termed "encephalopathy of prematurity" (Volpe, 2009c). The disturbance to the differentiation of glial progenitors and neuronal maturation which follows the response to primary injury has been suggested to result in a "primary cerebral dysregulation disorder" (Back and Miller, 2014). Pre-OLs remain in an immature state with atypical myelination following an initial insult and cell death, with relative axonal sparing (Back and Miller, 2014, Riddle et al., 2012). Axonal injury appears to be localised to larger axons in the pre-myelinating phase, rather than those that are smaller and not myelinated (Alix et al., 2012). Neurons, however, show difficulty in developing normal dendritic processes despite a lower incidence of cell death, which results in disruptions to synaptic transmission (Back and Miller, 2014). Preterm infants have comparably smaller cortical and subcortical structures when compared to infants born at term (Keunen et al., 2012, Nossin-Manor et al., 2012), secondary to growth failure associated with impairments in neuronal development or degradation associated with axonal injury or in grey matter structures (Back and Miller, 2014). Cerebellar involvement in preterm brain injury has been identified as an important factor. During a period of exponential growth during the third trimester (Limperopoulos et al., 2005b), the cerebellum is vulnerable to insult secondary to several inherent factors (Koning et al., 2016), the result of which has been linked to adverse neurological outcomes (Volpe, 2009b) (also see Section 1.3.3.4). As described in Section 1.3.3.2, recent evidence has supported involvement of disruption of neural connectivity in preterm brain injury (Ball et al., 2013). Considering the cerebellum as an example, the cerebello-thalamo-cortical (CTC) and cerebro-ponto-cerebellar (CPC) tracts are developing during the last trimester of pregnancy (Volpe, 2009b, Pieterman et al., 2016). However, it remains uncertain if later deficits are a direct result of insults to a primary structure such as the cerebellum or as a result of disruption to specific tracts and insults to secondary structures, such as the cortex (Pieterman et al., 2016).

1.5 Neuroimaging in preterm brain injury

1.5.1 Conventional imaging

Advances in imaging technology has furthered understanding of preterm brain injury as shown by the identification of the diffuse pattern of injury in preterm infants using structural MRI (sMRI) as shown in Figure 1.2. MRI is a safe, non-invasive and powerful technique that provides useful information about patterns of injury associated with preterm birth (Counsell et al., 2014). Structural T1- and T2-weighted sequences are commonly used to identify white matter damage and typically undertaken at term equivalent age (TEA) (Boardman et al., 2010, Plaisier et al., 2014a). MRI is able to overcome limitations associated with other neuroimaging modalities such as cranial ultrasound, allowing a more accurate examination of diffuse white matter lesions, posterior fossa and associated pathology (such as cerebellar haemorrhage) and punctate white matter lesions (Wezel-Meijler and de Vries, 2014, Benders et al., 2014, Maalouf et al., 2001). Further discussion regarding the accuracy of ultrasound is beyond the scope of this thesis and the focus from this point onwards will be MRI. Although previous studies have linked structural changes to later patterns of disabilities, this correlation is not firmly established (Dyet et al., 2006, Woodward et al., 2006). The clinical implications of diffuse white matter injury on conventional imaging will be fully explored in Chapter Two.

1.5.2 Quantitative diffusion imaging

Quantitative imaging methods lend themselves to overcome limitations associated with conventional imaging in fully examining the positive predictive value of features commonly reported at term equivalent age. Quantitative imaging measures when assessing preterm brain injury is a more objective method and improves specificity when compared to conventional imaging (Pandit et al., 2013a, Counsell et al., 2003). Quantitative MRI studies can examine microstructural changes either across the brain or in regions of interest (Pandit et al., 2013a). Regional differences are identifiable in the preterm brain using whole brain and regional methods and these have been used to link preterm brain structure to functional outcomes (Setänen et al., 2016, Lind et al., 2011). However, evaluation of the brain's microstructure may give a more accurate

understanding of underlying neuropathology and prediction of later neuro-impairment (de Kieviet et al., 2012, Narberhaus et al., 2008, Nosarti et al., 2004, Pandit et al., 2013a, van Kooij et al., 2012). Diffusion MRI (dMRI) can identify microstructural changes in the brain's white matter not seen on conventional structural MRI which allow a more detailed examination of individual fibres within white matter tracts (Li et al., 2015).

1.5.2.1 Diffusion magnetic resonance imaging

Diffusion MRI is a technology that can identify microstructural changes in underlying tissues (Basser and Pierpaoli, 1996) based on the molecular motion of water protons (Le Bihan et al., 1986). Within cerebrospinal fluid, the pattern of water diffusion is equal in all directions and this can be described as isotropic (Counsell et al., 2014). This is in contrast to anisotropic diffusion where the movement of water molecules is hindered by white matter tracts and is therefore directionally dependent (Pandit et al., 2013a). The pattern of water molecule diffusion within the brain can be quantified within a single voxel using parameters derived from the diffusion tensor (Basser and Pierpaoli, 1996), which can be represented as an ellipsoid (Counsell et al., 2014). Figure 1.4 (Pandit et al., 2013a) shows the three axes within the ellipsoid from which directional and scalar components representing the pattern of water diffusion can be expressed, specifically by three eigenvectors and eigenvalues (Pandit et al., 2013a, Basser and Pierpaoli, 1996). The largest eigenvalue (λ_1) indicates the highest degree of water molecule diffusion along the orientation of the first eigenvector (ϵ_1) while the two smaller eigenvalues (λ_2 and λ_3) show the pattern of water diffusion along the second (ϵ_2) and third (ϵ_3) eigenvectors which are perpendicular to ϵ_1 (Feldman et al., 2010, Pandit et al., 2013a, Pierpaoli et al., 1996). Mean diffusivity (MD / $\langle D \rangle$) utilizes the three eigenvalues to measure the magnitude of water diffusion in three dimensions as shown in Equation Two, Figure 1.5 (Basser and Pierpaoli, 1996). Fractional anisotropy (FA) measures the directional coherence of water molecule diffusion from λ_1 , λ_2 and λ_3 (Basser and Pierpaoli, 1996) as shown in Equation One in Figure 1.5 (Basser and Pierpaoli, 1996).

Figure 1.4 Diffusion tensor ellipsoids

From Pandit et al. 2013 (Pandit et al., 2013a). The top figure depicts anisotropic and the bottom figure depicts isotropic diffusion. λ_1 points along the orientation of the first eigenvector (ϵ_1) and eigenvalues λ_2 and λ_3 along eigenvectors ϵ_2 and ϵ_3 respectively. Reproduced with permission from Springer.

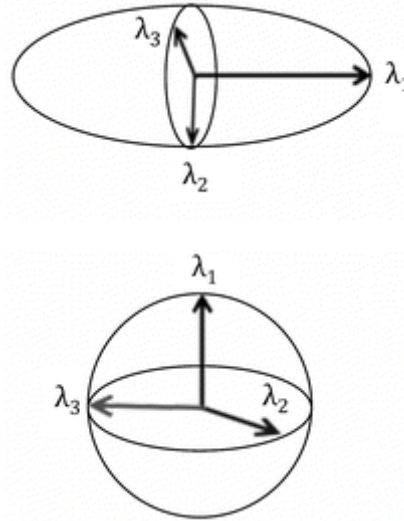


Figure 1.5 Equations of MD and FA

Equation 1: Fractional anisotropy

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

Equation 2: Mean diffusivity

$$MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3}$$

Values for FA are assigned between zero and one, with a value of zero representing isotropic and a value of one representing anisotropic diffusion (Pandit et al., 2013a, Pierpaoli and Basser, 1996). Axial diffusivity (λ_{ax}) is equal to the largest eigenvalue of

the tensor and represents water diffusion parallel to the axonal fibres (ϵ_1), whereas radial diffusivity (λ_{rad}) is the mean of the two remaining eigenvalues (λ_2 and λ_3) and represents an average of water diffusion perpendicular to the fibre direction (Madden et al., 2009).

MD and FA can be used to quantify white matter structural integrity, with low values of MD and high values of FA indicating healthy intact white matter (Madden et al., 2009, Alexander et al., 2007). Each of the dMRI metrics respond to different white matter characteristics such as degree of myelination and axonal conditions (Feldman et al., 2010): FA values are higher in the case of tight axonal packing or in areas with a high degree of myelination; λ_{rad} conversely in the same conditions decreases; λ_{ax} is unaffected by axonal density, but increased in areas of high myelination. White matter MD and FA have been shown to go through four specific age-related changes and attempts have been made to establish baseline values for each period (Watanabe et al., 2013). Deviations in these microstructural measures from their expected values (an increase in white matter integrity during development, stability in adulthood and reduction in older age) (Watanabe et al., 2013) may also suggest an underlying abnormality. In the case of prematurity, elevated diffusion anisotropy has been observed in periods of increased myelination in the post-natal developing white matter (Hüppi et al., 1998)

The combination of all four dMRI metrics and their deviation also aid in the interpretation of underlying pathological processes, such as in the case of white matter damage. In the case of myelin loss, FA would be expected to decrease, with a concurrent rise in λ_{rad} and no change in λ_{ax} (Feldman et al., 2010, Song et al., 2002). Conversely, in the case of axonal degeneration, FA and λ_{ax} values would be expected to decrease with an associated increase in λ_{rad} (Feldman et al., 2010). Furthermore, deviations in individual dMRI metrics have been suggested to be more representative of specific underlying pathological processes (Alexander et al., 2007). For example, deviations in λ_{ax} have been suggested to be reflective of an underlying loss in axonal integrity (Sun et al., 2006) or cerebral oedema which will result in an increase in MD (Alexander et al., 2007). Metrics derived from dMRI therefore correlate with

underlying biological factors which shows them to be sensitive markers of underlying white matter structure (Pandit et al., 2013a).

These measures of white matter microstructure can be quantified within user-defined regions-of-interest (ROI), voxel-by-voxel across the brain, or in specific tracts-of-interest (Pandit et al., 2013a). Having described how measures of white matter microstructure relate to the underlying structure, this thesis will now describe analysis methods using these metrics.

1.6 Analysis using dMRI metrics: Probabilistic Neighbourhood Tractography

Tractography is a method which is able to produce a three-dimensional representation of a specific white matter tract-of-interest based upon estimates of the direction of water molecule diffusion (essentially ϵ_1 which is assumed to point along the fibre direction) in each individual voxel (Basser et al., 2000, Conturo et al., 1999, Mori et al., 1999). This technique can allow comparison of tract structure between participants even if anatomical variation exists in terms of the tract-of-interest between the two (Feldman et al., 2010). There are two types of tractography; probabilistic and deterministic (Mukherjee et al., 2008a, Mukherjee et al., 2008b, Bastin et al., 2008) with the former potentially able to identify more than one fibre population within a voxel and track through regions with low diffusion anisotropy (Feldman et al., 2010, Anblagan et al., 2015). Both methods use a "seed-point" for each tract-of-interest to then propagate the tract through voxels with similar diffusion directions, and define their extent by using "operator-defined" regions through which the tracts are required to pass (Anblagan et al., 2015). Anblagan et al. (2015) overcame many of the challenges associated with neonatal datasets such as smaller head size, resolution, broad variations in normal anatomy and higher neural water content in the neonatal brain by using Probabilistic Neighbourhood Tractography (PNT) (Anblagan et al., 2015). PNT allows the automatic segmentation of tracts-of-interest by identifying tracts which are comparable to previously calculated reference tracts (Clayden et al., 2006, Clayden et al., 2007, Bastin et al., 2010). This method is particularly advantageous as it removes the subjective component in the identification of pathways since "waypoint" regions of interest are not required to constrain the tractography

output (Anblagan et al., 2015). The method works by the placement of the initial "candidate seed point" in a neighbourhood of voxels (typically three to seven voxels in each direction) surrounding a central voxel defined in standard space and transferred to the subject's native space. From this group of "candidate tracts," the one that is most representative of the reference tract is selected and tract-averaged values of MD, FA, λ_{ax} and λ_{rad} determined within it (Clayden et al., 2006, Clayden et al., 2007, Anblagan et al., 2015, Bastin et al., 2010). In addition, these measures of white matter integrity can then be correlated with other phenotypic data, such as cognitive ability, to examine links between brain structure and neurodevelopment after preterm birth.

1.6.1 Applications of Probabilistic Neighbourhood Tractography

PNT can be applied to the analysis of underlying white matter. A general factor g_{WM} explaining individual differences across white matter tracts-of-interest and variance within white matter microstructure can be generated using principal component analyses (PCA) and dMRI metrics. Penke et al (2010) used PNT from dMRI data obtained from 312 generally healthy older adults in order to segment eight white matter tracts-of-interest (genu and splenium of the corpus callosum, and bilateral cingulum bundles, uncinated fasciculi and arcuate fasciculi) in order to generate tract average values (Penke et al., 2010). Separate PCAs were conducted on all eight tracts-of-interest in order to investigate the shared variance between each white matter tract. All four tract averaged parameters (FA, MD, λ_{rad} and λ_{ax}) revealed a single general factor which explained approximately 45% of the variance between the tracts.

Evidence from the adult literature has shown white matter microstructure to be important in underlying cognition and in the context of disease. In the context of neurodegeneration in older adults and white matter damage, older age cognitive ability is altered (Downey et al., 2015, Amlien and Fjell, 2014). Understanding the degree of shared variance between tracts (in the generation of g_{WM}) can be used to relate structure and function. Penke et al (2010) showed that g_{WM} (denoted as g in the original citation) for both FA and λ_{rad} correlated with information processing speed (Penke et al., 2010). Further work is required to explore how this general factor relates, not just to overall cognitive function, but to individual cognitive processes in early life. Furthermore, it

remains uncertain how white matter damage as assessed using g_{WM} may affect cognition in the preterm infant.

This chapter has identified the adverse risk associated with prematurity and the underlying brain injury identifiable on MRI, focusing on the more common diffuse pattern of white matter injury. The ability to link brain structure and underlying cognition in the adult population has also been identified by the ability to generate g_{WM} of underlying white matter microstructure. This thesis will now examine the neurocognitive profile of preterm infants in more detail and how this relates to dMRI metrics. Finally, methods of assessing cognition in infancy will be addressed.

CHAPTER 2 : COGNITIVE OUTCOMES AFTER PRETERM BIRTH

As highlighted in Chapter One, prematurity confers risk for poor cognitive outcomes and preterm infants have evidence of white matter injury on MRI. In this chapter, the literature describing the cognitive outcomes associated with prematurity will be described in detail. The current understanding of the link between these adverse outcomes and early imaging will also be discussed. Finally, difficulties in the measurement of early infant cognition will be explored. Part of Section 2.8.2.3 was submitted as part of the first year review process for this degree.

2.1 Introduction

2.1.1 Cognitive outcomes after preterm birth

The neurocognitive profile associated with survivors of preterm birth is both diverse and lifelong. In addition to motor deficits, the preterm infant is at risk of global and specific learning difficulties, impairments in hearing and vision, executive dysfunction and neuropsychiatric problems. There is also an increased likelihood of screening positive for, or receiving a diagnosis of, autism spectrum disorder (ASD) (Johnson et al., 2010a, Johnson and Marlow, 2011, Guy et al., 2015, Gray et al., 2015) or a diagnosis of attention deficit hyperactivity disorder (ADHD) (Treyvaud et al., 2013). The preterm infant often demonstrates a subclinical manifestation of these deficits with features of both diagnostic categories, which has been described as the "broader preterm behavioural phenotype" and is defined by an increased risk of anxiety, attention and social deficits (Johnson and Marlow, 2011).

Early intervention programmes in other high-risk groups (such as infants who later receive an ASD diagnosis) have been successful (Warren et al., 2011, Koegel et al., 2014). For example, Green et al. (2015) were able to show an increase in the attentiveness of infants at high-risk of autism using an intervention applied in the first year of life (Green et al., 2015). Furthermore, following another intervention during pre-school years, (Green et al., 2010) there was a reduction in ASD symptom severity during the trial and at follow up following the intervention (Pickles et al., 2016). Early intervention programmes have been attempted in the preterm population with some

degree of success. Olafsen et al. (2006) looked at the effects of an intervention attempting to improve the infant-maternal relationship during the neonatal period and then evaluated joint attention at 12 months' corrected gestational age (CGA) (Olafsen et al., 2006). The preterm group that had received the intervention scored higher compared to control preterm infants. More effective risk stratification of infants at the highest risk of later difficulties in the preterm cohort would assist in the development of evidence based interventions aimed at improving the outcomes in these infants.

2.2 Vision

Prior to reviewing cognitive development, it is essential to briefly describe the visual competence of the term and preterm infant. Vision underpins an infant's ability to make sense of and interpret the world around him or her. Vision is detectable at birth, however this is not well refined (Atkinson, 2002). Attempts to measure visual acuity shortly after birth using preferential looking have estimated that visual acuity (measured in cycles / degrees) is approximate to the postnatal age (measured in months) (Atkinson, 2002). By two months of age, an infant can track, fixate and follow an object in the horizontal plane (Newell and Darling, 2008), with the development of colour vision occurring as early as this stage (Peeles and Teller, 1975). At approximately three to four months of age, an infant will develop binocular vision (van Hof-van Duin, 1989).

Visual fixation in the preterm infant is detectable at as early as 32 weeks' PMA and significantly improves over the period until 36 weeks' PMA (Hack et al., 1976). The ability to fix and follow a piece of red wool is identifiable in 90% of infants by 34 weeks' PMA (Palmer et al., 1982) and this ability is established by term equivalent age (Guzzetta et al., 2001).

2.3 Typical development in term infants

Prior to examining the diverging developmental trajectory of the preterm infant, the range of normal development in infants born at term will be briefly discussed. Typical neurodevelopment in a term infant (birth > 37 weeks' PMA) can be categorised into the following areas: cognitive, physical (including fine and gross motor skills),

language (expressive and receptive) and social milestones. Table 2.1 summarises the milestones in the first two years of typical development (Newell and Darling, 2008, Valman and Thomas, 2009, Bayley, 1993, Bayley, 2006).

The focus of this thesis from this point onwards will be on social cognition (Adolphs, 2001) and executive function (Hill, 2004) as these cognitive domains represent the largest burden of impairment within the preterm group (Marlow, 2004). Early infancy is a period of rapid development and so may represent the optimal period of intervention in this high-risk group. Furthermore, from a practical perspective these are cognitive constructs which can be measured during the first year of life. For these reasons, this section will focus on the ability of an infant in the six to twelve month period in these cognitive domains and how these areas map to later cognition.

Table 2.1 Developmental milestones

Approximate age shown for achievement of each milestone (Newell and Darling, 2008, Valman and Thomas, 2009, Bayley, 1993, Bayley, 2006).

Age of child	Area of Development				
	Gross motor	Fine Motor	Cognition	Language	Social
6 weeks	Head lag improving on pull to sit	Hands held in a fist		"Squeals"	Smiling
2 months	Lifts head when lying prone				
3 months	Some infants can roll Can lift chest when prone	Hands held together	Recognises parent	"Cooing"	
6 months	Sits with support Can weight bear if held when standing	Palmar grasp Transfers objects in the midline Plays with toys and feet	Aware of new surroundings Determination in reaching for toy	"Gurgling"	Responsive No stranger anxiety
9 months	Sits unaided Starting to crawl Starting to pull to stand	Scissor grasp	Shows simple object permanence: looking for a toy when dropped	"Babbling"	Begins to be apprehensive with strangers Plays peekaboo

12 months	Cruising or walking unaided Crawling	Pincer grasp	Looks at pictures in a book	Single words Comprehends simple instructions	Waves
18 months	Can walk unaided and bend down securely	Scribbling Tower of 3 bricks	Shows object permanence: can find hidden objects in more complex assessments	Beginning to join two words together Gestures Tries to gain attention from adults	Feeding: participates, drinks from cup
24 months	Runs Can go up and down stairs: two feet at a time	Tower of 6 bricks		Simple phrases Can find objects in book	Relational play

2.3.1 Social cognition

2.3.1.1 Social milestones from birth to one year

This section will firstly focus on social milestones. For the purpose of this thesis, the term “social cognition” will be used to refer to the underlying basis for an infant’s ability to orient to, respond to, and initiate social interaction (Adolphs, 2001, Pelphrey et al., 2004, Nelson et al., 2005). Effective social-emotional functioning is reliant on the interaction between social and motor skills, amongst others (Happé and Frith, 2014, Montagna and Nosarti, 2016). The developmental trajectory of social cognition passes through several stages of development (Jones et al., 2014), the first of which can be termed "social orienting" (Chevallier et al., 2012). This describes preferential looking at social content such as faces and bodies (Fletcher-Watson et al., 2008). Changes in these are also given attentional priority (Kikuchi et al., 2009). Very shortly after birth, neonates give preferential visual attention to faces (Johnson et al., 1991), with a subsequent focus on the eye region (Farroni et al., 2002). Infants then develop the ability to maintain a visual preference to a face when it is presented in other

formats, such as within multiple object arrays (Gliga et al., 2009) or animated scenes (Frank et al., 2009) from approximately three to nine months of age.

An infant's response to social interaction becomes more elaborate over the first year of life, from the strong preference for the mother's face in the newborn (Johnson et al., 1991), to the more sophisticated interpretation of gaze in the ten-month-old who will only follow a head turn if the other person's eyes are open (Brooks and Meltzoff, 2005). Furthermore, orientation to a target using gaze becomes increasingly accurate from nine to twelve months (Carpenter et al., 1998). Infants will also shift their attention to follow the motion of others at around a year of age (Furuhata and Shirai, 2015). Biological motion shows the movement of living objects using point-light displays over joints of the body (Johansson, 1973). The timing of onset of orienting preference for biological motion is under debate, however it continues throughout the first ten years of childhood and beyond (Furuhata and Shirai, 2015, Pavlova et al., 2001, Freire et al., 2006).

The initiation of social interaction follows next in the developmental sequence. Joint attention is an example of this and is defined as the ability to share attention with others on objects of interest including using visual cues (eye-gaze, head turn, pointing) to direct other's attention (Jaworski and Eigsti, 2015). Infants begin to gesture, including pointing to initiate joint attention, at around eight to ten months of age (Bates and Dick, 2002) which requires a prior period of motor and cognitive development. By nine months of age, infants are able to demonstrate the ability to initiate joint attention using gaze, and partake in games such as peek-a-boo (Carpenter et al., 1998, Hodapp et al., 1984). However, they are unable to fully participate in sophisticated joint "triadic attention episodes" at this stage (Moore, 2013).

2.3.1.2 Early social cognition and later outcomes

Early evidence from development in the different components of social cognition has been linked to later cognitive outcomes. The typical early social developmental trajectory allows the acquisition of skills which children will later require in order to form successful social relationships based on the interpretation of the behaviour of others (Soto-Icaza et al., 2015). Thus early differences in social-cognitive development

may act as early indicators of later deficits (Briggs-Gowan and Carter, 2008). For example, early markers of atypical social behaviour have been shown to be predictive of a later diagnosis of ASD (Yirmiya and Charman, 2010, Elsabbagh et al., 2013b). However, heterogeneity amongst studies exists when early markers of social deficits are first identifiable (Jones and Klin, 2013, Briggs-Gowan and Carter, 2008).

Performance in early social development is also predictive of later language development. Young et al. (2009) showed that increased fixation patterns to a mouth at six months of age relates to an increase in expressive language at 24 months of age (Young et al., 2009). Likewise, Mundy et al. (2007) found that infant response to joint attention at 12 months and initiation of joint attention at 18 months were both predictive of language development at 24 months (Mundy et al., 2007). In those infants who later develop ASD, home videos of infants from birth to 24 months show early social deficits (Adrien et al., 1991, Adrien et al., 1993). Such deficits can be reliably identified as young as eight to twelve months of age (Osterling and Dawson, 1994, Werner et al., 2000). Thus early social cognitive behaviours play a key role in development and can serve as markers of later difficulty.

2.3.2 Executive function

Executive function encompasses complex cognitive functions such as planning, working memory and control (regulating impulses and inhibition) (Barkley, 1997, Hill, 2004, Stuss and Benson, 1984). The overlap and use of several of these cognitive domains is required in order to complete an executive function task (Riva et al., 2013). Historically, executive function was a term used interchangeably with frontal lobe functions, however this is thought to be too simplistic as executive function tasks cannot usually be attributed to a single area within the cerebrum (Riva et al., 2013). In addition, there is no general consensus regarding the relationship or degree of interdependence of each key component of executive function within the normal developmental trajectory (Best and Miller, 2010).

Miyake et al. (2000) has provided an executive function framework in adults, identifying three key components: (I) shifting or "attention switching" (referring to the ability to switch between different tasks); (II) working memory (the ability to

constantly retain and act upon new information); (III) inhibition (the ability to suppress a natural response) (Miyake et al., 2000, Garon et al., 2008). This framework can be used to summarise evidence on executive function development in infancy, organised into measures of attention switching, memory and inhibition.

2.3.2.1 Early executive function milestones

The emergence of executive function skills is gradual (Jones et al., 2014), but some are detectable within the first year of life (Holmboe et al., 2008). Switching, working memory, and inhibitory control have been found to be evident as early as three to nine months of age, however the underlying neural correlates have yet to be fully explored (Moriguchi and Hiraki, 2013). Moreover, attention in infancy may underpin other executive function components (Garon et al., 2008). However, executive function development is a constant process and is ongoing into early childhood (Garon et al., 2008).

Switching of attention undergoes significant developmental changes in the first few months of life. Atkinson et al. (1992) examined the gaze fixation pattern between central and peripheral stimuli in infants aged one and three months within four conditions (Atkinson et al., 1992). Within the experiments, the younger infants were less focused in their fixation pattern when compared with the older typically developing (TD) infants. The improvement in the accuracy of fixation with age was deemed to be consistent with the development of the "executive cortical orientating systems." Beyond four months of age, infants have been shown to be able to fixate on a stimulus following a 200 milliseconds gap in a facilitatory pattern and 700 milliseconds in an inhibitory pattern, however only an inhibitory pattern was observed at six months (Johnson and Tucker, 1996). In another experiment by the same group, the speed of "spatial attention shifting" increased by seven months (Johnson and Tucker, 1996). The ability to disengage attention undergoes significant development between four and six months of age (Hood and Atkinson, 1993, McConnell and Bryson, 2005).

Infants have shown evidence of early memory formation occurring shortly after birth (Rovee-Collier, 1993). Simple memory can be measured from five months of age

using delayed response and more complex memory tasks can be assessed at 15 months of age (Garon et al., 2008). Gilmore and Johnson explored the ability of six month old infants to retain information over varying time periods (Gilmore and Johnson, 1995) using two different conditions within an oculomotor delayed response task. In the first condition, infants were shown an initial central fixation stimulus to maintain attention, before the concurrent presentation of a peripheral cue stimulus. After a varying time delay and "time-out", the presentation of bilateral peripheral target stimuli occurred. In the second experimental condition, infants were shown a central fixation stimulus, and this was then replaced by a central cue stimulus. After a varying time delay and "time-out", the single or double target stimuli were shown. Infants were able to remember the position of the stimuli for between three and five seconds. Conflicting opinions exist surrounding the neuroanatomical origins of early memory formation (Richmond and Nelson, 2007). More consistently, there is general agreement that early "implicit" or "non-declarative memory" is reliant upon the cerebellum, striatum and brainstem (Richmond and Nelson, 2007). This is in contrast to controversy that surrounds the origins of more complex, and often task-dependent "explicit" or "declarative" memory, in which the hippocampus, left pre-frontal cortex, anterior cingulate, parietal cortex and cerebellum have been implicated (Richmond and Nelson, 2007).

Infant recognition memory is often measured using the visual paired comparison task (Reynolds and Romano, 2016). A looking time preference for either the novel or the familiar stimulus in the second half of the task is suggestive of recognition memory. By contrast, a lack of preference in either direction is suggestive of a lack of recognition (Reynolds and Romano, 2016, Sokolov, 1963). Infants are able to show evidence of recognition after longer periods between familiarisation and testing, with increasing age (Reynolds and Romano, 2016). For example, a nine-month-old may show recognition after ten minutes, but only after ten seconds at four months (Diamond, 1990).

Another component of memory is recall, which has been observed in deferred imitation studies in infants as young as nine months of age (Bauer, 2002, Bauer et al., 2003) and is a skill which continues to develop throughout the first year and beyond

(Bauer et al., 2002). In deferred imitation studies, the investigator uses props to demonstrate actions, which after delay, the infant is invited to imitate (Bauer et al., 2003). Bauer et al. (2003) tested recognition memory using a previously unseen "two-step sequence" and event-related potentials (ERPs) in a group of 57 TD nine-month-olds. They tested for evidence of delayed recognition one week later and for recall after a further month (Bauer et al., 2003). The ERP measures after one week were predictive of performance at one month. The authors concluded that this study was able to give insights into the development of long-term memory and consolidation in young infants.

Some tasks, such as the A-not-B performance task, are dependent on the development of the frontal lobe and assesses multiple executive function components: working memory, inhibition and attention (Bell and Adams, 1999). Based on Piaget's "A-not-B-error" (Piaget, 1954), an examiner will initially hide an object in area "A" and then after subsequent trials, hide the same object in area "B." The infant would be deemed to have made a "perseverative error" should they have initially looked in the "A" rather than the "B" location for the hidden object "and this has been found to occur towards the end of the first year of life (Wellman et al., 1987). The A-not-B test is also closely related to visual displacement tasks (Lowe et al., 2009b, Bayley, 1993, Woodward et al., 2005), which can be used as measures of object permanence. Object permanence is defined as acknowledgement of an object's presence when it can no longer be visualised (Baillargeon and DeVos, 1991) and involves a memory component. It must however be highlighted that object permanence is not a direct measure of memory as demonstration of memory would be required but not sufficient to pass this task.

In its simplest form, early manifestations of inhibitory control can be observed when a child pauses before eating a snack (Garon et al., 2008). Simple response inhibition ("withholding" / "delay of an automatic response") can be undertaken under a year of age, depending on the task design (Garon et al., 2008). Holmboe et al. (2008) used a visual inhibition task, termed the "Freeze-Frame task" to demonstrate inhibition at nine and twenty-four months of age. Infants were encouraged to resist the urge to fixate on peripheral stimuli which acted as distractors. They used three measures of inhibitory function ("general inhibitory learning, selective inhibition and selective inhibitory

learning") and compared these to outcomes on frontal cortex tasks also administered. Using this task, infants demonstrated an ability to learn to inhibit in a general way (Holmboe et al., 2008). Inhibitory control is not assessed in this thesis, it is however described above for completeness.

2.3.2.2 Executive function and cognitive outcomes

Executive function skills in infancy have been shown to be predictive of later cognitive performance in childhood. Cuevas and Bell (2014) linked attention style (i.e. short or long lookers) in infants as young as five months of age to executive function in later childhood at 24, 36 and 48 months (Cuevas and Bell, 2014). Infants who were described as "short lookers," and better at processing information, performed better on measures of executive function when compared to "long lookers" after controlling for verbal ability. Rose and Feldman (1997) showed that visual recognition memory in seven-month-old infants is linked to processing speed, memory and Intelligence Quotient (IQ) at 11 years in both term and preterm children (Rose and Feldman, 1997). Fagan and colleagues (2007) showed that infant visual recognition memory at six to twelve months was predictive of adult IQ (Fagan et al., 2007). Executive function in toddlers has also been linked to later intelligence and language development (Friedman et al., 2006, Hughes, 1998) and to school readiness and academic performance (St Clair-Thompson and Gathercole, 2006, Blair and Peters, 2003). McCall and Carriger (1993) undertook a meta-analysis examining the relationship between infant habituation and recognition memory performance as predictors of later IQ (McCall and Carrier, 1993). They firmly established that habituation and recognition memory performance under one year of age are predictive of later IQ assessed between one and eight years of age. Tamis-LeMonda and Bornstein (1989) were able to show that infant habituation at five months was predictive of language comprehension and play at 13 months (Tamis-Lemonda and Bornstein, 1989). These studies collectively highlight the relevance of early assessment, as experimental tasks administered in early life can reliably predict performance several years later in development.

2.4 How does neonatal anatomy link to later function?

Developmental and anatomical changes seen during the first year of life may explain childhood functional performance. Here, the relationship between neural networks and areas, and their relationship with social cognition and executive function in typical development (up until around nine months) will be discussed in order to provide a foundation for consideration of the special case of prematurity in subsequent sections.

2.4.1 Neonatal anatomy and function: social cognition

Recent MRI data gathered in the adult population has expanded knowledge of neural structures involved in different aspects of social cognition (Van Overwalle, 2009). The "social brain" has traditionally been mapped to neural areas which underpin social processes (Brothers, 1990, Blakemore, 2008), however there is now a move to consider individual structures within networks based on function rather than in isolation (Kennedy and Adolphs, 2012). There are particular processing features which can be attributed to the social brain as highlighted by Kennedy and Adolphs: (i) it relies on several "structures and their connectivity"; (ii) it requires fast and "efficient, and interactive processing." Therefore, even minor damage to a single area of the brain, or a more global insult to white matter can cause later deficits (Kennedy and Adolphs, 2012). Figure 2.1 highlights both structures (a) and networks (b) within the social brain which have been identified, either due to there being evidence of injury in the relevant area in individuals with social difficulties or in imaging studies (Kennedy and Adolphs, 2012). Table 2.2 summarises the underlying structures and associated functions described within networks shown in Figure 2.1 (Kennedy and Adolphs, 2012, Kanwisher et al., 1997, Rolls, 2004, Carlson, 2010, Adolphs, 2003, Van Overwalle, 2009). This thesis will now focus on the developing brain up until nine months of age.

Table 2.2 The social brain

Structure(s)	Function
Temporal lobe	Processing faces
Orbitofrontal areas	Reward / punishment behaviour Emotional regulation
Amygdala	Response to emotion
Medial pre-frontal areas Superior temporal regions	Attribution of mental states
Parietal and pre-frontal areas	Processing the actions of others

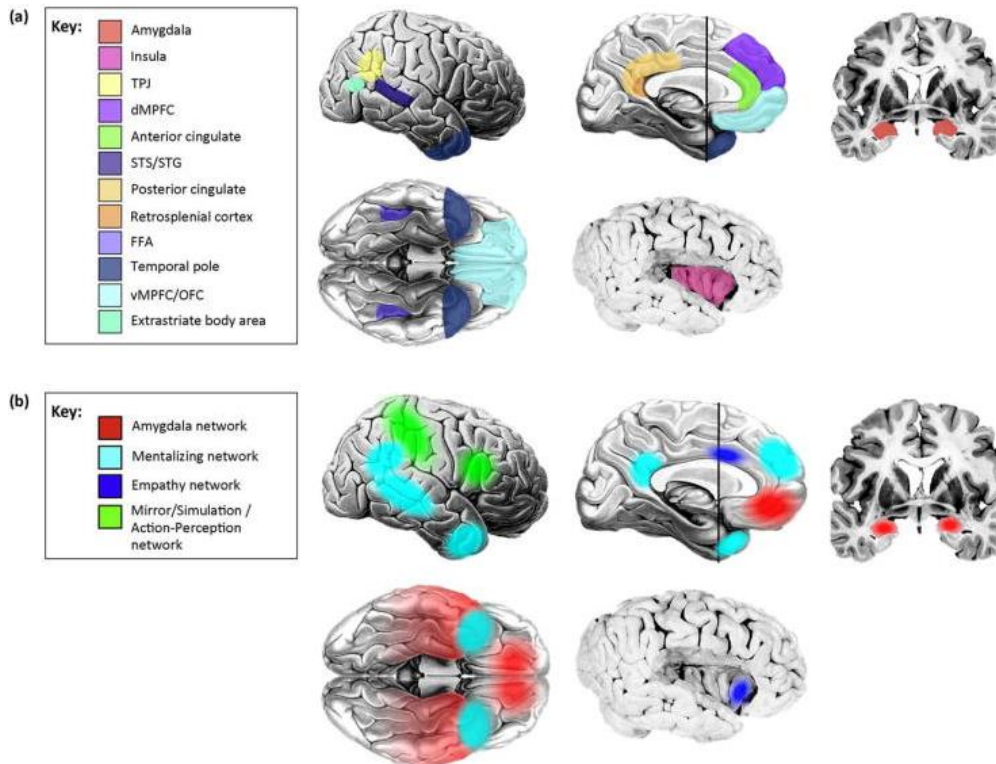
References for Table 2.2: Kennedy and Adolphs, 2012, Kanwisher et al., 1997, Rolls, 2004, Carlson 2010, Adolphs, 2003, Van Overwalle, 2009.

As previously highlighted, human infants will preferentially look at the face (Johnson et al., 1991). Initial facial preference in the newborn is thought to be driven by subcortical brain structures (Johnson et al., 1991), including the superior colliculus, pulvinar and amygdala (Johnson, 2005). In addition, it has been suggested that the developmental progression of facial recognition is dependent on the maturation of visual cortical areas (Johnson, 2005). The amygdala may also play a key role in social and emotional development (Adolphs, 2003).

Studies examining the neural components underlying facial processing in infants have been challenging due to technical and ethical considerations (Tzourio-Mazoyer et al., 2002). Tzourio-Mazoyer et al. (2002) were able to examine the response to face processing using positron emission tomography (PET) in two-month-old infants with hypoxic-ischaemic encephalopathy (HIE) (n = 6) (Tzourio-Mazoyer et al., 2002). This study revealed activation of the right inferior temporal gyrus in response to static face stimuli, which as they suggested is akin to fusiform face area activation in the adult (Kanwisher et al., 1997). Infant discrimination between upright and inverse faces between five and eight months of age is related to the right lateral area and the bilateral superior temporal sulci (Otsuka et al., 2007).

Figure 2.1 Structures (a) and networks (b) within the social brain

Reproduced with permission from Elsevier (Kennedy and Adolphs, 2012). Abbreviations: "temporoparietal junction (TPJ), dorsomedial prefrontal cortex (dMPFC), superior temporal sulcus / gyrus (STS / STG), fusiform face area (FFA), ventromedial prefrontal cortex / orbitofrontal cortex (vMPFC / OFC)."



By six months of age, infants are able to distinctly discriminate between the face of their mother or a stranger and this is linked to development in cortical midline structures (de Haan and Nelson, 1997, Parsons et al., 2010). Eye gaze is important for social orienting even in early developmental stages. This can be shown by the newborn's preference for open rather than closed eyes (Batki et al., 2000). Areas within the fusiform gyrus are involved in gaze direction in infants (Grossmann and Johnson, 2007). Like face processing, eye-gaze development shows early common patterns of cortical activation which later specialise (Johnson, 2001). In the interpretation of more complex social stimuli, multiple cortical areas are recruited (Lloyd-Fox et al., 2010).

These findings indicate that despite the immaturity of cortical regions, areas underpinning social cognition are functional early in postnatal life (Grossmann and Johnson, 2007). Furthermore, activation of the inferior and superior frontal gyri in infants as part of the social developmental trajectory suggest an overlap with later language acquisition as these brain areas are part of the adult language network (Tzourio-Mazoyer et al., 2002).

Information gained from dMRI in TD infants in early infancy is predictive of later joint attention at nine months. Elison et al. (2013) scanned 50 TD infants at six months of age and invited the infants back for an assessment at approximately nine months of age. During the follow-up session, a social interaction was set-up between the infant and examiner using play (Elison et al., 2013b). Infants also completed the language subscales from the Mullen Scales of Early Learning (Mullen, 1995). The study showed that FA in the right uncinated fasciculus (a white matter bundle connecting the amygdala to the ventral-medial prefrontal cortex and anterior temporal pole) at six months was predictive of performance in response to joint attention at nine months, but not in language. The study concluded that the development of nonverbal social communication skills in infancy is dependent on developments within the right lateralised frontotemporal brain systems.

2.4.2 Atypical social outcomes associated with neuroanatomy in infancy

Anatomical changes in the brain during the neonatal period also relate to function in later childhood with regard to social cognition, particularly in deviations from the normal developmental trajectory: e.g. in ASD, which is thought to have a genetic component secondary to structural or biochemical maldevelopment in the brain (Carlson, 2010). Infants who later receive a diagnosis of ASD have different patterns of brain growth, for example the frontal and temporal cortices grow more quickly prior to a relative slowing when compared to other areas (Courchesne et al., 2007, Courchesne et al., 2005). Evidence regarding the neurological substrates for social cognitive development in infancy often comes from studies of children at risk of ASD. For example, Shen et al. (2013) were able to use structural MRI to identify brain abnormalities in infants between six and nine months of age who would later be diagnosed with ASD (Shen et al., 2013). Three scans were undertaken at different time

points between six and 24 months of age. Infants in the ASD group had significantly greater amounts of extra-axial fluid, particularly over the frontal lobes, at six months. This was also predictive of later symptom severity. The same infants also had larger brain volumes at 12 - 24 months.

dMRI has been used to investigate the microstructural differences in children with ASD. Studies have generally shown a reduced FA and increased MD during childhood, however there is significant variation in the regional patterns of findings (Walker et al., 2012). Wolff et al. (2012) recruited 92 infants that were deemed to be high-risk for ASD (Wolff et al., 2012). Participants had an MRI scan at six months and a behavioural assessment at 24 months, with some of the infants having further imaging within the study period. Of the 28 infants who met the diagnostic criteria for ASD at 24 months, there was a significantly different FA trajectory over time in 12 out of 15 tracts in the brain when compared to the infants who did not have ASD. As highlighted above, at six months most white matter tracts had an elevated FA, followed by a more static period in the ASD group, so they had lower FA values by 24 months.

2.4.3 Neonatal anatomy and function: executive function

Executive function development relies on both individual neural structures and connective networks. The prefrontal cortex and neighbouring structures in particular underpin many areas of executive function (Squire et al., 2008). Posner and colleagues presented attention as being described by three separate networks (Posner and Fan, 2008, Peterson and Posner, 2012, Posner and Peterson, 1990, Keehn et al., 2013) which provide the basis for the summary that follows below.

The orienting network (highlighted in red, Figure 2.2) is involved in interpreting and responding to sensory information (Cuevas and Bell, 2014) and includes bilateral dorsal frontoparietal areas (superior parietal lobe / intraparietal sulci, frontal eye fields), superior colliculus, pulvinar and parts of the cerebellum (Keehn et al., 2013, Posner and Peterson, 1990). Subcortical systems including the superior colliculus also underpin the initial attentional ability of newborns (Atkinson et al., 1992, Atkinson, 1984). The orienting network undergoes significant developmental changes in the first six months of life (Colombo, 2001) and the ability to disengage attention occurs with

the development of cortical systems (Atkinson et al., 1992). This has been postulated to be the foremost network under a year of age (Posner et al., 2012) when compared to other networks.

When assessing neural substrates of orienting attention, two paradigms are commonly used: the fixation shift (Atkinson et al., 1992) and the gap-overlap paradigm (Csibra et al., 1998). Csibra et al. (1998) used high-density event-related potentials in 12 TD six-month-old infants to explore the cognitive processes involved in saccade planning. Infants' gaze behaviour was videoed as they watched the computer screen. Infants fixated on the peripheral stimuli in both the gap and overlap conditions, however fixations on peripheral stimuli during the overlap trials were less efficient when the central stimulus was still on the screen. Evidence from the infant participants highlighted the prominent role of the frontal cortex at the time of assessment with concurrent evidence of cortical immaturity.

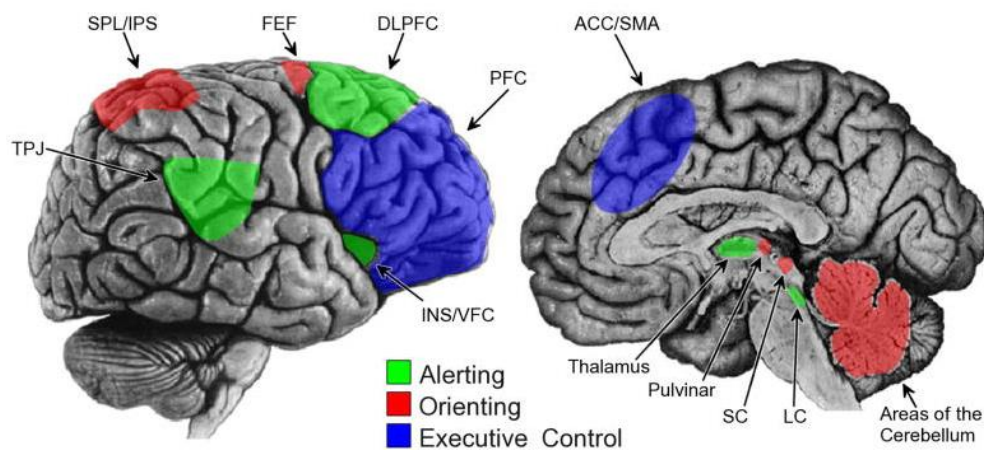
The alerting network (highlighted in green, Figure 2.2), is involved in readiness for incoming information and consists of the right lateralised ventral frontoparietal cortical regions (including the temporal-parietal junction and dorsolateral prefrontal cortex), the insula / ventral frontal cortex, the thalamus and the locus coeruleus (Keehn et al., 2013). It undergoes a period of rapid development during the first year of life (Posner et al., 2012, Keehn et al., 2013) and is related to the ability to sustain attention. (Peterson and Posner, 2012). Sustained attention (defined as the "voluntary maintenance of alertness at a certain level") (Keehn et al., 2013) in infancy is closely related to habituation, in which a sustained fixation to a novel stimulus decreases over successive or prolonged presentation periods (Atkinson and Braddick, 2012).

The executive control network involves several components, including: planning; error detection; novel response; working memory and overcoming habitual actions (i.e. inhibition) (Posner and Fan, 2008, Keehn et al., 2013). It includes (Figure 2.2, highlighted in blue) rostral brain locations (prefrontal cortex, anterior cingulate gyrus / supplementary motor area) (Posner and Fan, 2008, Keehn et al., 2013). Lateral areas are generally involved in working memory and medial areas in conflict detection (Posner and Fan, 2008). The development of executive attention occurs before 12

months (Diamond, 1991), and neural responses in infancy at seven months for certain areas (error detection), match those of adults (Berger et al., 2006).

Figure 2.2 Three attention networks

Reproduced with permission from Elsevier (Keehn et al., 2013). Abbreviations: temporal-parietal junction (TPJ), dorsolateral prefrontal cortex (DLPFC), insula/ventral frontal cortex (INS / VFC), locus coeruleus (LC), superior parietal lobe/intraparietal sulci, (SPL / IPS), frontal eye fields (FEF), superior colliculus (SC), prefrontal cortex (PFC), anterior cingulate gyrus / supplementary motor area (ACC / SMA).



2.4.4 Evidence of overlapping executive function networks

There is evidence to support the specialisation and synchronisation of networks using functional magnetic resonance imaging (fMRI) as development progresses (Grossmann and Johnson, 2007). There is also evidence of overlap between networks during the developmental period from the neonatal period to two years of age (Posner et al., 2012, Gao et al., 2009). For example, in neonates, parietal areas (associated with the orienting network) are strongly associated with lateral and medial frontal areas (associated with the executive control network) (Posner et al., 2012, Keehn et al., 2013) and by two years there is a strong relationship between the anterior cingulate (associated with executive control network) and the parietal and frontal areas (and their respective networks) (Gao et al., 2009, Cuevas and Bell, 2014). These three networks

are not only relevant in the development of executive function, but also in social cognition and the convergence between these areas in development. For example, from the age of seven months, infants are able to identify facial expression and this pre-dates the emergence of stranger anxiety (Squire et al., 2008). It has been postulated that these occur after developmental improvements in memory and in the orbital pre-frontal cortex (Schore, 1996). This finding is an example of the overlap between functions in development, as the maturation of the orbital-frontal cortex by the end of the first year of life contributes to memory and social-emotional development. The posterior parietal lobe underpins the ability to shift attention to different spatial locations (Squire et al., 2008). Measuring concurrent social and executive function skills, adult eye-gaze has been shown to alter how four-month old infants interpret objects (Reid et al., 2004, Grossmann and Johnson, 2007). The ERPs from electrodes placed over the fronto-temporal region recorded an enhanced slow wave response to uncued objects when compared to cued objects. Based on this finding, Grossman and Johnson suggested that eye-gaze is part of the process of memory encoding and it may be used to aid development (Grossmann and Johnson, 2007).

This thesis has now reviewed typical infant development in two domains: social cognition and executive function and reviewed evidence linking these to relevant neuroanatomical substrates and markers of connectivity. Deficits in these areas found in the preterm population and associated clinical diagnoses, will be now be addressed in turn.

2.5 Adverse neurological outcomes associated with prematurity

2.5.1 Cognitive deficits in preterm infants

As highlighted in Chapter One, the neurocognitive outcomes associated with preterm birth are diverse and include increased rates of risk for specific diagnostic outcomes. This section will focus on deficits in social cognition and executive function in preterm infants and broader cognitive deficits associated with prematurity.

2.5.1.1 Social cognition

Preterm infants are at an increased risk of atypical social-emotional development and this is identifiable in infants under 12 months of age (Telford et al., 2016). Several studies have shown early differences and deficits in ex-preterm infants in areas related to social development, such as reduced attention to biological motion or interpreting facial expressions (Pavlova and Sokolov, 2005, Wocadlo, 2006). Williamson et al. (2014) showed that VLBW preterm infants show difficulties in the interpretation of emotion, (as assessed in their response to non-verbal cues from faces, bodies and situations), identifiable between the ages of eight and eleven years (Williamson and Jakobson, 2014). Preterm infants with a low birth weight also show deficits in joint attention during the first two years of life in both medically low and high-risk subgroups (Garner et al., 1991).

In the social setting, preterm infants demonstrate different gaze behaviour (in that they look away more frequently) when compared to term infants, and this has been suggested to be secondary to increased parental stimulation in the preterm group (Landry, 1986, De Schuymer et al., 2012). De Schuymer et al. noted attentional deficits within this population (De Schuymer et al., 2012) and so they examined the relationship between attention switching abilities and gaze behaviour during a social interaction in infants aged between four and six months. Preterm infants demonstrated a poorer performance during attention switching and disengagement and fixated less on social content, when compared to their term peers. Furthermore, in the preterm infants, gaze behaviour at six months during the infant-mother interaction was related to earlier measures assessing attention. The authors concluded that the deficits in social gaze behaviour may be related to the development of attention (De Schuymer et al., 2012).

2.5.1.2 Executive function

Preterm infants are known to perform relatively poorly in several areas of executive function when compared to term infants. For example, at around eight years of age very preterm infants have shown inferior performance in areas such as verbal fluency, response inhibition, planning, verbal and spatial working memory (Aarnoudse-Moens

et al., 2012). These deficits may be explained by a slower processing speed in the very preterm group (Mulder et al., 2011b). Poor performance in executive function can also be identified at earlier stages in development (Blair and Razza, 2007). For example, preterm infants show difficulties in processing new information in an object permanence task at two years (Woodward et al., 2005).

Although deficits in attention in children born prematurely may improve in time until they catch up with their term peers, executive function problems commonly persist into adolescence (Mulder et al., 2009, Luu et al., 2011, Nosarti et al., 2007). Despite the identification of a diverse spectrum of deficits, it remains unclear whether preterm infants have a tendency towards global deficits in executive function or if deficits are localised to a specific cognitive skill. For example, results looking at selective or sustained attention have been inconsistent, whereas more reliable findings have been established with deficits in inhibition and attention shifting (Pizzo et al., 2010). When assessing pre-school children, performance in executive function has a strong predictive relation with school readiness irrespective of Intelligence Quotient (IQ) (Blair and Razza, 2007). Executive function performance is also related to academic success and behaviour regulation (Mulder et al., 2011a, Mulder et al., 2010). However, deficits may not be identified until school age. For example children who were born with a VLBW may demonstrate deficits in planning, cognitive flexibility, and non-verbal working memory at six years despite a seemingly typical period of early development up until two years of age (Ni et al., 2011).

2.5.1.3 Neurodevelopmental disorders diagnosed in the preterm population

The diverse range of adverse neurocognitive outcomes associated with preterm birth has been highlighted above. A triad of symptoms consisting of inattention / hyperactivity, anxiety and social deficits has been proposed under the label "broader preterm behavioural phenotype" by Johnson and colleagues (2011). This preterm phenotype represents common diagnostic overlaps, and attempts to account for subtle differences in clinical manifestations seemingly unique to the preterm cohort (Johnson and Marlow, 2011). The high prevalence of clinically relevant neurodevelopmental problems in extremely low birth weight infants (ELBW; birthweight $\leq 1000\text{g}$), with a

comparatively low referral rate, shows that a much higher number of preterm children are at risk of more subtle problems (Elgen et al., 2012, Johnson and Marlow, 2011). It remains uncertain how these relate specifically to markers in infancy. Specific diagnoses prevalent in the preterm population will now be discussed in more detail.

ASD is defined as: "persistent deficits in social communication and social interaction across multiple contexts; deficits in social-emotional reciprocity and deficits in developing, maintaining and understanding relationships" (American Psychiatric Association, 2013) and is normally diagnosed at around three years of age (Boyd et al., 2010). Compared to that of the general population (Baxter et al., 2015), there is a much higher incidence of ASD in the preterm population (also see Chapter Seven), especially in those children born at earlier gestations and with lower birthweights (Hack et al., 2009, Johnson et al., 2010a, Limperopoulos, 2009). ASD in preterm children is plausibly a result of a different causative pathway compared to term infants (Limperopoulos, 2009, Johnson and Marlow, 2014), possibly secondary to brain injury associated with preterm birth (Johnson and Marlow, 2011, Rutter et al., 1994). ASD in children born preterm can often be less severe which has led to the description of a preterm "autistic phenotype" (Indredavik et al., 2008, Williamson and Jakobson, 2014). Early social difficulties can also exist in isolation (Williamson and Jakobson, 2014) and persist into adulthood (Pyhälä et al., 2014).

ADHD is defined in DSM-5TM as a "persistent pattern of inattention and / or hyperactivity-impulsivity that interferes with functioning or development, has symptoms presenting in two or more settings, and negatively impacts directly on social, academic or occupational functioning." Several symptoms must have been present before 12 years of age (American Psychiatric Association, 2013). ADHD is one of the commonest psychiatric outcomes affecting very preterm birth infants (Treyvaud et al., 2013), affecting approximately 10% of VLBW infants and up to 20% of ELBW infants (Stjernqvist and Svenningsen, 1999, Taylor et al., 2000, Foulder-Hughes and Cooke, 2003). The ADHD aetiological pathway in preterm infants similarly differs from that in term infants (Johnson and Marlow, 2014). ADHD in preterm infants has been linked to preterm brain injury (Johnson and Marlow, 2011, Indredavik et al., 2005) and suggestions of altered connectivity have been made

(Skranes et al., 2007). As these studies suggest, this deviation from typical brain development may explain the differences seen in the clinical picture. Preterm infants show features of inattention rather than hyperactivity / impulsivity typically described in term infants who are later diagnosed with ADHD (Indredavik et al., 2004, Jaekel et al., 2013). The prominence of inattention also carries a different pattern through childhood and beyond for the preterm cohort (Breeman et al., 2016).

Behavioural problems associated with preterm birth are diverse and encompass difficulties in / with self-regulation, interactive attention, hyperactivity or aggression, sleep, eating, sensory sensitivity problems, somatic symptoms, depression or anxiety (Arpi and Ferrari, 2013) and deficits have been identified as young as two years of age (Montagna and Nosarti, 2016). In addition to those listed above, preterm infants have showed a high incidence of emotional problems, conduct disorder, peer rejection, bullying and poor self-esteem (Johnson et al., 2010b). There is a relative lack of study of behaviour in the pre-school preterm child relative to studies looking at problems at school age (Johnson and Marlow, 2014). However, behavioural problems are associated with poor school performance (Delobel-Ayoub et al., 2009) and especially with inattention which is a key predictor of academic attainment (Jaekel et al., 2013).

The common thread associated with diagnoses in the preterm cohort is the need for an accurate early diagnosis in order to optimise the long-term outcome for these children. In the case of ASD, there is evidence that early intervention is likely to improve outcome (Pickles et al., 2016) or in ADHD the identification of the correct pattern of behaviour associated with a preterm infant may decrease the risk of misinterpretation (Brogan et al., 2014). Early and reliable indicators of later cognitive deficits measurable during infancy may provide a target for intervention which can improve school performance.

Having now identified the spectrum of difficulties associated with preterm birth, eye-tracking as a methodological approach to identify deficits in this population, will be reviewed, using examples from other high-risk groups.

2.6 Early markers of atypical cognition - evidence from eye-tracking

Eye-tracking is a technique that can quantify and objectively assess gaze behaviour in response to visual stimuli (Jones and Klin, 2013, Falck-Ytter et al., 2013) with "high temporal and spatial accuracy" (Gredeback et al., 2010). Such gaze behaviour – i.e. the movement of eyes across a stimulus and the time spent looking at items within a stimulus - can be used to infer underlying cognitive processes (Aslin, 2007). As a method, it has several advantages (Jones and Klin, 2013, Wass and Smith, 2014, Gillespie-Smith et al., 2016): it has an ability to reliably assess preverbal and complex populations; detect individual differences in a wide range of tasks assessing different areas of cognition; and early performance has been shown to relate to later function in childhood.

This thesis will briefly review some of the key findings from studies of ASD, which demonstrate how eye-tracking can be used to capture early cognitive development and relate this to later outcome and neurological data. This section will finally highlight previous success using eye-tracking in older children born preterm.

2.6.1 Early markers of atypical social cognition - evidence from ASD literature

Recent research has demonstrated altered gaze behaviour in infants who later receive a diagnosis of ASD. Studies assessing social cognition (please refer to Section 2.3.1.1) use an array of stimuli such as faces (static or dynamic), naturalistic scenes (in which complex scenes mirror real life) or paired visual preference paradigms (Falck-Ytter et al., 2013). Within each stimulus or task design, interpretations are based on calculations generated from fixations to pre-defined regions of interest.

Infants and pre-school age children who later develop ASD typically show reduced preference for social stimuli. For example, in an interesting but preliminary finding (Jones and Klin, 2013), Jones and Klin demonstrated a comparably atypical fixation pattern in a group of infants who would later develop ASD: a reduction in fixation to the eyes of a presented face, which occurred from two to six months of age. Likewise studies using preferential looking tasks report that those with ASD show a preference

for the non-social rather than the social content (Falck-Ytter et al., 2013). A similar pattern can manifest in pre-school children with ASD, who show atypical looking times to facial features (Chawarska and Shic, 2009, Hosozawa et al., 2012).

The predictive value of markers of social cognitive difficulties in infancy is less certain. Young et al. (2009) investigated the relationship between fixation patterns at six months to language acquisition at two years of age. In this small-sample study there was no evidence that children with ASD looked at the face in an atypical manner and, irrespective of ASD-risk, increased fixation to the mouth related to later language acquisition (Young et al., 2009). This result was also demonstrated by Elsabbagh and colleagues (Elsabbagh et al., 2014).

Current evidence supporting the idea that attention is an important early sign of ASD has arisen from studies using the gap-overlap task (Elsabbagh et al., 2009, Elsabbagh et al., 2013a). In this task, attention switching ability is measured using time taken to fixate a peripheral target in the presence or absence of a central one. Gap trials represent simple attention switching and overlap trials include an additional disengagement component (Elsabbagh et al., 2009). Elison et al. (2013) used a version of the gap-overlap task at seven months to assess children both high and low risk of ASD as part of a longitudinal study (Elison et al., 2013a). The study found infants who demonstrated ASD-symptoms at 25 months were slower to switch and disengage attention at seven months. This is similar to findings from Elsabbagh et al. (2009) who found that high-risk (of autism) infants showed longer latencies in both gap and overlap conditions (Elsabbagh et al., 2009). When another group of infants were followed-up, disengagement at seven months was not associated with ASD assessments at 36 months of age, but disengagement was slower at 14 months in the ASD group. Furthermore, there was no development in orienting ability in the ASD group between seven and fourteen months (Elsabbagh et al., 2013a).

2.6.2 Early markers of atypical executive function and social cognition - evidence from the preterm literature

Eye-tracking as an assessment tool has been used successfully to capture social cognitive and attention differences in preterm toddlers and beyond. Sekigawa-

Hosozawa et al. (2017) showed evidence of atypical fixation patterns suggestive of later social impairment in a group of very preterm children from the chronological ages of 15 - 120 months (Sekigawa-Hosozawa et al., 2017). De Jong and colleagues (2015) used eye-tracking methods at 18 months' CGA as part of a longitudinal study in late preterm infants to assess early attention (de Jong et al., 2015). The preterm group showed a poorer performance on "orienting" and "alerting". Both of these studies are proof of concept that eye-tracking can be used to detect differences in the preterm cohort. However, despite its value, eye-tracking has not generally been a feature of longitudinal studies of prematurity, such as EPICURE 1 and 2.

The above section has explored the diverse range of cognitive outcomes in other high-risk groups which can be detected using eye-tracking methodology. This thesis will now present the case for using eye-tracking as a predictor of outcome in the preterm cohort during infancy (i.e. under 12 months).

2.7 Predicting outcome in preterm infants from measures in infancy

Early indicators of cognitive performance in infancy, including those captured using eye-tracking, can be reliable predictors of performance in childhood. Eye-tracking within the preterm cohort in infancy is novel and has several potential advantages (see Section 2.6): it provides highly sensitive measurement (e.g. saccadic reaction times) which can be used to titrate individual differences, not just summarise group behaviour; it can capture early cognitive processes in pre-verbal infants and it can be used to measure a range of specific cognitive dimensions relevant to prematurity.

More crude measures of gaze behaviour have already been used to identify atypical development in the preterm cohort within the first year of life. Rose et al. (2001) measured attention and recognition memory in a cohort of preterm and term infants at five, seven and twelve months using two display screens and human raters (Rose et al., 2001). Term infants consistently had shorter fixation durations, faster shift rates and better concentration across nine pair-comparison trials (faces and patterns). Improved recognition memory scores were linked to lower mean looking times and "higher shift rates" during familiarisation (Rose et al., 2001). Rose et al. (2002) also

demonstrated, using a similar method, that deficits in processing speed in preterm infants are present in the first year of life (Rose et al., 2002).

In addition to using the method described above, efforts have been made to predict outcome from more naturalistic observations of infant attention. For example, from gaze behaviour and patterns of play. Studies examining sustained attention in infancy within a preterm cohort suggest that this is predictive of later cognitive performance (van de Weijer-Bergsma et al., 2008). Ruff et al. (1990) undertook a longitudinal study examining whether early measures of inattention or attention would be predictive of later performance and if there was any evidence of change over time (Ruff et al., 1990). Play (structured and free) was assessed in both the preterm and term groups at three time points: one, two and three and a half years of age. In the preterm group, inattention measures at one year were predictive of behavioural and maternal rating (on the Connors Hyperactivity subscale) at three and a half years only. Furthermore, Lawson and Ruff (2004) were able to demonstrate that "focused attention" to objects at seven months was a predictor of attention and cognitive function at pre-school age in VLBW infants (Lawson and Ruff, 2004). Infants were tested initially at seven months of age and then at two, three and / or four / five years of age (Lawson and Ruff, 2004). Attention at seven months old was predictive of ADHD symptoms at four to five years of age and cognitive abilities at all follow up time points. This study demonstrates the validity of early assessment in the accurate prediction of later performance (Lawson and Ruff, 2004), however more precision could be gained from eye-tracking.

2.8 Linking preterm brain injury with cognitive outcomes

Chapter One described the assessment of preterm brain injury using MRI. In this next section, the current understanding of the correlation between evidence of preterm brain injury from imaging and later clinical outcome measures will be discussed.

2.8.1 Links from focal brain injury to outcome

Cognitive outcomes associated with focal lesions have been relatively infrequently explored and no clear link to precise outcomes such as social-emotional behaviour or deficits in executive function have been demonstrated. Studies which exist assessing

the predictive value of cystic lesions tend to focus on very broad definitions at two years of age, such as the psychomotor developmental index (PDI) component of the Bayley Scales of Infant Development, Second or the composite scores within the Third Edition (BSID-II or III) (Kidokoro et al., 2014, Bayley, 1993, Bayley, 2006). In addition, some studies have broad inclusion criterion and include preterm infants up until 34 weeks' gestation (Soltirovska Salamon et al., 2014), which can make direct comparisons challenging. However, the relationship between cystic PVL on structural MRI and increased risk of later motor deficits such cerebral palsy in the preterm infant is consistent (Kidokoro et al., 2014, Roelants-van Rijn et al., 2001). As previously stated, in light of its relative rarity, it will not be dealt with further in this thesis.

2.8.2 Links from diffuse brain injury in preterm infants to outcome

A diffuse pattern of preterm brain injury on structural MRI is seen in approximately one half to two thirds of preterm infants at term equivalent age and is considered to be a candidate substrate for long-term impairment (cross reference Chapter One) (Boardman et al., 2006, Boardman et al., 2010). Several studies using both qualitative and quantitative methods have attempted to relate this more common diffuse pattern of injury to later neurocognitive impairment with mixed results (Pandit et al., 2013a).

2.8.2.1 Conventional imaging

There is still a high degree of imprecision when trying to ascertain the clinical manifestation of "preterm at term equivalent changes." The predictive value of conventional imaging has been explored by several studies with two of the largest undertaken by Dyet et al. and Woodward et al. (Dyet et al., 2006, Woodward et al., 2006). Dyet et al. (2006) included 68 infants at follow up with median age at follow up 23.93 months (range 19.5 - 34.43), however despite the link between diffuse white matter damage and an adverse neurological outcome, the sample size is inadequate to evidence specific abnormalities. Woodward et al. (2006) found that moderate-severe white matter injury was associated with neurocognitive impairment in very preterm infants, measured at term equivalent age using structural MRI. However, 50% of infants with moderate-severe white matter injury had no later impairment. Furthermore, 22% of infants with no white matter injury had mild impairment on

follow up, thus demonstrating both low sensitivity and low specificity of early white matter injury as a predictor of neurocognitive outcome (Woodward et al., 2006). Whilst Woodward et al. had a much larger sample size (n = 161 at follow up), the adverse neurological outcomes at two years associated with earlier MRI findings, were broadly categorised and confidence intervals were large. The later developmental implications of the location and severity of white matter damage remain largely inconclusive (Rose et al., 2014). However, the more severe patterns of white matter injury at TEA have been associated with cerebral palsy at 30 months' CGA (Skiöld et al., 2012).

Fewer studies have focused on cognitive outcomes in relation to diffuse white matter injury. The "Fixation Shift test" has shown to be a sensitive marker of cerebral white matter damage secondary to a wide range of pathologies, including white matter damage associated with preterm birth (Atkinson and Braddick, 2012, Atkinson et al., 2008). Atkinson et al. (2008) recruited 26 preterm infants who had an MRI scan at TEA and then an "orientation-reversal event-related potential" (OR-VERP) and a "behavioural test of cortically controlled visual attention-fixation shift under competition" within the first year of life, followed by a Griffiths Scales neurodevelopmental assessment at 24 months (Huntley 1996). The "Fixation Shift test of cortically controlled attention" involved an infant undertaking twenty trials on a computer under two conditions. An infant was initially shown a centrally located target ("face-like figure") and then a second striped target appeared on either the right or left-hand sides of the central target. The second target appeared either when the central target was still present or after it had disappeared. The experimenter pressed a button to record the timing and direction of the infant's fixation. The OR-VERP is a visually evoked potential (VEP) technique which detects "orientation-selective responses" in the visual cortex" (Braddick et al., 1986). Infants are shown the "orientation stimulus" which consists of sine waves at differing orientations and the VEP is detected using scalp electrodes. The structural MRI was graded on a score of "0 - 2" of increasing severity based upon the white matter and the presence of pathological features. Thirteen infants demonstrated substantial OR-VERP responses and 12 infants had a normal attention-fixation shift under competition performance. This level of performance decreased as the severity of white matter damaged worsened on MRI.

The attention-fixation shift under competition performance and OR-VERP related to the Griffiths Scales score. This study, however, involved only a small number of participants and demonstrated a limited classification of white matter damage.

One study linked white matter injury and adverse cognitive outcomes beyond infancy and into childhood. Murray et al. (2014) showed an association between adverse attention and processing speed at seven years of age and high scores of white and grey matter damage in the neonatal period (Murray et al., 2014). More recently, Ure et al. (2016) showed very preterm infants who were diagnosed with ASD aged seven years appeared to have structural changes, with an increase in cystic lesions (OR 8.68, 95% CI 1.47 - 51.28) at term equivalent age when compared to infants who did not develop ASD (Ure et al., 2016). This study, however, had a very small sample size in the ASD group (n = 8) and large confidence intervals (Ure et al., 2016).

There have also been a variety of methods used to analyse MRI data and relate these to later outcomes. Image analysis methods including volumetric and regional methods have attempted to increase accuracy in predicting clinical outcomes from early neurological markers and beyond (Pandit et al., 2013a). Specific regional changes in the neonatal period have also been associated with specific cognitive delays in working memory (Beauchamp et al., 2008). For example, Beauchamp et al. (2008) explored the predictive value of neonatal regional brain volumes and working memory deficits (using a behavioural delayed alternation task) at two years of age, with a focus on the dorsolateral pre-frontal and parietal cortices, and the hippocampus (Beauchamp et al., 2008). In this study, 156 infants had an MRI scan at TEA and were then followed up at two years. Infants who demonstrated deficits at two years in their working memory also had small hippocampal volumes at TEA. Structural differences within the preterm brain which relate to cognitive outcomes are also detectable in childhood and adolescence (Soria-Pastor et al., 2009, Indredavik et al., 2005). Soria-Pastor et al. (2009) set out to determine if low-risk preterm infants demonstrated any volumetric differences in grey or white matter on MRI (Soria-Pastor et al., 2009). Furthermore, the authors linked the MRI volumes to later cognition. Twenty preterm infants were recruited born between 30 and 34 weeks' PMA (in the absence of additional medical or cerebral risk factor for later impairment) and matched to 22 term control subjects

between eight and ten years of age. MRI data were analysed using voxel-based morphometry and children underwent cognitive, behavioural and emotional assessments. Despite widespread global and regional grey and white matter differences in the preterm group, only the temporal areas were significant. In addition, cognitive testing revealed relative impairments in global intelligence in the preterm group (despite being in the normal range). When examining the whole cohort, positive correlations were found between grey matter volume (in the middle temporal and in the post central gyri) and IQ. Indredavik et al. (2005) investigated the relationship between structural MRI changes and psychiatric symptoms in VLBW adolescents aged 14 - 15 years (Indredavik et al., 2005). The preterm group had an increased rate of all outcome variables, especially symptoms related to ADHD and evidence of brain injury associated with prematurity (ventricular dilatation, white matter reduction, thinning of the corpus callosum and gliosis). White matter reduction and thinning of the corpus callosum were associated with ADHD symptoms (Indredavik et al., 2005). De Kieviet et al. (2012) undertook a meta-analysis showing global whole brain reductions in preterm infants, including white and grey matter, cerebellum, hippocampus and in the corpus callosum (de Kieviet et al., 2012), which were also related to adverse cognitive outcomes. Although these studies demonstrated reductions in volume in specific brain regions to be related to more specific neurocognitive outcomes, the MRI data is from outwith the neonatal period and so there is no prognostic information to be gained. For example a study by Taylor et al. scanned individuals, who had been born prematurely, during adolescence and a range of neurocognitive outcomes were assessed (Taylor et al., 2011). Reductions in total brain volume were associated with a wide range of deficits in language, motor skills and executive function. Reductions in white matter volume were associated with language, memory and executive function and grey matter volume was associated with memory problems. More specific regions such as the cerebellar volume and corpus callosum were associated with a wide range of deficits.

2.8.2.2 Relationship between dMRI metrics and neurocognitive outcome

Microstructural changes on dMRI in the neonatal period have proven successful in linking underlying structure and function. Many studies have linked water diffusion

metrics in the neonatal period to cognitive and motor outcomes at approximately 24 months of age and below (Anderson et al., 2015, Duerden et al., 2015). Duerden et al. (2015) showed a significant relationship between FA in the corpus callosum and corticospinal tracts at TEA and motor and cognitive outcomes at 18 months' CGA (Duerden et al., 2015). De Bruïne et al. (2013) scanned 84 very preterm infants at TEA and followed them up at two years of age using the BSID-III (De Bruïne et al., 2013). They showed that infants with psychomotor delay and cerebral palsy at two years had a significantly lower FA and shorter fibre length of the posterior limb of the internal capsule using tractography. Furthermore, infants with psychomotor delay alone had microstructural alterations in the splenium of the corpus callosum. Van Kooij et al. (2012) by contrast used Tract-based Spatial Statistics and voxel-wise analysis in order to analyse dMRI data of 63 preterm infants scanned at TEA and follow up at two years' CGA (assessed using the BSID-III) (van Kooij et al., 2012). This study showed that cognitive scores correlated with FA values in the corpus callosum; fine motor scores correlated with FA and λ_{rad} throughout the white matter and gross motor scores were associated with λ_{rad} in the corpus callosum, fornix and internal and external capsule. However, this study was subject to limitations associated with the BSID-III assessment (see Section 2.8.2.3). Furthermore, there were no term infants recruited and so no comparison group was available. Similar to studies involving conventional imaging, many studies employing dMRI metrics and outcomes use a variety of analysis techniques as shown by these examples.

Diffusion metrics from scans at TEA have also been linked to other cognitive outcomes rather than the motor and cognitive scales on the Bayley Scales of Infant Development. Rogers et al. (2012) scanned 184 very preterm infants at TEA and MRI and assessed cognitive outcomes at two and five years of age (Rogers et al., 2012). Social-emotional development was assessed with the Infant Toddler Social and Emotional Assessment (ITSEA) at two years and the Strengths and Difficulties Questionnaire (SDQ) at aged five years (Spittle et al., 2009, Goodman, 1997, Goodman, 1999). They showed higher water diffusivity in the right orbitofrontal cortex was associated with social-emotional problems at five years. Gender differences in regional brain volumes during the neonatal period related to behavioural deficits at five years. A subset of female infants with smaller right-sided hippocampal volumes

at TEA, also showed a higher incidence of peer problems at five years and comparable problems at two years.

Microstructural alterations affecting the whole brain or specific regions within the preterm cohort persist and relate to cognitive deficits throughout childhood and beyond. Children who were born preterm had lower mean whole brain volumes and FA detected between eight and eleven years of age, with whole brain volume and lower FA associated with IQ (Yung et al., 2007). Skranes et al. (2007) scanned adolescents at 15 years of age who had been born with a VLBW, assessed a wide range of cognitive outcomes and screened for psychiatric disorders (Skranes et al., 2007). FA maps were calculated and areas of significant differences in mean FA values between subjects and controls were compared with their clinical data. The VLBW adolescents had reduced FA values in the internal and external capsule, corpus callosum and superior, middle superior and inferior fasciculus. A reduced FA in the external capsule, posterior part of the internal capsule and the inferior fasciculus related to visual, motor and perceptual deficits and a lower IQ was associated with low FA values in the external capsule and inferior and middle superior fasciculus. Fine motor deficits were related to lower FA values in the internal and external capsule and superior fasciculus. A subset of adolescents with subclinical or diagnostic features of ADHD had reduced FA in several brain areas and mild social deficits could be related to FA values in the external capsule and superior fasciculus. Finally, Allin et al. (2011) were able to demonstrate the persistence of deficits in early adulthood and how these relate to cognitive measures such as IQ or memory (Allin et al., 2011).

2.8.2.3 Limitations in studies linking white matter damage and phenotypic data

The studies above collectively show that microstructural changes in white matter do map to phenotypic data, however limitations exist. In the current literature, neuroanatomical features correlate relatively poorly to FA and MD metrics and the heterogeneity observed across imaging and analysis method can make generalisable interpretations of the dMRI metrics challenging (Pandit et al., 2013a). Heterogeneity does not only exist in the analysis of dMRI metrics, but also in the timing, range and mode of outcome measures. Many studies of brain injury and later function focus on

outcomes such as death, survival to discharge, co-morbidities or early cerebral palsy at two years or beyond (Inder et al., 2005, Woodward et al., 2006, Draper et al., 2009, Ancel et al., 2015). At present, many studies are limited in that they do not indicate the presence of cognitive outcomes. Such a distinction is important, as cognitive difficulties represent the greatest burden of impairment (Marlow, 2004).

In an attempt to standardise outcome measures, many studies use validated assessment tools which cover broad cognitive domains such as the Griffiths Mental Development scales (Griffiths, 1954, Griffiths, 1970) or the Bayley Scales of Infant Development, Second or Third Edition (BSID-II or III) (Bayley, 1993, Bayley, 2006, Marlow, 2004). However, many studies linking MRI and neurodevelopmental outcome undertake their follow-up at different ages (Dyet et al., 2006, Inder et al., 2005, Boardman et al., 2010) which can limit the generalisability.

The impact of variable age of assessment on drawing conclusions from the literature is complicated further by the fact that not all studies correct for the degree of prematurity (Wilson and Craddock, 2004, Miller et al., 1984) which makes comparisons between studies difficult (Ross and Lawson, 1997). This is further confounded by debate as to when to stop correcting for the degree of prematurity (Johnson and Marlow, 2006), although this is typically 24 months.

From a parental perspective, the time lag between an MRI scan at TEA and an outcome measure at two years could be problematic. Many hospitals even in their clinical practice use clinical assessment and the meeting of developmental milestones with a motor focus to ensure satisfactory progression. There is currently no reliable method to assess cognition in early infancy, and especially identify subtle areas of development such as social cognition or executive function.

This section has shown that although white matter damage does map to later cognitive outcomes, limitations do exist especially in the generalisability and interpretation of outcome measures.

2.9 MRI predicting eye-tracking measures

Success shown in other high-risk groups with the use of eye-tracking as a measure of infant cognition was described in Section 2.6. In addition, the difficulties linking white matter damage and phenotypes in the preterm cohort are described above. In this section, the successful linkage of MRI in infancy and eye-tracking as a measure of structure and function are shown, with examples from the autism literature.

Elison et al. (2013) used eye-tracking and dMRI to examine the gaze behaviour and associated underlying brain structure of infants who would later receive an ASD diagnosis (Elison et al., 2013a). At aged seven months, these infants demonstrated slower visual orienting during the overlap condition within the gap-overlap task. In the low-risk infants (who did not develop ASD), visual orienting was associated with λ_{rad} in the splenium. Also, FA in the right uncinate fasciculus (white matter bundle linking the amygdala to the prefrontal cortex) at six months has been shown to be predictive of joint attention at nine months, although there was no relationship with language ability at the same age (Elison et al., 2013b). The authors suggested that the maturation of the right lateralised frontotemporal brain system is imperative for later non-verbal social development (Elison et al., 2013b). Dalton et al. (2007) also used functional MRI and eye-tracking tasks concurrently in siblings of children with ASD, those with ASD and a control group (Dalton et al., 2007). The results in the ASD siblings group were uniformly more consistent with the ASD group, with reduced fixations, brain activations and amygdala size relative to the control group. These examples illustrate that eye-tracking can successfully be used as an outcome measure when linked to dMRI metrics in atypical cohorts.

2.10 Conclusions and future directions

In this chapter, the abilities of term infants during the first year of life were summarised, before exploring deviations from the normal developmental trajectory in the case of the preterm infant and the identification of areas requiring further study. Current knowledge surrounding the predictive value of both conventional and dMRI for later cognitive outcomes was highlighted. The role of eye-tracking as a methodology to capture the consequences of prematurity in early life was explored and

the possibility of linking early neurological markers to these outcomes was discussed. This review of the literature has flagged social cognition and executive function (specifically attention and memory) as important skills to capture in the early lives of infants born preterm. Furthermore, they have the potential to be related to early white matter markers and later educational and diagnostic outcomes.

CHAPTER 3 : HYPOTHESES

The hypotheses tested in this thesis will be:

- I.
 - a) Diffusion MRI tractography reveals changes in tract-average FA, MD, λ_{rad} and λ_{ax} between preterm and term infants.
 - b) Variance in tract-average FA and MD is shared across major tracts.
- II.
 - a) Infants born preterm have altered social cognition compared to term born peers assessed by eye-tracking.
 - b) Infants born preterm have altered executive function compared to term born peers assessed by eye-tracking.
- III. Neonatal g_{WM} generated from dMRI tractography data is associated with cognitive function in infancy.

CHAPTER 4 : MATERIALS AND METHODS

A summary of the methods described in this chapter was submitted as part of the first year review process for this degree.

4.1 Recruitment

4.1.1 Ethics

Ethical approval was obtained from the National Research Ethics Service (South East Scotland Research Ethics Committee: REC numbers 11/SS/0061 and 13/SS/0143) for all participants recruited from hospital services; ethical approval for the recruitment of community participants was granted by the School of Education Ethics Sub-Committee, University of Edinburgh. Informed written parental consent was obtained for all participants.

4.1.2 Inclusion and exclusion criteria

Preterm infants (birth weight \leq 1500g) were recruited from the Royal Infirmary of Edinburgh, and healthy term control infants (\geq 37 weeks' PMA) were recruited from the postnatal wards or community groups between February 2013 and August 2015. Preterm infants were excluded in the presence of major congenital malformations, chromosomal abnormalities, congenital infection or major overt parenchymal lesions (cystic periventricular leukomalacia, haemorrhagic parenchymal infarction) and post-haemorrhagic ventricular dilatation. In addition to the above exclusion criteria, term infants were not approached for recruitment if there was any history of sepsis (proven or suspected requiring treatment with antibiotics). Infants were also excluded if they did not meet the safety criteria for MRI scanning as pre-defined by the Clinical Research Imaging Centre (CRIC).

4.1.3 Recruitment pathway

All infants were invited for an MRI scan at term equivalent age (38 – 42 weeks' CGA) and an eye-tracking assessment as close to 6 – 9 months' CGA as possible. Preterm infants received a BSID-III assessment as part of standard National Health Service (NHS) follow up. Table 4.1 demonstrates the overall recruitment pathway numbers for

both term and preterm infants and the number of infants included with different combinations of elements of the study. Infants were initially recruited for the MRI scans by Emma Telford, Sarah Sparrow, Chinthika Piyasena and Rozalia Pataky from the Royal Infirmary, Edinburgh. Emma Telford followed up all infants for the eye-tracking assessment recruited from the hospital, with the exception of one preterm infant who was assessed by Dr Gillespie-Smith. Thirty term infants were recruited from the community by Dr Karri Gillespie-Smith for eye-tracking assessments alone.

Of the 147 preterm infants who were consented to participate in the study, MRI acquisition was attempted in 133 infants and was successful in 121. Imaging data were excluded during the analysis stage in 12 infants as described in Chapter Five, Figure 5.1. MRI acquisition was not attempted in the remaining 14 preterm infants for the following reasons: too unwell or transferred out of hospital ($n = 4$), parents cancelled or did not attend ($n = 4$), infant no longer met inclusion criteria due to diagnoses of trisomy 21 and congenital lobar emphysema after consent ($n = 2$), the family formally withdrew consent ($n = 2$) and other reasons ($n = 2$). Structural MRI alone or no imaging data were acquired in 12 preterm infants. In the term group, 48 infants were consented and an MRI scan was attempted. dMRI data was successfully acquired in 40 infants and data for four infants was excluded during the analysis stage. Structural MRI or no imaging data were acquired in eight infants.

Data from the eye-tracking assessment was included if it had been collected by December 2015 and from the BSID-III assessment if it had occurred prior to the 14th of April 2016. Data were included for analysis from all successful eye-tracking and BSID-III assessments, even if dMRI acquisition had been unsuccessful or if data were excluded during the analysis stage. Eye-tracking assessments were not performed in 60 preterm and 11 term infants due to being lost to follow up, withdrawing from the study or not being old enough for assessment prior to the cut-off date. Furthermore, an eye-tracking assessment was added as an amendment to the ethics submission under which the first 75 preterm infants were recruited.

Of the 47 successful BSID-III assessments carried out in the preterm group with dMRI data, one participant was excluded as the assessment was undertaken in Polish which did not generate standardised results. Of the additional infants who were old enough

for a BSID-III assessment with dMRI data: three infants had not had an appointment made by the cut-off date for inclusion in the study; five infants were lost to follow-up; nine infants received alternative follow up or were out of region; two infants were unable to complete the assessment. Only infants with dMRI data were included in the BSID-III correlations in Chapter Six. A further five infants with structural data only successfully completed a BSID-III assessment. This data is included in Chapters Seven and Eight in the correlations with the eye-tracking data. A further two infants in whom dMRI data was unobtainable undertook an eye-tracking assessment and a BSID-III assessment. The BSID-III data in these two infants were not included in the analysis.

In summary, Chapter Four includes all infants from whom dMRI data were successfully acquired or a scan was attempted and the infant completed an eye-tracking assessment as described below (in 4.2.1). Chapters Five and Six include all infants on whom there was usable PNT tract data ($n = 36$ term infants and $n = 109$ infants). The published paper in Chapter Seven includes a subset of 100 infants (term and preterm), some of whom have had an MRI and eye-tracking assessment or just an eye-tracking assessment. The BSID-III correlations in Chapter Seven include all eligible infants who have had both BSID-III and eye-tracking assessments, irrespective if they have received an MRI ($n = 26$ preterm infants). Similarly, Chapter Eight includes all infants who have usable eye-tracking data ($n = 60$ term and $n = 73$ preterm infants), and later in the same chapter, all eligible infants who have received both BSID-III and eye-tracking assessments irrespective of MRI data acquisition ($n = 15$ preterm infants).

Table 4.1 Recruitment numbers

	Preterm (number of infants, n)	Term (number of infants, n)
Number of infants with included dMRI data, eye-tracking assessment and BSID-III assessment	22	N/A
Number of infants with included dMRI data and eye-tracking assessment	37	24
Number of infants with included dMRI data and BSID-III assessment only	24	N/A
Number of infants with included dMRI data only	26	12
Number of infants with eye-tracking data but no dMRI data	14	3*

*Please note an additional 33 term infants were recruited for eye-tracking.

4.2 Clinical data

4.2.1 Whole sample infant demographics

Tables 4.2 - 4.6 show a summary of relevant clinical information of included infants and corresponding maternal details. The tables refer to infants from whom dMRI data were successfully acquired or a scan was attempted and the infant completed an eye-tracking assessment. Data are also included for infants who did not undergo an MRI, but had a successfully eye-tracking assessment; therefore 73 term and 123 preterm infants are included. Figures relate to relative percentages or values after missing data has been excluded. All data were collected from the infants' or maternal hospitalised computer system or from a medical history taken from the mother at the time of MRI acquisition. Within this chapter, the description of the Scottish Index of Multiple Deprivation was taken from the published paper in Chapter Seven. The clinical data is presented to categorise the sample and is not included in statistical analyses unless otherwise stated.

4.2.2 Definitions for clinical data

4.2.2.1 Maternal factors

Maternal hypertension (HTN): any cause of high blood pressure during pregnancy

Maternal diabetes mellitus (DM): any cause of diabetes (types one, two or gestational)

Illicit drug use: the use of any illegal substance during pregnancy

Education level: the highest reached by the mother including current study

Body Mass Index (BMI): {as calculated by: weight (kg) / (height (m))² from the first antenatal booking appointment

Maternal chronic or mental health problems: the presence or absence of any mental health or chronic condition

Smoking status: current, previous, or never

Assisted reproduction technique (ART): included any assisted technique

4.2.2.2 Delivery factors

Mode of delivery: spontaneous vaginal delivery (SVD) or caesarean section, *c-section*

Apgars: at one and five minutes of age (summary of newborn health based on colour, tone, heart rate, respiratory effort and reflexes)

Cord gases: venous and arterial cord gases pH and base excesses (BE)

4.2.2.3 Infant factors

Bronchopulmonary dysplasia: was defined as an oxygen requirement at 36 weeks' PMA (Shennan et al., 1988). The need for home oxygen was defined as an oxygen requirement after discharge.

Retinopathy of Prematurity: was defined as "yes" if it was present and laser treatment had been required

Late onset Sepsis (LOS): was defined as per the Vermont Oxford Network (VON) as infections on day three of life and (1) positive blood culture growing pathogenic bacteria; *or* (2) blood cultures negative or positive for coagulase negative staphylococcus (CoNS) *plus* generalised signs of infection *plus* physician decision to

treat with antibiotics for five days or more. Generalised signs of infection include apnoea, temperature instability, feeding intolerance, worsening respiratory distress or haemodynamic instability (Vermont Oxford Network, 2014).

Chorioamnionitis: was based upon the histological staining or findings within the placental pathology report. Chorioamnionitis was deemed to be present if an inflammatory response was present in the placental membranes of any grade or stage. For a subset of infants, inclusion was based on the pathology report, both acute (including sub-acute) and chronic descriptions were accepted definitions.

Necrotizing Enterocolitis (NEC): grading was based upon the Modified Bell's Staging for NEC and defined as stages two or three (Bell et al., 1978).

Days of ventilation: each calendar day was counted as one day. If the mode of ventilation was changed in a 24 - hour period, then that day will have been counted twice; once for each mode of ventilation. This was counted until discharge from hospital and was measured for continuous positive airway pressure support (CPAP), bilevel continuous level support (BiPAP), high flow nasal cannulae (HFNC / vapotherm) and low flow nasal cannulae (NC).

Antenatal (AN) Steroids: was defined as any administration to the mother, irrespective of the time period before birth. It is also documented if the mother received a complete course (two doses) and if this was less or more than seven days prior to delivery.

Antenatal (AN) Magnesium Sulphate (MgSO₄): was defined as any administration to the mother for fetal neuroprotection, irrespective of the time period before birth.

Intrauterine Growth Retardation (IUGR): was defined as birth weight \leq third centile for sex and gestation using the Royal College of Paediatric and Child Health Neonatal and Close Monitoring growth charts (Royal College of Paediatrics of Paediatrics and Child Health, 2009).

Postnatal (PN) steroids: was defined as the requirement for post-natal dexamethasone to allow the weaning of ventilation. It did not include hydrocortisone administered for hypotension.

Days in neonatal unit (NNU): number of days admission from birth to discharge in all hospitals. This was based on discharge letters and maternal recollection of discharge.

Periventricular Leukomalacia: evidence of multiple cystic lesions in a periventricular distribution (Volpe et al., 2011).

Intraventricular Haemorrhage (IVH) grade three or four: As per Papile's definition (Papile et al., 1978).

Inotropes: if any inotropes were required in order to sustain the infants' blood pressure whilst in the neonatal unit.

Blood products or transfusion: if any blood products were administered during admission.

Total parenteral nutrition (TPN): the number of days the infant received TPN.

Breast milk days: term infants to date of scan and preterm infants to date of discharge from hospital.

The Scottish Index of Multiple Deprivation (SIMD) was used to characterise deprivation. The SIMD is the official Government tool^b used to identify areas of deprivation: it divides Scotland into around 6505 areas each containing around 350 households and assigns an index to each area based on multiple measures of deprivation. The data are ranked from most to least deprived and are presented as quintiles. The original postcode at birth was used where possible, unless an infant was recruited for an eye-tracking assessment alone, then the postcode at the time of eye-tracking assessment was used. If an infant was discharged into foster care from hospital, then the birth mother's address was used. Furthermore, if the family moved house whilst the infant was in hospital, the new long-term address was used.

^b <http://www.gov.scot/Topics/Statistics/SIMD>

Table 4.2 Maternal clinical factors

Group	Smoking Current (%)	Ethnicity: any white / European (%)	Marital Status: Married / single supported/ single unsupported (%)	Mean maternal age / years (sd)	Highest Educational level* (%)	Median BMI / kg / m² (IQR)	Chronic health problems (%)	Mental health problems (%)	Primi-gravida (%)	Illicit drug use (%)
Term	2.5	95.9	76.2 / 21.4 / 2.4	32.6 (4.24)	93.1	24.3 (21.8-27.5)	12.5	16.7	52.5	0
Preterm	15.4	89.4	56.9 / 39.8 / 3.3	33.33 (5.89)	54.5	24.1 (21.2-27.1)	23.6	20.3	52	6.5

* undergraduate or above

Table 4.3 Maternal antenatal factors

Group	Pre - * folic acid (%)	Post -* folic acid (%)	History of HTN (%)	History of DM (%)	Multiple pregnancy (%)	ART (%)	Chorio- amnionitis (%)	AN steroids (any) (%)	AN (complete) (%)	AN steroids (> 7 days prior to delivery) (%)	MgS04 (%)
Term	65	90	15	2.5	5	10	-	5	5	5	5
Preterm	49.6	78	20.3	7.3	34.1	17.1	33.6	95.1	73.2	25.2	52.8

*conception

Table 4.4 Infant clinical factors at birth

Group	Mean birth weight / kg (sd)	Mean gestation at birth / weeks (range)	Gender (F: M)	IUGR (%)	Delivery Method SVD: C-section (%)	Median Apgars 1, 5 min	Mean Cord gases Venous pH, BE / mmol / L	Mean Cord gases Arterial pH, BE / mmol / L
Term	3.52 (0.43)	40 ⁺⁰ (37 ⁺⁰ - 42 ⁺³)	34: 39	0	33.3:66.7	9, 9	7.31, -4.78	7.24, -3.66
Preterm	1.13 (0.25)	28 ⁺⁶ (23 ⁺² - 34 ⁺⁶)	62: 61	6.5	52.5:47.5	5, 8	7.32, -4.05	7.27, -4.77

Table 4.5 Infant post-natal clinical factors

	Group	
	Preterm	Term
NNU*	63 (42 - 80)	0 (0 - 0)
TPN*	8 (6 - 11)	-
Breast milk**	55.24 (24.9)	14.51 (10.7)
BPD (%)	33.3	-
Feeding at discharge (%):		
Breast	42.3	66.7
Formula	30.9	12.8
Mixed	26.8	20.5
ROP laser (%)	4.1	-
NEC (%)	5.7	-
PVL (%)	0	-
LOS (%)	29.3	-
IVH grade 3 or 4 (%)	1.6	-
Ventilation*	1 (0 - 4)	-
CPAP/ BiPAP**	13.24 (13.43)	-
HFNC**	12.91 (16.7)	-
NC*	0 (0 - 13)	-
Inotropes (%)	5.7	-
PN steroids (%)	0	-
Blood products (%)	41.5	-

*Median days (IQR) **Mean days (sd)

Table 4.6 Infant factors at time of scan

Group	Home oxygen (%)	Mean occipital frontal circumference (OFC) at scan / cm (sd)	Mean weight at scan / kg (sd)
Term	0	36.33 (1.27)	3.75 (0.53)
Preterm	15.4	34.8 (1.37)	2.96 (0.50)

4.3 MRI procedure and analysis methods

4.3.1 MRI procedure

MRI scanning was carried out at CRIC using established research procedures and infants were 38 - 42 weeks' PMA at the time of image acquisition. All scanning was supervised by a clinical research fellow and a paediatric research nurse. All infants were examined by the clinical research fellow prior to the applications of monitoring leads and ear protection including ear plugs and ear muffs (MiniMuffs, Natus Medical Inc., CA). Physiological stability and infant safety was ensured by monitoring procedures and safety features as set out by Merchant et al. (2009) (Merchant et al., 2009). Infants were offered a feed and non-pharmacological measures were used to encourage natural sleep. Once settled, the infant was placed in the MRI scanner for a maximum period of one hour. Oxygen saturation and heart rate were documented every five minutes throughout the scan and the scan was paused if any concern or infant distress arose. The infant was reviewed after the scan and allowed home if observations were within normal limits. Procedures were in place for any adverse event, however these were not required.

4.3.1.1 Image acquisition

Details of the image acquisition protocol can be found in Chapter Six, Section 6.4.2. An optimised bipolar gradient pulse scheme was selected with a manually selected shim box covering a region extending from the top of the head to several centimetres below the chin in order to minimise the effect of eddy current induced artefacts and shimming errors.

4.3.2 Image analysis

4.3.2.1 Structural image analysis

Structural scans were scored using the system by Woodward and colleagues who developed a scoring system for grading MRI data with evidence of cerebral damage in neonates (Woodward et al., 2006). The scoring system examined several different grey and white matter parameters. White matter parameters include signal abnormality, periventricular white matter loss, cystic change, size of the lateral ventricles and evidence of corpus callosum thinning. Grey matter parameters include the size of the subarachnoid space, signal abnormality in the cortical grey matter and gyral maturation. A score is applied to each parameter on a measure of one to three, with three indicating a higher level of damage. A summary score is calculated across five domains to determine the degree of white matter injury and three domains for grey matter injury. The white matter scoring system ranges from 5 - 15 using Woodward et al.'s system: > 6 is abnormal and ≤ 6 is normal. The grey matter scoring system by contrast ranges from three to nine and scores are classified using a modified scoring system described by Leuchter et al.: normal ≤ 4 and abnormal > 4 (Leuchter et al., 2014). If one value was missing for an infant for either grey or white matter, that participant was counted as missing data for that score only.

4.3.2.2 Image analysis

The image processing protocol has previously been published by our group (Anblagan et al., 2015). dMRI data were processed using FSL tools (FMRIB, Oxford, UK; <http://www.fmrib.ox.ac.uk>). Diffusion-weighted EPI volumes were registered to the first T2-weighted EPI volume for each participant in order to ensure accurate brain extraction and the removal of infant motion and eddy current artefacts. MD and FA volumes were calculated for each participant using DTIFIT. White matter connectivity was analysed using the BedpostX / ProbTrackX algorithms with the following parameters: 2-fiber model per voxel,

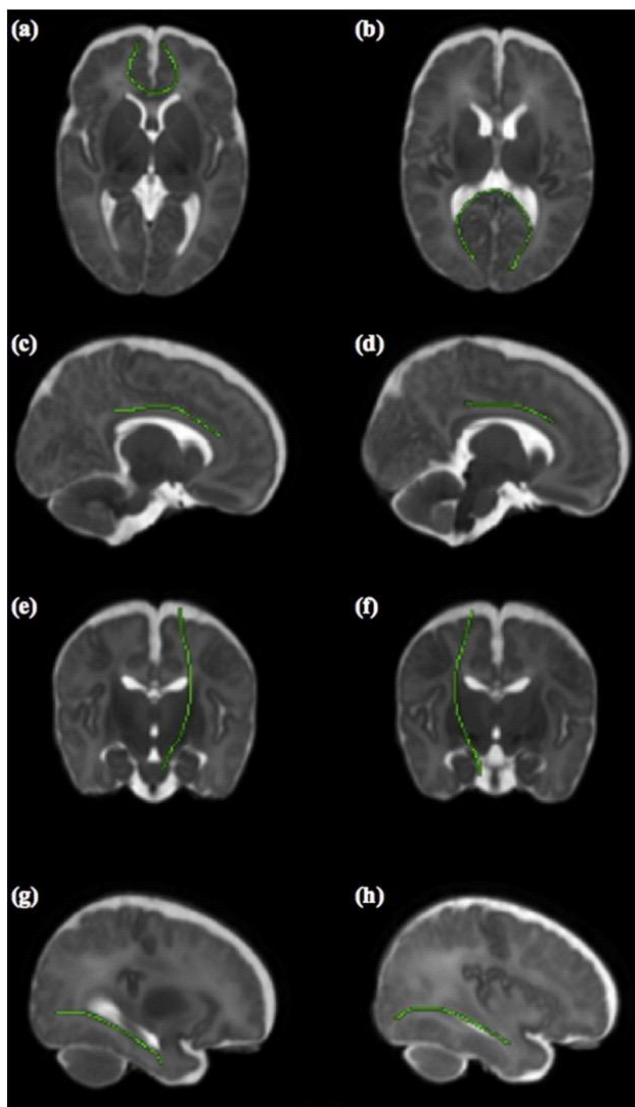
5000 probabilistic streamlines for each tract with a fixed separation distance of 0.5 mm (Behrens et al., 2007, Behrens et al., 2003).

4.3.2.3 Reference tracts

Eight reference tracts-of-interest for the neonatal brain have previously been generated from 20 control subjects by our group and published by Anblagan et al. (2015); see Figure 4.1. The eight reference tracts were: genu and splenium of corpus callosum, left and right inferior longitudinal fasciculi (ILF), left and right corticospinal tracts (CST) and cingulum cingulate gyri. Firstly, sets of candidate tracts were generated for each pathway of interest in every control subject by seeding within a $7 \times 7 \times 7$ neighbourhood of native space voxels around a standard space seed placed within white matter regions defined from a T2-weighted age appropriate template (Kuklisova-Murgasova et al., 2011). Dr Anblagan then visually inspected all candidate tracts and chose the one that best matched the pathway of interest for each subject. Tract-shape models for each pathway were then generated from these 20 tractography datasets using maximum likelihood (Clayden et al., 2007) and the reference tract, which represents the average tract size and shape from these 20 controls, determined. Probabilistic Neighbourhood Tractography (PNT) was then run over a neighbourhood of $3 \times 3 \times 3$ voxels for each subject using these reference tracts to provide tract-average measures of MD and FA for the eight fasciculi of interest. All computerised analysis was undertaken using TractoR (<http://www.tractor-mri.org.uk>) (Clayden et al., 2011).

Figure 4.1 Tracts-of-interest from 20 term controls

The mean reference tracts generated from 20 term control infants. "The reference tracts (green) are overlaid on age-specific standard space templates." The tracts displayed are: axial slices (a genu, b splenium or corpus callosum), sagittal slices (c left and d right cingulum cingulate gyri, g left and h right inferior longitudinal fasciculi, coronal slices (e left and f right cortical spinal tracts) (Anblagan et al., 2015). Reproduced from Elsevier (Anblagan et al., 2015).



4.3.2.4 Data cleaning for MRI

A total of eight tracts were therefore generated for each participant. Generated tracts were visually inspected by an experienced rater (Dr Devasuda Anblagan). Tracts were excluded from analysis if they were deemed not to be anatomically plausible or if significant motion artefact was evident. If data were missing or excluded in four tracts or more, each individual tract was inspected again and the data excluded if the tract seemed anatomically implausible on a second inspection. Tracts were also excluded if pathological features were identified on the structural MRI which would invalidate the original inclusion criteria. Tract-averaged values of FA and MD, λ_{ax} and λ_{rad} , weighted by connection probability, were generated from masks of the best fit tract. The goodness-of-fit of the best match tract to the reference tract (R) was calculated from the log-ratio of the matching likelihood of the candidate tract to the reference. Since the reference tract has, by definition, a log-ratio of zero, R will be negative for all other tracts. Thus, the more negative the value of R , the poorer the match between the matching track and the reference (Anblagan et al., 2015).

4.3.2.5 Statistical analysis

The distributions of FA, MD, λ_{ax} , λ_{rad} and R in each tract for the whole cohort were assessed for normality using the Shapiro-Wilk test. Unadjusted group level differences were explored using independent t-tests and a general linear model univariate ANOVA, correcting for age at scan, examined the effect of this on the group-level differences. For each tract of interest, group (preterm vs. term) acted as a fixed factor and PMA at scan as a covariate. The Mann-Whitney U test was used to compare R values between groups and Spearman's rho was used to investigate correlations between R and PMA at scan. Type one error was controlled for using False Discovery Rate (FDR) ($p < 0.05$) (Benjamini and Hochberg, 1995).

4.3.2.6 Determining a general factor of brain white matter microstructure

Principal component analysis (PCA) was then run on the correlations between all eight tracts for each of the four tract-averaged values: MD, FA, λ_{ax} and λ_{rad} . This was to determine whether there was a clear one-factor solution that explained a significant

proportion of the variance between tracts using methods described in (Penke et al., 2010). All available tracts were included. The group mean (either preterm or term) was imputed in the case of missing data for each dMRI biomarker value (e.g. FA, MD, etc.) and tract.

4.4 Eye-tracking procedure, task designs and analysis methods

4.4.1 Eye-tracking procedure

All recruited infants were invited for a single eye tracking assessment as close to six to nine months of age as possible. Term infants were assessed based on their PMA and preterm infants were assessed on their CGA (corrected for the degree of prematurity at birth). This is a standard method when assessing neurodevelopmental assessment in VLBW infants in both clinical and research settings (Johnson and Marlow, 2006). All eye-tracking assessments lasted a maximum of 90 minutes and were undertaken at University of Edinburgh research sites.

Infants were positioned on a parent's lap 50 - 60 cm from a display monitor used to show visual stimuli (see Figure 4.2). Eye movements were detected using a Tobii© x60 eye-tracker, and Tobii Studio© (version 3.1.0) software was used to present stimuli and record eye movements for analysis. Images were presented on a display monitor with a resolution of 1440 × 900 pixels. The Tobii© x60 system tracks both eyes to a rated accuracy of 0.3 degrees at a rate of 60Hz. Prior to data collection, eye-tracking calibration was performed using a five-point system. In a minority of cases, a two-point system was employed if there was difficulty in encouraging the infant to fixate on the screen (n = 5). Additionally, in one case a child was initially calibrated using the five-point system, however part way through the assessment they were accidentally recalibrated, this time using a two-point system. One term infant was excluded due to experimenter error during data acquisition.

Preterm infants were screened for deficits in visual acuity using Keeler© acuity cards prior to eye-tracking, and infants were excluded if visual acuity was below the estimated norm for age (Speedwell, 2003), see Appendix I. Child friendly music was played from speakers next to the display screen to encourage the infant to maintain

attention. Additionally, if a child became distracted, neutral noises were employed (such as clicking fingers) without indicating to the child where to fixate.

Figure 4.2 Infant and the eye-tracker



Parents were also asked to complete validated questionnaires during their child's assessment visit. Parents were asked to complete the very short form of the Infant Behaviour Questionnaire Revised (IBQ-R) (Gartstein and Rothbart, 2003) which is a measure of infant temperament (n = 111). One infant did not return the completed questionnaire after administration. Of the 111 infants who completed the questionnaire, four infants did not complete one question. A maternal history of postnatal depression was explored by either the administration of the Edinburgh Postnatal Depression Scale (Cox et al., 1987) (n = 58) or by asking at the time of eye-tracking assessment (n = 63). Three parents screened positive on the Edinburgh Postnatal Depression Scale (as defined as a score of >10) which indicates possible depression. Six parents had a positive history as defined as receiving medication or counselling and one parent was awaiting a follow up assessment.

Six bespoke free-viewing tasks assessing social cognition and EF were presented in a variable order across up to three sequences (a number of predefined different task types in a single run). These tasks are summarised in Table 4.7 below. Attention grabbers (cartoon images of toys on a black background with a backing of non-social sound effects) were presented in between each trial (each presentation of each task) to maintain infant attention. These were also presented as inter-stimulus interval (ISI) within a task. Accompanying sounds were obtained from www.freesfx.co.uk.

Looking time (LT) and time to first fixation (TFF) to the pre-defined areas of interest (AOIs) were collected (as described in Table 4.7). The sum of each variable per participant was extracted from the Tobii x60 tracker.

Table 4.7 Task and associated area of cognition assessed

Label	Psychological construct assessed	Task design	Areas of interest (AOIs)
Face-scanning	Social cognition	Free viewing of static faces	Top half face, bottom half face, eyes, mouth
Pop-out	Social cognition	Free viewing of animate and inanimate objects	Face, face-noise, phone, bird, car
Social Preferential Looking	Social cognition	Free viewing of neighbouring scenes	Social, non-social, bodies, faces
Recognition Memory	Demonstrating memory for an item previous seen	Preferential looking to familiar verses novel shapes	Novel and familiar shapes
Attention switching paradigm	Attention	Ability to switch and disengage attention	Central and peripheral stimuli
Object permanence	Complex measure of memory	If infant acknowledges the existence of an object when it can no longer be observed.	N/A: video coding

Previously unpublished results were generated by Dr Gillespie-Smith for the memory and object permanence tasks in a TD cohort. However, these tasks were not sufficiently sensitive to detect differences and modification was required in order to increase the sensitivity. The object permanence task used a two-dimensional object which appeared, disappeared and reappeared before disappearing again. The infant was then expected to anticipate the reappearance of the object. It is hypothesised that attention for this task may have been lacking due to there being no associated sound

with the appearance of the two-dimensional object; also a three dimensional object may be required (Johnson and Aslin, 1996) for an infant to detect object permanence. Similarly, interest in the memory task may have been limited due to the presence of static shapes with no interest generated by sound or motion. Improvement of these two tasks is required in order to establish whether they are effective assessment methods of these cognitive domains.

4.4.2 Social cognition tasks

Three previously validated tasks of increasing complexity were presented (Gillespie-Smith et al., 2016, Gliga et al., 2009) in order to assess social cognition. These are described in detail below.

4.4.2.1 Face-scanning: design of stimuli, AOIs and task details

The stimuli consisted of photographs of faces with a neutral expression (three male, three female). All stimuli are from the University of Stirling (<http://pics.psych-stir.ac.uk>). Stimulus (a) in Figure 4.3 is reproduced from Gillespie-Smith et al. (Gillespie-Smith et al., 2016) and Telford et al. (Telford et al., 2016), both from John Wiley and Sons^c. Stimulus (a) in Figure 4.4 is reproduced from Gillespie-Smith et al. (Gillespie-Smith et al., 2016) both from John Wiley and Sons^c.

Each stimulus measured approximately 18 × 24 cm. Each stimulus was viewed for 10s and each block contained two stimuli (one male and one female). Figure 4.3 depicts the stimuli which were presented across three sequences. Pre-defined AOIs described in Table 4.7 were used as a basis for analysis. Visual depictions of all AOIs are shown in Figure 4.4. The sizing of each AOI can be found in Appendix II.

^cReproduced under the Creative Commons Attribution License

Figure 4.3 Face stimuli presented



(a)



(b)



(c)



(d)



(e)



(f)

Figure 4.4 Visual depiction of examples of AOIs for face-scanning task showing: (i) eyes and mouth only (ii) all AOIs superimposed



(a)

(b)

4.4.2.2 Face-scanning: generation of variables and analysis

LT to AOIs, LT at the whole screen and TFF to AOIs were analysed, as measures of sustained attention and attentional priority respectively. Fixations to elsewhere on the screen were defined as "not on AOI." In addition to analysing raw LT scores, a proportional looking score was calculated as the ratio of LT per AOI to LT at whole stimulus [(proportional looking score = $LT(AOI) / LT(whole\ stimulus)$)]. Specific to this task, a difference score of LT on eyes minus mouth was calculated to explore potential preferences in fixation.

Trials were initially excluded if they had not been shown or fixated upon for all measures. TFFs < 100 ms were excluded and treated as missing data: in these cases it is likely that the saccade started prior to image onset (Liversedge and Findlay, 2000) or if the participant did not look at a particular AOI. LTs < 500 ms were excluded because this was not considered a sufficient quantity of data to represent the result of a series of planned eye-movements to particular AOIs. Means were generated per AOI for each participant across all valid trials. There was no missing data for the LT. Missing data for TFF measures (as defined above) was excluded. There was no statistical difference in the percentage of missing data between groups in the whole

sample for the face-scanning task as defined as fixations under 500 ms to trials that were presented ($p = 0.75$) or in the number of trials presented and not fixated on ($p = 0.055$).

4.4.2.3 Pop-out: design of stimuli, AOIs and task details

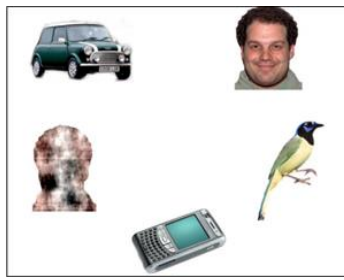
Photographs of a natural face and a “face-noise” image alongside non-social content against a white background in a grid like array (Gliga et al., 2009) were presented and are from the British Autism Study of Infant Siblings (BASIS) Network (<http://www.basisnetwork.org>). Stimulus (a) in Figure 4.5 is reproduced from Gillespie-Smith et al. (Gillespie-Smith et al., 2016) and Telford et al. (Telford et al., 2016), both from John Wiley and Sons^d. The non-social content included pictures of mobile phones, cars and birds. The “face-noise” image is an artificial scramble of the pixels in the face-stimulus, thus having the same low-level visual properties while being unrecognisable as a face. A total of seven stimuli were presented measuring approximately 25×20 cm. Each stimulus was viewed for 10s and each block contained two or three stimuli with a maximum of seven across three sequences. Figure 4.5 below shows all stimuli presented across all trials. The AOIs are described in Table 4.7 and are visually presented in Figure 4.6. Further detail regarding the size and location of AOIs can also be found in Appendix II.

^d Reproduced under the Creative Commons Attribution License

Figure 4.5 Pop-out stimuli presented



(a)



(b)



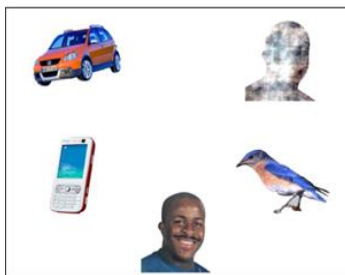
(c)



(d)



(e)

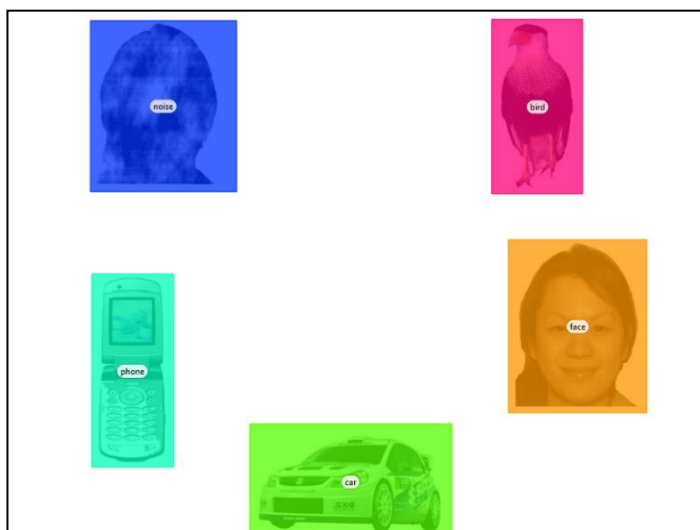


(f)



(g)

Figure 4.6 Visual depiction of an example all AOIs on a single Pop-out slide



4.4.2.4 Pop-out: generation of variables and analysis

The AOIs for the pop-out task (as described above) were analysed in the same manner as for the face-scanning task. In addition, the location of first fixation as a percentage was calculated for the pop-out task in a sub-sample of participants as further described in Appendix III. There was no statistical difference in the percentage of missing data between groups in the whole sample for the pop-out task as defined as fixations under 500 ms to trials that were presented ($p = 0.472$) or in the number of trials presented and not fixated on ($p = 0.595$).

4.4.2.5 Social Preferential Looking: design of stimuli, AOIs and task details

This task contained two neighbouring photographs with each pair consisting of a real world scene: one with social content (one or two children) and one without (i.e. containing no people) (Fletcher-Watson et al., 2008). All stimuli were created by Dr Gillespie-Smith. Written informed consent was obtained from all parents of the children in the stimuli. Stimulus (d) in Figure 4.7 is reproduced from Gillespie-Smith

et al. (Gillespie-Smith et al., 2016) and Telford et al. (Telford et al., 2016) both from John Wiley and Sons[°].

A total of 12 stimuli were presented measuring approximately 27×19 cm. Each stimulus was viewed for 5s and each block contained four stimuli (Figure 4.7). The AOIs are described in Table 4.7 and are visually presented in Figure 4.8 in an example slide. Further detail regarding the size and location of AOIs can also be found in Appendix II.

4.4.2.6 Social Preferential Looking: generation of variables and analysis

The AOIs for the social preferential looking task (as described above) were also analysed in the same manner as for the face-scanning task. In addition, an image-wise proportional score was calculated for a subsample of participants for the social preferential looking task for the fixation duration on the bodies and faces as a proportion of the overall fixation duration, relative to the size of the social AOI (results of these latter analyses are in Appendix III). There was no statistical difference in the percentage of missing data between groups in the whole sample for the social preferential looking task as defined as fixations under 500 ms to trials that were presented ($p = 0.67$) or in the number of trials presented and not fixated on ($p = 0.572$).

[°] Reproduced under the Creative Commons Attribution License

Figure 4.7 Social Preferential Looking stimuli presented



(a)



(b)



(c)



(d)



(e)



(f)



(g)



(h)



(i)



(k)

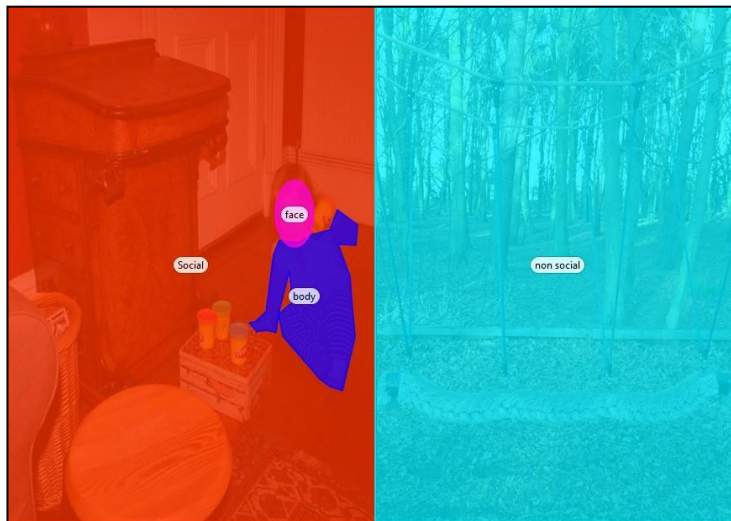


(l)



(m)

Figure 4.8 An example of all AOIs on a single Social Preferential Looking slide



4.4.2.7 Composite Social score

Four outcome variables were used from the eye-tracking metrics in order to produce a composite measure of eye-tracking measures, including a composite social score. The composite social preference score is a mean of the proportional fixation score (mean of LT to social content / mean overall LT to the task) across all three social cognition tasks. This has been proposed to be a reliable and comprehensive assessment of social cognitive ability in an infant rather than using multiple single constructs (Gillespie-Smith et al., 2016).

4.4.3 Executive function

In her pilot group of 30 term infants, Dr Gillespie-Smith trialed three tasks in combination to assess two domains of executive function: attention switching and memory. Infant memory was assessed using two tasks: recognition memory and object permanence as a complex measure of memory. The attention switching paradigm or "gap-overlap task" measures attention switching and disengagement and has been well validated in other high-risk groups such as those at risk of ASD (Elsabbagh et al., 2013a, Elsabbagh et al., 2009).

4.4.3.1 Attention switching paradigm: design of stimuli, AOIs and task design

This task uses two conditions from Elsabbagh et al.'s "Gap-overlap task" (Elsabbagh et al., 2009) in order to measure attention switching in two conditions: attention switching and attention disengagement. The stimuli are from the British Autism Study of Infant Siblings Network (<http://www.basisnetwork.org>). Within the switching condition the peripheral stimulus appears after the disappearance of the central stimulus (Figure 4.9 below). Within the disengagement condition, the peripheral stimulus appeared when the central stimulus was still present (Landry and Bryson, 2004). The timings for the appearance and disappearance within each condition is summarised in Appendix II. A total of four stimuli were shown for each condition over three sequences, with a potential of up to 24 trials presented. When presented on screen, the overall stimulus size ranged from 30×28.6 to 37.3×28.6 cm. Figure 4.10 below shows an example of AOIs within a single slide within the task as described in Table 4.7.

Figure 4.9 Attention switching paradigm

Two conditions after the initial presentation of the central stimulus are shown: the onset of the peripheral stimulus after the disappearance of the central stimulus and the onset of the peripheral stimulus whilst the central stimulus is still present. Timings are shown in Appendix II.

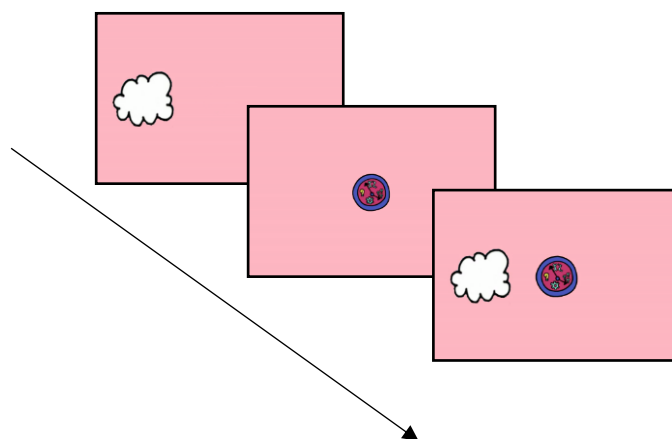
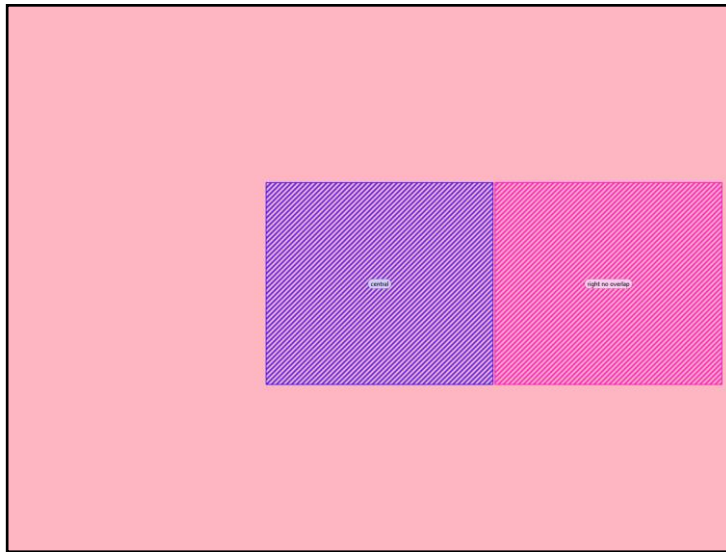


Figure 4.10 Example of AOIs in a single slide within the attention switching paradigm



4.4.3.2 Attention: generation of variables and analysis

The attention switching measure was calculated from TFF to the peripheral stimuli in two conditions: the switch condition where the peripheral stimulus appeared on the screen after the central stimulus had disappeared and the disengagement condition where the peripheral stimulus appeared on the screen when the central stimulus was still present. The following equation was used to calculate how quickly each participant fixated on the peripheral stimulus after its appearance on the screen:

Initial TFF timing – the timing of the onset of the peripheral stimulus

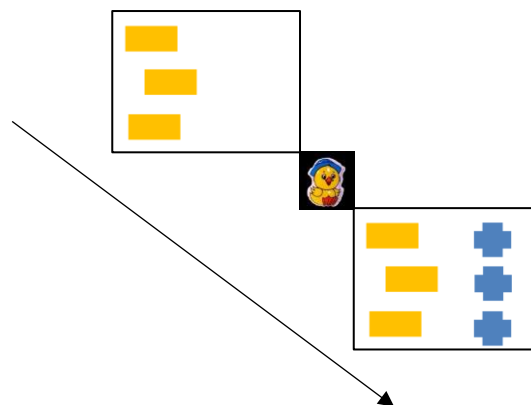
One stimulus was excluded due to incorrect timings in each condition. Therefore, a mean was taken across up to nine trials per participant for the remaining three stimuli presented in each condition. Trials were also excluded if they were not shown to the participant or if the child did not look at the screen during their presentation. Trials were also excluded if the timings after subtraction were < 100 ms. Missing data were excluded in SPSS version 21 (Chicago, IL). Attention switching and disengagement were included in four outcome variables generated from eye-tracking metrics in order to produce a composite measure of eye-tracking measures.

4.4.3.3 Recognition memory: design of stimuli, AOs and task design

Preferential looking to novel or familiar shapes was used as a basis to assess recognition memory. A set of three identical shapes were drawn freehand within Microsoft Powerpoint© on a slide sized 19.05 × 25.4 cm. Motion was added within Microsoft Powerpoint© and sound added (www.freesfx.co.uk) to encourage infant attention. A second paired slide was created in the same manner containing an identical set of shapes to the initial slide, with a neighbouring second trio of shapes. From this point onwards, the first slide in the pair will be referred to as slide "A" and the second slide "B" (see Figure 4.11). Slide B contains both familiar (the same identical shapes as slide A) and novel shapes (the new neighbouring trio of shapes not previously viewed on slide A). Each shape within the three groupings in both the familiar and novel shape were animated for the following durations: shape one for two seconds; shape two for one second; shape three for two seconds.

Figure 4.11 Example of memory task

This image slide A with the familiar shapes (yellow rectangles), ISI (not to scale) and slide B with familiar (yellow rectangles) and novel (blue crosses) shapes.



This was then repeated four times for the familiarisation period of 20s (Fagan, 1974). The shape pairs were consistent (either round or with 90° angle edges) and the colour red was avoided to ensure a bias was not introduced due to babies' visual preference for red (Taylor et al., 2013, Franklin et al., 2010, Adams, 1987). The moving shapes

were recorded and edited with the addition of sound files using Microsoft Expression Encoder 4 and Screen Capture©. An ISI was then played for two, five or eight seconds before the infant was presented with the same set of familiar shapes and a neighbouring new set of novel shapes (i.e. slide B) for a period of five seconds. A total of four pairs of shapes were shown during each sequence, with a maximum of 12 stimuli. Each sequence showed one or two pairs with an ISI of two, five or eight s in a random order, with a total of four pairs with each timing across three sequences. The sizing of presented stimuli and detailed description for each shape set is summarised in Table 4.8. Figure 4.12 shows a visual representation of an example of the A and B slide pairing within the memory task with example AOIs.

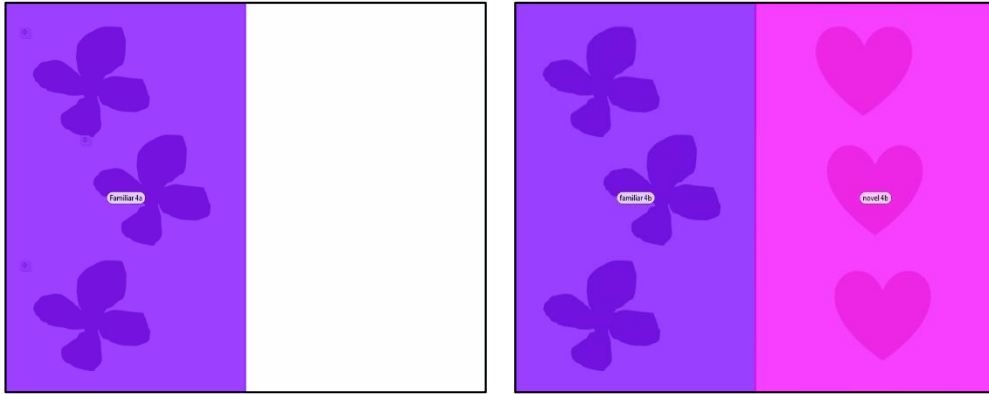
Table 4.8 Memory task detailed description

Memory task shapes pairing	Description (familiar and novel shapes)	Motion	Pairing name	Accompanying sound	Familiar shapes stimuli size (cm approx)	Novel shapes stimuli size (cm approx)	ISI duration (seconds)
1	Yellow rectangles and blue crosses	Teeter	Angular 1	Short chimes	24.8 x18.8	24.8 x 18.6	2
2	Peach wotsits and purple flowers	Teeter	Curvy 1	Short chimes	24.8 x18.8	24.8 x 18.6	5
3	Yellow squares and grey arrows	Pulse	Angular 2	Bubbles	24.8 x18.8	24.8 x 18.6	8
4	Purple flowers and pink hearts	Spin	Curvy 2	Music box	24.8 x18.8	24.8 x 18.6	2
5	Blue clouds and green circles	Pulse	Curvy 4	Boing 4	24.8 x18.8	24.8 x18.6	2
6	Blue rhombus and green rhombus	Spin	Angular 6	Bangkok frog	24.8 x18.8	24.8 x18.6	5
7	Brown triangle and pink flag	Teeter	Angular 7	Bubbles	24.8 x18.8	24.8 x18.6	8
8	Purple rhombus and blue star	Pulse	Angular 8	Squeak	24.8 x18.8	29 x 22	5
9	Blue triangles and yellow rhombus	Pulse	Angular 3	Chimes	24.8 x18.8	29 x 22	8
10	Yellow hoops and blue ovals	Spin	Curvy 3	Minisynth	24.8 x18.8	29 x 22	5

11	Brown rhombus and pink hexagons	Teeter	Angular 4	Pop	24.8 x18.8	24.8 x18.6	8
12	Grey lightning and lilac cross	Spin	Angular 5	Chomp	24.8 x18.8	29 x 22	2

Figure 4.12 Example of AOIs within the A and B slide pairing

The initial familiar slide and then the familiar and novel shapes after the pre-defined ISI are shown.



4.4.3.4 Recognition memory: generation of variables and analysis

LT to the whole of the A stimulus was used as a measure of attentiveness. LT to the familiar and novel shapes in the B slide was also calculated for each of the three ISI timings: twos, five and eight s. Zeros were added for the mean calculations per AOI across up to 12 trial pairs, if the participant fixated upon one AOI and not another. Entire slide pairs (A and B, for example pairing shown in Figure 4.12) were excluded if the LT to the A slide was $LTs < 500$ ms because this was not considered a sufficient quantity of data to represent the result of a series of planned eye-movements to particular AOIs. Therefore, any B slide fixations would be void as the infant had been unable to demonstrate recognition and therefore memory of either of set of novel or familiar shapes. Similarly, B trials within the slide pair were excluded if the overall LT was < 500 ms. Trials were also excluded if they were not shown or a participant did not look at the screen. A difference score was calculated for LT to familiar minus fixation to novel shapes for the B stimulus. If a single outlier was causing the data to be skewed, this subject was excluded from the analysis. All missing data was excluded within SPSS. There was no statistical difference in the percentage of missing data between groups for the memory task as defined as fixations under 500 ms to trials that were presented ($p = 0.732$) or in the number of trials presented and not fixated on ($p = 0.297$).

A memory summary variable was constructed as the number of fixations (defined as the number of times a participant fixated on an AOI) divided by the number of visits (defined as the time interval between the first fixation on the active AOI and at the end of the last fixation within the same active AOI where there had been no fixations outside the AOI). A high number indicates a participant has demonstrated many fixations and few visits suggesting their fixations have predominantly been within an AOI and not back and forth between AOIs. This is in contrast to a low number indicating a fewer fixations and more visits to an AOI i.e. the child has been scanning between one AOI and another. Means were calculated across all valid trials per ISI timing and then the division of number of fixations by the number of visits.

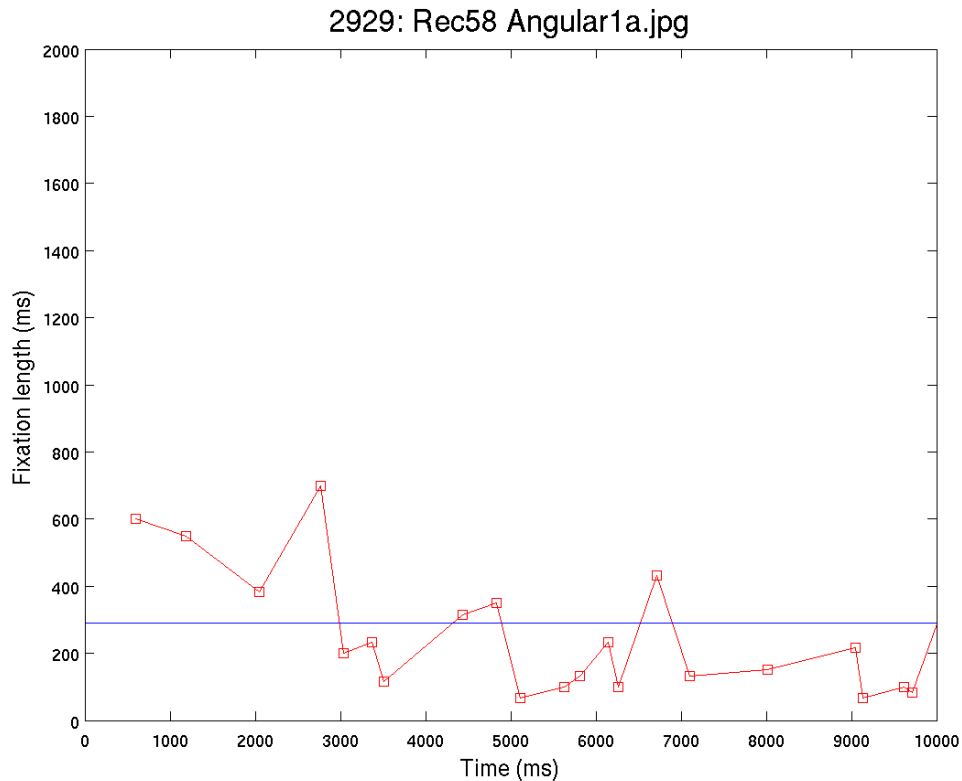
Infants who successfully encode and retain a memory of stimulus A for the duration of the ISI should show a stimulus preference during presentation of stimulus B. This may either manifest as a novelty (greater looking time to novel content) or familiarity (greater looking time to previously-presented, familiar content) preference. Infants with no memory of Stimulus A should distribute their attention roughly equally between the two areas of interest in Stimulus B. A difference score was therefore calculated for fixation to the familiar shapes minus fixation to the novel shapes on stimulus B. However, analysing means using this score conflates two types of evidence for memory: a novelty preference (low negative scores) and a familiarity preference (high positive scores). The absolute value of the difference score was consequently taken to create a variable which is a more accurate measure of memory, without conflating both novelty and familiarity preference.

Another method to estimate evidence of retention from the collected data is to set an absolute cut-off for the size of preference required to indicate that memory has been demonstrated. Drawing on the work of Fagan (Fagan, 1974) a cut-off of 54% preference (to either the novel or the familiar stimulus) was set as an indicator that memory had been demonstrated and this threshold was used to categorise infants as showing a novelty, familiarity or no preference at each ISI level.

As stated earlier, four outcome variables were used from the eye-tracking metrics in order to produce a composite measure of eye-tracking measures. Using the memory task, a "habituation score" was generated as a measure of information processing

speed. The habituation score has been designed to calculate the point at which the infant habituates to the stimulus (or becomes disinterested). The habituation score was generated from raw data extracted from the Tobii software for each fixated stimulus A for each participant for the memory task: mean fixation duration, fixation index, saccade index, gaze event type and gaze event duration. This data was then run on Matlab (<https://www.mathworks.com/products/matlab.html>) code designed by Dr Mark Bastin which has previously been trialed on a data set of 36 term infants. This code generated output data for each participant and for each stimulus: mean fixation duration, mean first fixation number, and mean time elapsed to the boredom point (see below). The mean fixation length was calculated across all stimuli for each participant. The first fixation number with a mean fixation duration below the overall mean with a minimum of one preceding value which was higher than the participant mean taken to be the boredom point or the point of habituation based on the fixations alone. For example, in Figure 4.13 the boredom point would be the fifth point on the x-axis. The mean time elapsed at this point then includes fixations, saccades and unclassified events and is taken to be the mean time elapsed. The habituation score was defined as the fixation number to the boredom point and termed "the fixation index number." The habituation score was also calculated by hand for two participants (data not shown) in order to ensure the validity of the code in this dataset.

Figure 4.13 Habituation graph showing the point of habituation (or boredom point)



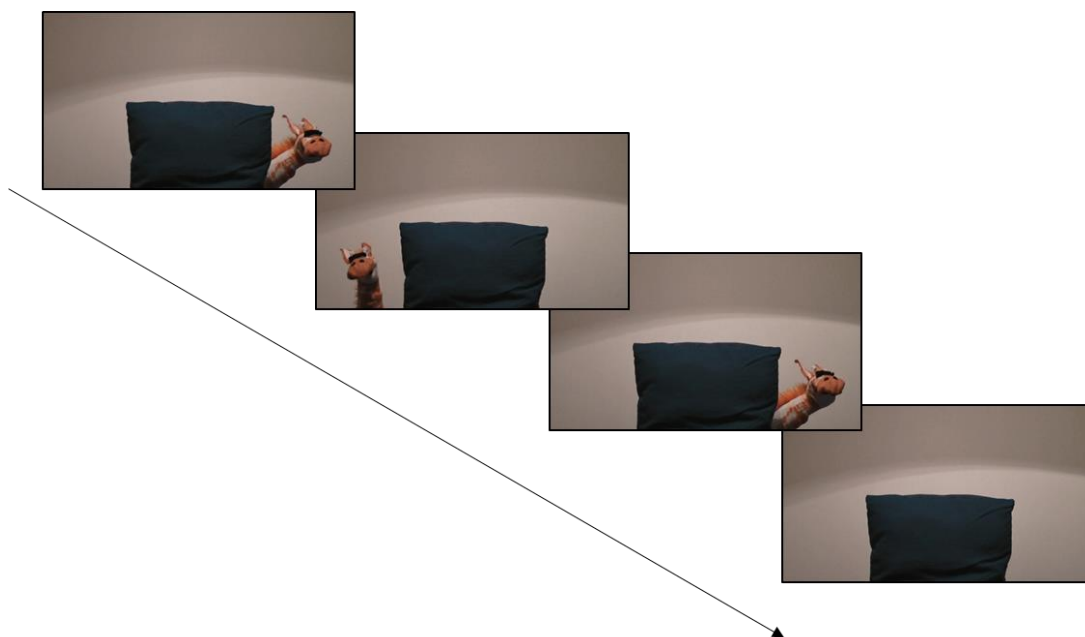
4.4.3.5 Object permanence: design of stimuli and task design

Object permanence is defined as acknowledgement of an object's presence when it can no longer be visualised (Baillargeon and DeVos, 1991). In this instance, object permanence is used as a complex measure of memory. The object permanence task was also developed from unpublished pilot data collected by Dr Gillespie-Smith. A total of six animations were recorded in real time using three puppets: lion, giraffe and polar bear using a green cushion and white background. The animation was designed such that the puppet began hidden from view and then appeared in the following sequence from behind, to either side of the cushion (timings shown): on the right-hand side (4.3 s), left-hand side (4.3 s) and then right-hand side (4.3 s) before disappearing from sight (4.3 s). Three trials started on the right-hand side and three trials from the left-hand side. The puppet hid behind a central cushion for one second in between each reappearance. This was also edited within Microsoft Expression Encoder 4. Two trials

were presented within each sequence, with a maximum possible of six. Each sequence contained a puppet beginning from both the right and left-hand side as indicated in Figure 4.14. Stimuli viewed on screen was sized 21.2×17 cm.

Figure 4.14 Object permanence task

The giraffe puppet begins from the left-hand side, appears, reappears to the right and then the left-hand side before disappearing.



4.4.3.6 Object permanence: generation of variables and analysis

LT, TFF or AOIs were not used in this task, instead each trial was visually inspected and independently coded by two raters (Emma Telford and Sarah Hampton). Sarah Hampton was blinded to the coding of participants. The trials were inspected to determine if the participant demonstrated object permanence for that trial after the final disappearance of the puppet. If disagreement occurred within coding of the trials, these were then re-watched by both coders together, to ensure an agreed score was given. A subset of trials were coded by both raters as training and agreement of each score category. Inter-rater agreement, based on the proportion of trials coded on which two raters gave identical scores independently, (for the whole sample: preterm and term

infants combined) was 79.1% based upon 330 trials. 142 training trials were excluded from the inter-rater agreement.

The performance for each participant for each trial was coded as summarised in Table 4.9. Two variables were constructed: did the participant demonstrate object permanence in fifty percent of trials (out of four or six) or in a minimum of two trials? Trials were excluded if the child scored a "three" in a trial they viewed or if a trial was not shown. Please note some participants did not complete all three sequences. Missing data was excluded in SPSS.

Table 4.9 Object permanence coding

Code assigned	Interpretation
1	Participant clearly fixated on the puppet at any point in the three visualisations and were deemed to look for it (either above or either side of the cushion where the puppet would be expected to appear from) once the puppet had disappeared for the final time, therefore demonstrating object permanence.
2	Participant fixated on the puppet but did not look for it once the final puppet had disappeared.
3	Participant did not fixate at any point or they did not fixate upon the puppet in the early stages of the task.

4.5 Testing for normality

Normality was assessed using measures of skew and by visual inspection of histograms. For normally distributed data, mean and standard deviation (sd) are reported and for non-normally distributed data, the median and interquartile range (IQR) are reported. Normally distributed data was defined as kurtosis score of -2 to +2 (Kerr et al., 2002) and visually inspected for evidence of a skew. For group-wise comparisons of normally distributed variables, independent sample t-tests or repeated measures ANOVA were used. For group-wise comparisons of skewed data, the Mann-Whitney *U* test was used. Repeated measures ANOVA or paired sampled t-tests and related samples Wilcoxon signed-rank test were used to investigate within-group differences for normally distributed and skewed data, respectively. Chi-squared and Fisher's exact tests were used for nominal data. Paired and one-sample t-tests were

used for the image-wise proportional scores for the social preferential looking task. Paired samples t-tests and related samples Wilcoxon signed rank test were used for normally distributed and skewed data respectively for test-retest analyses. Two-tailed *p* values are reported and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 21.

4.6 Eye-tracking test-retest reliability

To determine test-retest reliability, six preterm and two term infants were recalled for a repeat eye-tracking assessment. Infants were analysed as one cohort for all six tasks. There were missing data for one infant for one task only (8s ISI of the memory task). The median duration between assessments was 14.5 days (IQR 10.25 - 16.5 days). The infants' performances during both visits were generally consistent. The sample size is too small to be able to conclusively support the internal validity of the eye-tracking tasks, therefore further test-retest analyses would be required with a much higher sample size to confirm this. Figures 4.15 - 4.17 show the fixation duration (as measured by the composite score) for each participant for both assessments for the social cognition tasks. Figures 4.18 and 4.19 show the attention switching and disengagement timings for each assessment and Figures 4.20 - 4.22 show the absolute difference value (fixation to familiar minus novel shapes) for the mean fixation to slide B in the memory task for each ISI (two, five and eight seconds). Tables 4.10 and 4.11 show the object permanence accuracy counts (shown in two or more trials or 50 %) for each assessment visits.

Figure 4.15 Face-Scanning task test-retest

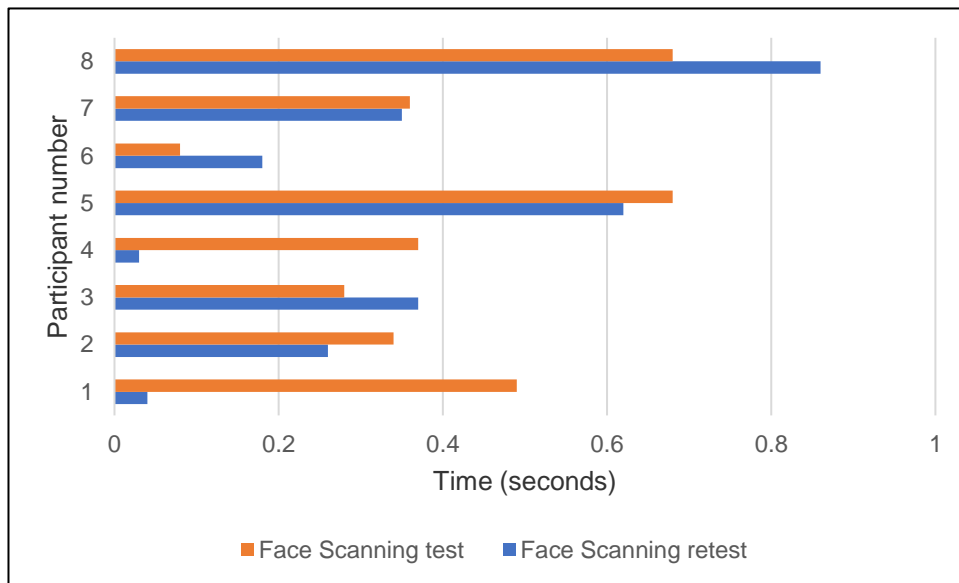


Figure 4.16 Pop-out task test-retest

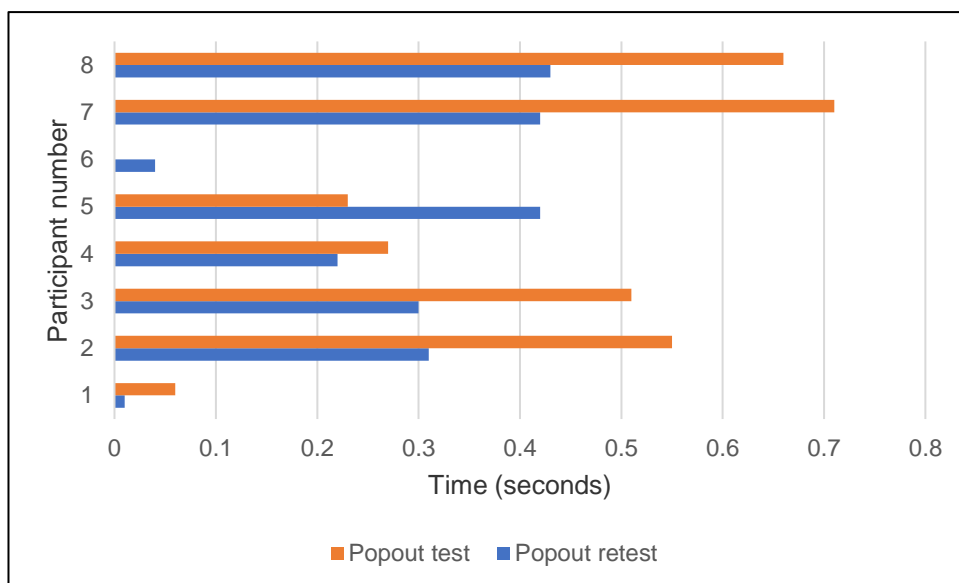


Figure 4.17 Social Preferential Looking task test-retest

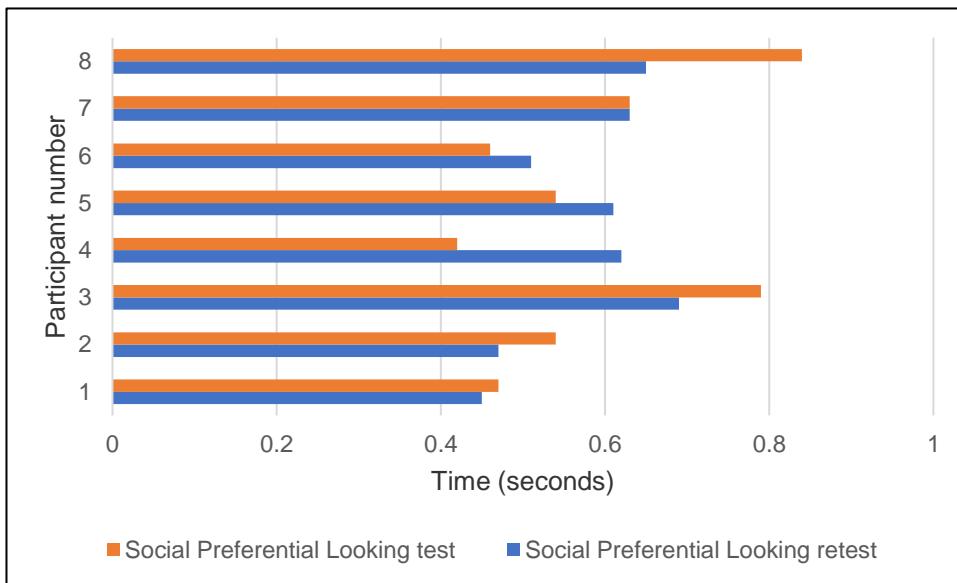


Figure 4.18 Attention switching test-retest

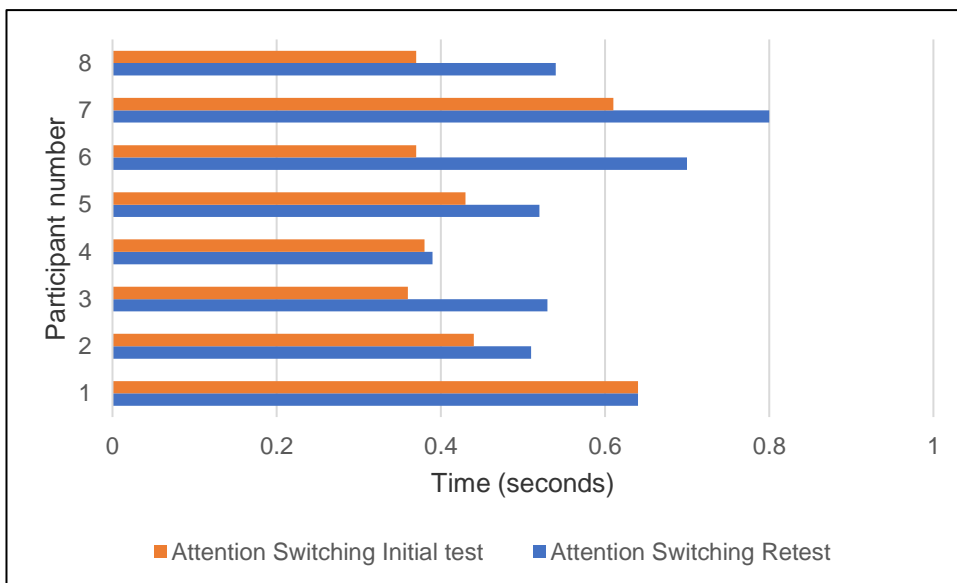


Figure 4.19 Attention disengagement test-retest

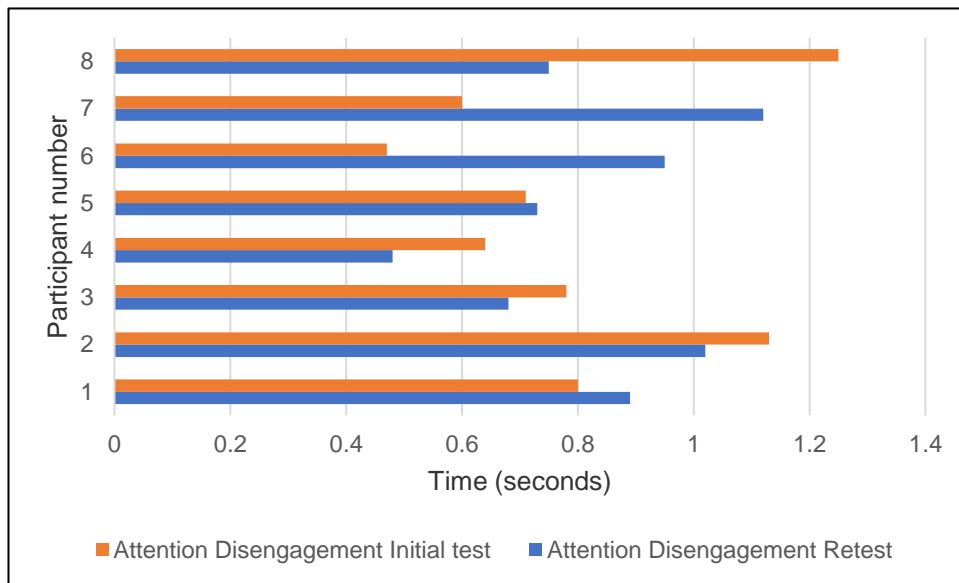


Figure 4.20 Absolute value for difference score of fixation duration to familiar minus novel shapes on slide B for 2s ISI (test-retest)

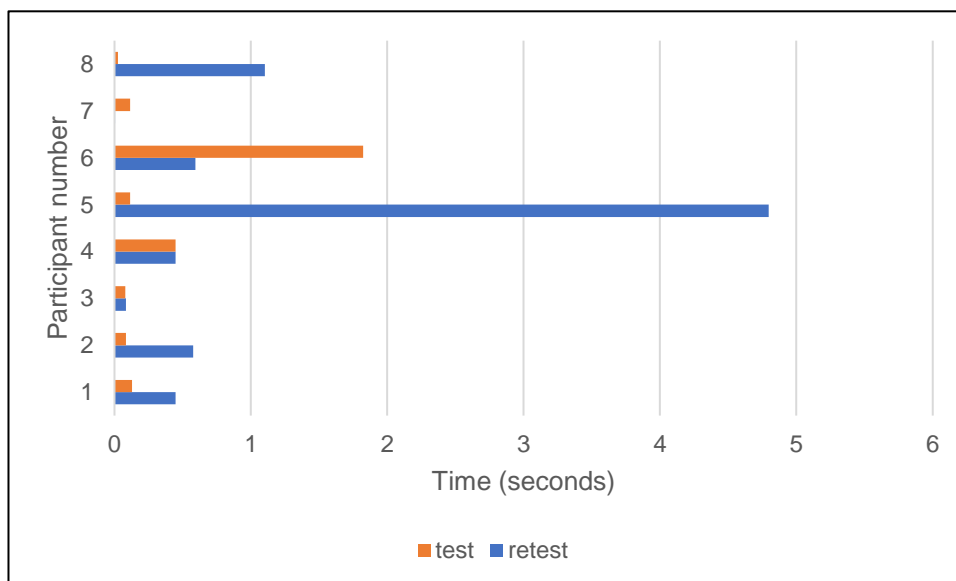


Figure 4.21 Absolute value for difference score of fixation duration to familiar minus novel shapes on slide B for 5s ISI (test-retest)

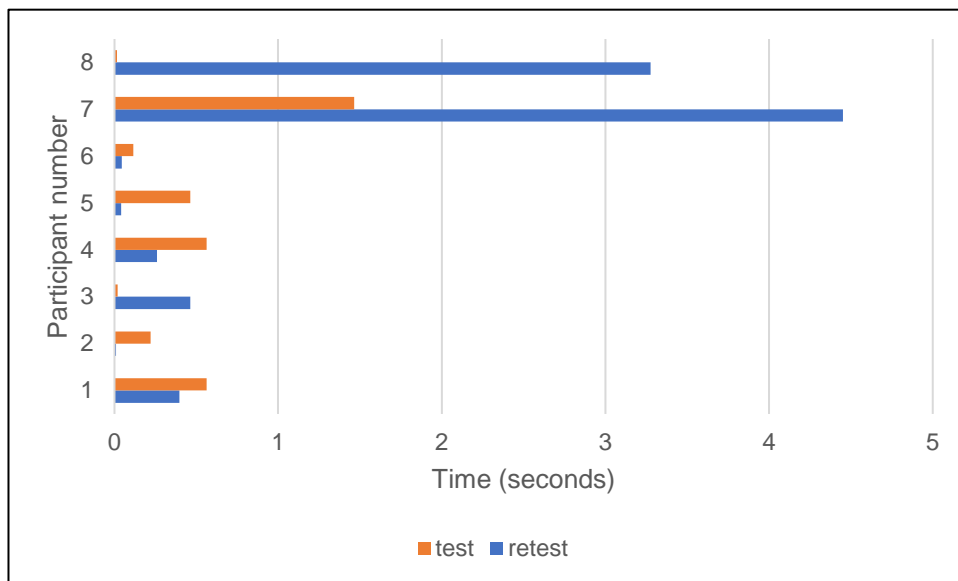


Figure 4.22 Absolute value for difference score of fixation duration to familiar minus novel shapes on slide B for 8s ISI (test-retest)

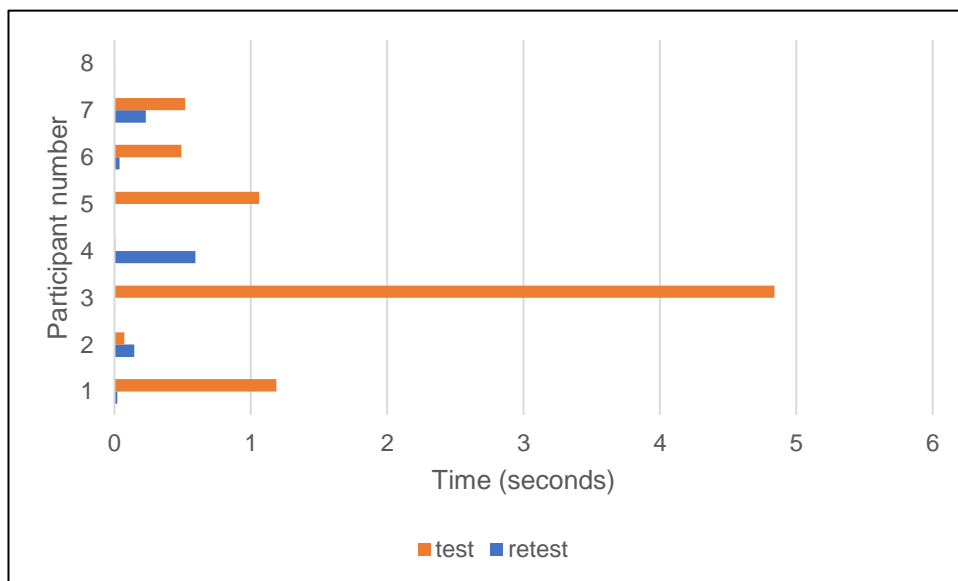


Table 4.10 Object permanence accuracy counts in 50% of trials (test-retest)

		Object permanence in at least 50% of trials: first time	
Object permanence in at least 50% of trials: second time		yes	no
	yes	4	1
	no	2	1

Table 4.11 Object permanence accuracy counts in two or more trials (test-retest)

		Object permanence in at least two trials: first time	
Object permanence in at least two trials: second time		yes	no
	yes	5	1
	no	1	1

4.7 Testing the relationship between a general factor of brain white matter microstructure and later cognitive outcomes

The general factor of each of the tract-averaged biomarker values (FA, MD, etc.) generated by PCA was used to assess the relationship between neonatal brain white matter microstructure and later cognitive performance. A regression model was used to assess the relationship between each general factor of brain white matter microstructure and the summary variables of eye-tracking at seven to eight months' CGA (social preference score, attention disengagement and switching and the habituation score). Prior to entering the model, the imaging and cognitive variables were corrected for age at testing in each domain. Gender was also entered as a covariate, with "1" denoting male and "2" denoting female for inclusion in the regression model. A Pearson correlation was used to assess the relationship between each g factor of brain white matter microstructure and the composite scores in motor, language and cognition generated by the Bayley Scales of Infant and Toddler Development, Third Edition at two years' CGA.

4.8 Bayley Scales of Infant and Toddler Development, Third Edition

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) allows a global assessment of five main areas of development: cognition and

communication, and physical, social, emotional or adaptive development. These areas are assessed through a structured examination of cognition, fine and gross motor skills and receptive and expressive language, alongside validated parent questionnaires to examine the social-emotional and adaptive scales. The BSID-III has been standardised to allow accurate assessments. Each assessment generates a raw score which is generated into a scaled score and finally a composite score from the summation of subsets of scaled scores. These composite scores are scaled to a metric with a mean of 100 and a standard deviation (sd) of 15. Percentile ranks are also available ranging from 1 to 99 with 50 being the mean and median. This allows the comparison of an individual to the standardised sample. It is an assessment scale with the benefit of scales able to be administered independently of each other (Bayley, 1993, Bayley, 2006). The composite scores for cognitive and language scales in the BSID-III replace the Mental Developmental Index (MDI) in the BSID-II and the fine and gross motor scores replace the previous psychomotor developmental index (Bos, 2013).

All VLBW infants receive a BSID-III assessment as part of their standard NHS Lothian follow up at two years' CGA. Each assessment lasted up to 75 minutes and one parent was present with the child at all times. Assessments were predominantly undertaken by Hilary Cruickshank or Dr Magda Rudnicka. A subset of assessments were also undertaken by Drs Gopi Menon, Deepa Patil or Emma Telford.

Infants who completed alternative assessments were not included as the scores for the Griffiths Mental Development Scales and the BSID-III assessment would not be directly comparable.

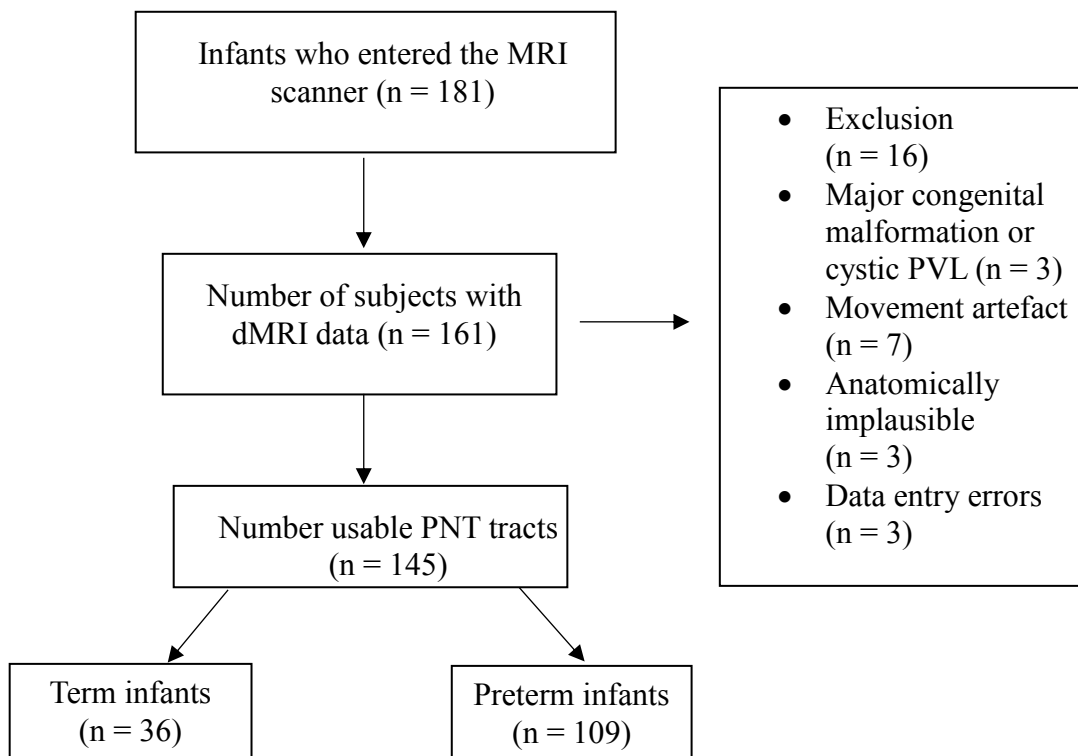
CHAPTER 5 : MAGNETIC RESONANCE IMAGING

In earlier chapters, the pitfalls associated with conventional imaging methods and the benefits associated with more objective measures of brain structure generated from dMRI were explored. In addition, the link between quantitative measures of brain structure and prematurity in the neonatal period and beyond were highlighted. This chapter will test the following hypothesis: diffusion MRI tractography reveals changes in tract-average FA, MD, λ_{rad} and λ_{ax} between preterm and term infants.

5.1 Processing pathway

Figure 5.1 shows a flow diagram which represents the MRI processing pathway.

Figure 5.1 Flow diagram of included subjects



5.2 Sample demographics

dMRI data was available on 145 eligible infants (36 term, 109 preterm). Post-menstrual age at birth and scan are summarised in Table 5.1 below for the whole sample and per group. There is a significant difference between groups at age of scan, with the term infants being older than the preterm infants (42 weeks vs. 39⁺⁶ weeks, $p = < 0.0001$).

Table 5.1 Sample demographics

	PMA at birth <i>Mean (range)</i>	PMA scan <i>Median (IQR)</i>
Whole sample	31 ⁺⁵ (23 ⁺² - 41 ⁺⁵)	40 ⁺⁶ (39 ⁺¹ - 41 ⁺⁶)
Preterm infants	29 ⁺⁰ (23 ⁺² - 34 ⁺⁶)	39 ⁺⁶ (39 ⁺⁰ - 41 ⁺⁴)
Term infants	39 ⁺⁶ (37 ⁺² - 41 ⁺⁵)	42 ⁺⁰ (41 ⁺² - 42 ⁺⁶)

5.3 Conventional magnetic resonance imaging

All infants who had usable dMRI data were included in the scoring of structural images. Table 5.2 shows the summation of the degree of white or grey matter damage and if this is scored as normal or abnormal. These summations use the structural scoring system as described by Woodward et al. and Leuchter et al. (Woodward et al., 2006, Leuchter et al., 2014). White matter abnormalities are graded as none (a score of 5 to 6), mild (a score of 7 to 9), moderate (a score of 10 to 12) and severe (a score of 13 to 15). Similarly, grey matter is categorised as normal (a score of ≤ 4) or abnormal (a score of > 4). The table shows the results by group. Missing data has been excluded from the table. In the preterm group, 45.9 % had mild white matter damage, 5.2 % had evidence of moderate damage and 1 % of infants had severe white matter damage. In the term group, 2.8% of infants had mild white matter damage. Three percent of

preterm infants had abnormal gray matter. In a sub-sample of 88 preterm infants, punctate white matter lesions were identified in seven infants. One further infant had a single cyst in the left peritrigonal white matter.

Table 5.2 Conventional magnetic resonance imaging

	Preterm	Term
Percentage of infants with mild white matter damage (%)	45.9	2.8
Percentage of infants with moderate white matter damage (%)	5.2	0
Percentage of infants with severe white matter damage (%)	1	0
Percentage of infants with abnormal gray matter (%)	3	0

5.4 Diffusion MRI

From this point onwards, the focus will be on dMRI tractography analysis in eight tracts-of-interest: genu and splenium of the corpus callosum, left and right cingulum, bilateral corticospinal tracts and inferior longitudinal fasciculi.

5.4.1 Group differences between tracts

It was hypothesised that preterm infants would consistently exhibit a lower FA and higher MD across all eight tracts-of-interest^f. Group differences are shown in Tables 5.3 and 5.4 below. Mean and sd are presented for values for each tract, except *R* where the median (IQR) is shown. There is a significant uncorrected difference between groups for all values for all tracts except in the left corticospinal tract λ_x . Term infants consistently have higher FA and lower MD values across all tracts. The number and percentage of missing tracts are shown per group.

^fData on 87 preterm infants and 24 term infants within this cohort have been published elsewhere (Anblagan et al., 2015).

Table 5.3 Group differences between tractsAll values (except FA) use the unit $\times 10^{-3}$ mm²/s.

		Preterm		Term			
Tract		Number (n), % of missing tracts		Number (n), % of missing tracts		abP value	bcP value
Genu of corpus callosum	FA	7, 6.4	0.21 (0.04)	0,0	0.25 (0.04)	<0.0001	0.023
	MD	7, 6.4	1495.96 (83.83)	0,0	1359.65 (62.27)	<0.0001	<0.0001
	λ_{ax}	7, 6.4	1829.89 (96.44)	0,0	1737.43 (83.01)	<0.0001	0.001
	λ_{rad}	7, 6.4	1329.00 (94.08)	0,0	1170.75 (73.84)	<0.0001	<0.0001
Splenum of corpus callosum	FA	13, 11.9	0.26 (0.04)	0,0	0.31 (0.04)	<0.0001	<0.0001
	MD	13, 11.9	1549.24 (150.29)	0,0	1376.39 (63.56)	<0.0001	<0.0001
	λ_{ax}	13, 11.9	1991.07 (159.29)	0,0	1854.93 (106.97)	<0.0001	0.005
	λ_{rad}	13, 11.9	1328.32 (156.12)	0,0	1137.12 (63.63)	<0.0001	<0.0001
Left cingulum	FA	11, 10.1	0.20 (0.03)	5, 13.9	0.23 (0.03)	<0.0001	0.301
	MD	11, 10.1	1369.10 (88.07)	5, 13.9	1304.77 (49.50)	<0.0001	0.107

	λ_{ax}	11, 10.1	1651.03 (104.94)	5, 13.9	1611.76 (54.84)	0.048	0.285
	λ_{rad}	11, 10.1	1228.14 (86.14)	5, 13.9	1151.28 (56.53)	<0.0001	0.067
Right cingulum	FA	18, 16.5	0.19 (0.03)	5, 13.9	0.21 (0.02)	0.006	0.638
	MD	18, 16.5	1348.31 (60.89)	5, 13.9	1285.54 (50.57)	<0.0001	0.011
	λ_{ax}	18, 16.5	1614.10 (79.55)	5, 13.9	1563.63 (59.94)	0.002	0.089
	λ_{rad}	18, 16.5	1215.41 (61.60)	5, 13.9	1146.49 (52.53)	<0.0001	0.007
Left CST	FA	1, 0.9	0.29 (0.03)	1, 2.8	0.32 (0.02)	<0.0001	0.123
	MD	1, 0.9	1220.03 (69.75)	1, 2.8	1165.51 (54.98)	<0.0001	0.500
	λ_{ax}	1, 0.9	1599.23 (73.95)	1, 2.8	1576.09 (71.26)	0.107	0.718
	λ_{rad}	1, 0.9	1030.43 (77.34)	1, 2.8	960.22 (53.80)	<0.0001	0.238
Right CST	FA	0,0	0.27 (0.03)	1, 2.8	0.30 (0.02)	<0.0001	0.181
	MD	0,0	1167.98 (70.39)	1, 2.8	1105.89 (43.49)	<0.0001	0.108
	λ_{ax}	0,0	1507.85 (70.22)	1, 2.8	1472.46 (54.27)	0.007	0.523

	λ_{rad}	0,0	998.05 (78.47)	1, 2.8	922.60 (43.45)	<0.0001	0.057
Left ILF	FA	4, 3.7	0.20 (0.03)	4, 11.1	0.23 (0.03)	<0.0001	0.009
	MD	4, 3.7	1646.64 (230.74)	4, 11.1	1416.41 (78.67)	<0.0001	0.001
	λ_{ax}	4, 3.7	1991.84 (243.54)	4, 11.1	1765.78 (95.48)	<0.0001	0.001
	λ_{rad}	4, 3.7	1474.05 (229.01)	4, 11.1	1241.72 (79.53)	<0.0001	0.001
Right ILF	FA	2,1.8	0.22 (0.03)	1, 2.8	0.24 (0.03)	<0.0001	0.035
	MD	2,1.8	1691.59 (247.60)	1, 2.8	1530.02 (180.21)	0.001	0.015
	λ_{ax}	2,1.8	2080.03 (272.24)	1, 2.8	1929.68 (213.71)	0.003	0.037
	λ_{rad}	2,1.8	1497.36 (239.26)	1, 2.8	1330.19 (167.89)	<0.0001	0.009

^aPreterm vs. term GLM univariate analysis of variance, unadjusted for age at scan ^bFDR applied, 0.05 significance value. Results that remained significant after FDR correction are in bold. ^cPreterm vs. term GLM univariate analysis of variance, adjusted for age at scan

Table 5.4 Median (IQR) values of R for each tract ($\times 10^{-3}$ mm²/s).

Tract	Preterm		Term		abP-value	bcP-value
	Number (n), percentage (%) of missing tracts		Number (n), percentage (%) of missing tracts			
Genu of corpus callosum	7, 6.4	-3.26 (-6.64, -1.40)	0,0	-2.14 (-4.11, -0.93)	0.032	0.818
Splenium of corpus callosum	13, 11.9	-6.14 (-10.40, -3.10)	0,0	-4.11 (-10.43, -2.39)	0.193	0.523
Left cingulum	11, 10.1	-1.50 (-5.13, -0.27)	5, 13.9	-0.61 (-2.14, 0.66)	0.006	0.945
Right cingulum	18, 16.5	-1.46 (-4.88, -0.17)	5, 13.9	-0.33 (-2.31, 0.57)	0.018	0.826
Left CST	1, 0.9	-2.49 (-4.29, -1.06)	1, 2.8	-0.85 (-2.25, -0.22)	<0.0001	0.005
Right CST	0,0	-2.03 (-3.66, -1.10)	1, 2.8	-0.97 (-2.47, -0.18)	0.005	0.034
Left ILF	4, 3.7	-0.30 (-2.57, 0.65)	4, 11.1	0.59 (-1.06, 1.26)	0.005	0.621
Right ILF	2,1.8	-2.76 (-5.48, -0.99)	1, 2.8	-1.59 (-3.23, -0.05)	0.024	0.804

^aBetween group tested using Mann-Whitney U for unadjusted for age at testing ^bFDR applied (0.05 significance value). Bold indicates the p-value remains significant after FDR ^cCorrelation between R for each tract and PMA at scan using Spearman's Rho.

5.5 Discussion

As hypothesised, these results uniformly demonstrated higher MD and lower FA (unadjusted values) in the preterm group in all eight tracts-of-interest even after FDR correction. The age at scan is significantly different between the two groups. For this reason, and the fact maturational changes take place around term equivalent age, the results were adjusted for age at scan (Tusor et al., 2014, Hüppi et al., 1998) and FDR correction applied to reduce the likelihood of type one error with multiple comparisons. Compared to the unadjusted p-values, significance persists in the genu (FA, MD), splenium (FA, MD), right cingulum (MD) and bilateral inferior longitudinal fasciculi (FA and MD) after correction for age at scan and multiple comparisons. Compared to adjusted p-values generated in a smaller cohort reported by Anblagan et al. (Anblagan et al., 2015), all previously significant results persist with one exception: the previously significant MD in the right CST is no longer significant in the larger cohort. In addition, significance can now be found in FA of the genu and MD of the right cingulum. The consistency of the findings across both cohorts highlights the reproducibility of PNT within the neonatal brain and indeed highlights the advantage of a larger sample size in detecting subtle significance differences between tracts. Further to work by Anblagan et al. (Anblagan et al., 2015), this study also showed significant differences between groups for higher λ_{ax} and λ_{rad} values in the genu, splenium, bilateral inferior longitudinal fasciculi and in the λ_{rad} in the right cingulum after adjusting for age at scan and multiple comparisons. Similar to Anblagan et al., correlations were only found between PMA at scan and R in the CST, and only in the left CST after correction for multiple comparisons. The reduction in the number of significantly different tracts after adjusting for age of scan in Tables 5.3 and 5.4 shows the importance of timing of scan around term equivalent age which impacts on the interpretation of the tract averaged values.

A reduction in FA at term equivalent age in cerebral white matter in this preterm cohort is consistent with previous work (Anjari et al., 2007, Thompson et al., 2011, Hüppi et al., 1998). A concurrent rise in MD accompanied the low FA value in the preterm group across several tracts. This pattern has been observed elsewhere (Hüppi et al., 1998), however the exact tract-specific differences remain inconsistent (Anblagan et

al., 2015). Furthermore, many dMRI studies of the preterm brain have previously focused on FA values within the corpus callosum, however the current study has broadened the examination of microstructural changes in cerebral white matter by examining eight tracts-of-interest using PNT (Li et al., 2015).

The observed pattern of distributions of tract-averaged water diffusion parameters can be explained by changes within the white matter maturational process. In early life, an increase in FA is typically observed with increasing age and the degree of myelination (Hüppi et al., 1998). Therefore, the degree of myelination and timing of neural pathway formation will likely impact on the vulnerability of each tract to damage in the case of preterm birth. For example posterior aspects of the corpus callosum are some of the last to form but first to myelinate around term equivalent age (Thompson et al., 2011). This may explain the lack of difference in FA between groups in the bilateral corticospinal tracts or cingula. In the presence of white matter damage, areas with a high degree of diffusion anisotropy and organisation such as in the splenium of the corpus callosum often see an increase in λ_{rad} , but not λ_{ax} (Henry et al., 2003, Counsell et al., 2006) with a concurrent rise of both values in less anisotropic areas. This was not observed in the current study, where the consistently higher λ_{ax} values in the preterm group likely reflects axonal damage (Budde et al., 2009). An increase in λ_{rad} has previously been shown to correspond to a reduction in FA values (Anjari et al., 2007, Vangberg et al., 2006) in both infants and young adults and be strongly associated with the degree of myelination (Song et al., 2005). This, however, does not fully explain the relative differences of FA within the preterm group. The reduction in FA in the preterm group in the callosal fibres could not be explained by a lack of myelination in the early neonatal period as myelination has not begun at this stage (Baumann and Pham-Dinh, 2001). This supports the possibility of the vulnerability of the pre-oligodendrocyte as a candidate for insult (Li et al., 2015). Pre-myelinating factors, however, also influence diffusion anisotropy (Wimberger et al., 1995) which makes the interpretation challenging (Pandit et al., 2013a). Finally, the term infants in the current study were older than the preterm infants at the time of scan acquisition. A higher degree of myelination at term may partially explain the differences observed in FA, MD, λ_{ax} and λ_{rad} values between the groups.

Preterm infants demonstrated a larger deviation from the term reference tracts, as indicated by a more negative R value, which was also significant in all tracts except the splenium. The value of R represents each of the tracts' shape and length and how this deviates from the reference tracts (Anblagan et al., 2015). This study has therefore shown that the preterm infants have a significantly different tract shape when compared to their term peers. This is not surprising given the diffuse white matter damage and different developmental trajectories observed on structural imaging, such as that shown in Chapter One. Previous studies have also supported volumetric changes in the grey and white matter in the neonatal period within the preterm infant (Padilla et al., 2015, Beauchamp et al., 2008). Further work could explore the direct relationship between R and underlying white matter changes. The tract shape also appears to be relatively unaffected by the timing of scan which may increase its clinical use (Anblagan et al., 2015) .

Within the structural data, this study found 52% of preterm infants had some degree of white matter damage (mild 45.9%; moderate 5.2%; severe 1%) and three percent of infants had abnormal grey matter scores. The overall rates of white matter damage within the preterm cohort in the current study are less than those reported by Woodward et al. (52 vs. 72% respectively), however the proportions of infants with each grade of severity of white matter injury is more comparable (mild 51%, moderate 17% and severe 4%) (Woodward et al., 2006). Although the proportion of preterm infants with white matter injury in the current study is lower than that found in the Woodward cohort, it is consistent with broader figures in the literature (Moore and Boardman, 2014) and therefore indicative of a representative sample. However, the rates of grey matter damage of three percent in the current cohort are significantly less than those found by Leuchter et al., who reported a difference of 26%. It may be the proportion of infants with concurrent grey matter damage is not representative as recent work suggests grey matter damage generally occurs at a higher prevalence (Woodward et al., 2006, Boardman et al., 2006). Interestingly, some degree of white matter damage was not restricted to the preterm group. Allowing for the small percentage (nearly three percent) of infants with white matter damage in the comparatively small term group, it could be hypothesised that some degree of white matter damage in otherwise healthy term infants is a normal variation (Thompson et

al., 2011). It also blurs the distinction between preterm white matter injury and the normal spectrum. Some degree of white matter injury has also been reported elsewhere in a small cohort of 22 full term infants in a control sample (Thompson et al., 2011). Replication in a much larger sample with a longitudinal component would be required to assess the true frequency of this finding and if there would be any long-term consequence. Furthermore, direct correlation with the dMRI metrics may aid the understanding of how the microstructural changes relate to diffuse patterns of preterm brain injury.

The application of dMRI within the neonatal population also experiences challenges, especially in the consideration of study design. For example, the scans within neonatal populations are highly sensitive to motion artefact due to their higher resting heart and respiratory rate and smaller head size (Mathur et al., 2008, Kozák et al., 2013). The tendency for infants to lean to one side in the scanner may be a potential reason for group difference in missing tracts, although the overall subject exclusion rates were relatively low. Furthermore, different tracts-of-interest are more sensitive to, or more likely to have missing tracts due to the relative small size and associated technical difficulty in measuring them within the neonatal brain e.g. the cingula. An adult head coil was used for scanning; however, debates exist as to whether a specialised neonatal head coil is preferable. A smaller head coil produces a higher-signal-to-noise ratio, but there are several other factors which would impact on this (Keil et al., 2011, Pannek et al., 2012, Pieterman et al., 2015) such as magnetic field strength (Pannek et al., 2012). Not surprisingly, datasets are potentially subject to a high rate of data loss and the choice of processing methodology will heavily impact on the results obtained (Plaisier et al., 2014b, Pieterman et al., 2015) in both the pre- and post-processing stages (such as tractography). PNT as a method is able quantify neural tracts within the relatively small neonatal brain, however it is not always able to identify the high number of neural tracts seen in the adult brain. For example Clayden et al. were able to identify the uncinate and arcuate fasciculi in their training sets within the adult brain (Clayden et al., 2007), but this was not possible within the neonatal term training sets used to create the reference tracts here.

The absolute relationship between early identifiable microstructural changes in the preterm brain and later function remains under debate. The differences observed within multiple tracts within the preterm group supports previous results highlighting the importance of global damage in the relationship with later function (Anderson et al., 2015). As discussed in Chapter One, evidence from adult literature has identified a high degree of shared variance amongst white matter tracts in healthy adults which is predictive of information processing speed. The application of the same PCA methods used in the adult literature (Penke et al., 2010) to the neonatal population may help in the explanation of the relationship between early white matter damage and infant cognition.

5.6 Conclusions

PNT can be used to identify group level microstructural differences between preterm and term infants in eight major tracts-of-interest. Preterm infants have a consistently lower FA and higher MD in the bilateral inferior longitudinal fasciculi and in the genu and splenium of the corpus callosum after correction at age of scan and multiple comparisons potentially indicating reduced structural integrity in these fibre pathways in the former group (also see Chapter One). In addition, preterm infants have a higher MD in the right cingulum. Tract specific differences, however, remain inconclusive between studies and interpretation of underlying biological relationships with diffusion parameters remain challenging. Further work is required to fully appreciate the clinical implications of microstructural differences observed in preterm infants. In the following chapter, dMRI metrics generated using PNT will be used to investigate links between white matter structure and cognitive function in the neonate brain.

CHAPTER 6 : ASSOCIATION BETWEEN WHITE MATTER MICROSTRUCTURE AND EYE-TRACKING MEASURES

In Chapter Five, group level differences in dMRI metrics between preterm and term infants were explored. The primary focus of this chapter is to test the following hypotheses: (i) variance in tract average FA, MD, λ_{rad} and λ_{ax} is shared across major tracts and (ii) neonatal MRI g_{WM} is associated with cognitive function in infancy. Hypothesis (ii) will examine the relationship between g_{WM} and later cognitive outcomes at both seven months' CGA and at two years' CGA. Part of Section 6.4.2 was submitted as part of the first year review process for this degree.

6.1 General Introduction

In Chapter One, possible applications of PNT to investigate underlying white matter structure and assess the relationship with later cognition were highlighted. Comparisons were made with the adult literature, where a general factor of white matter microstructure had been identified and could be related to cognitive measures in healthy older adults. The question of shared variance between neural tracts is particularly important to analyse. Only a few studies investigating the relationship between brain structure and function approach this question (Penke et al., 2010). Previous work has often made inferences regarding causal relationships between brain structure and function based on mere correlations, however this is insufficient (Salthouse, 2011). It is undoubtedly imperative to determine what factors fully underpin this relationship (Lövdén et al., 2013). Furthermore, it must be determined how many between-subject white matter differences are generalised or localised to a specific tract-of-interest (Lövdén et al., 2013).

Several questions in the neonatal literature remain unanswered when compared to this finding in the adult population. For example, when this common factor of white matter microstructure is first detectable or when it occurs within the developmental trajectory and how this relates to cognitive function in early life. This information would help address gaps in the literature to fully appreciate how dMRI metrics change over time within the preterm brain and how these relate to the diverse range of cognitive deficits.

Given the success in detecting differences in social cognition at seven to eight months' CGA using eye-tracking (see Chapter Seven), it is hypothesised that variance in tract averaged water diffusion parameters is shared across major tracts in the newborn period and contributes to the neural substrate of infant social cognition. The first part of this chapter is a formatted version of a paper accepted for publication in Brain Structure and Function which tests this hypothesis. The paper has been reformatted for the purpose of this thesis. Emma Telford was involved in the recruitment of infants and in the undertaking of MRI scanning and eye-tracking assessments, generation of the eye-tracking statistics and in the review of the draft of the paper before submission. The statistics within the paper below were undertaken by Dr Simon Cox, in addition to the relationship with variables in Table 6.4. The second part of this chapter assesses the relationship between g_{WM} and other cognitive outcomes at seven months' and two years' CGA. Emma Telford undertook the correlations with the BSID-III outcomes at two years' CGA and g_{WM} .

6.2 Abstract for 'A latent measure explains substantial variance in white matter microstructure across the newborn human brain.'

A latent measure of white matter microstructure (g_{WM}) provides a neural basis for information processing speed and intelligence in adults, but the temporal emergence of g_{WM} during human development is unknown. We provide evidence that substantial variance in white matter microstructure is shared across a range of major tracts in the newborn brain. Based on diffusion MRI scans from 145 neonates (gestational age [GA] at birth range 23⁺² to 41⁺⁵ weeks), the microstructural properties of eight major white matter tracts were calculated using probabilistic neighborhood tractography. Principal component analyses (PCAs) were carried out on the correlations between the eight tracts, separately for four tract-averaged water diffusion parameters: fractional anisotropy, and mean, radial and axial diffusivities. For all four parameters, PCAs revealed a single latent variable that explained around half of the variance across all eight tracts, and all tracts showed positive loadings. We considered the impact of early environment on general microstructural properties, by comparing term-born infants with preterm infants at term equivalent age. We found significant associations between GA at birth and the latent measure for each water diffusion measure; this effect was

most apparent in projection and commissural fibers. These data show that a latent measure of white matter microstructure is present in very early life, well before myelination is widespread. Early exposure to extra-uterine life is associated with altered general properties of white matter microstructure, which could explain the high prevalence of cognitive impairment experienced by children born preterm.

Keywords: Neonate, brain, magnetic resonance image, tractography, preterm.

6.3 Introduction

White matter tracts connecting cortical networks are fundamental substrates of higher cognitive function in humans. ‘Disconnection’ of networks, which can be inferred from the microstructural properties of tracts, characterizes a number of diseases and contributes to functional impairment through reduced information transfer efficiency (Bartzokis et al., 2004, Penke et al., 2010, Ritchie et al., 2015b, Ball et al., 2015, Uddin et al., 2013, Liston et al., 2011). Tract connectivity has been widely investigated *in vivo* using diffusion magnetic resonance imaging (dMRI) which is a non-invasive method that provides voxel-wise measures of water molecule diffusion. Since the molecular motion of water in the brain is influenced by biological factors including macromolecules, axonal diameter, membrane thickness and myelination, dMRI enables inference about underlying tract microstructure (Le Bihan et al., 1986, Basser and Pierpaoli, 1996).

In adulthood, microstructural properties of white matter are shared among major tracts (for example, an adult individual with high fractional anisotropy (FA) in one tract is likely to have high FA in all other tracts in the brain). This property allows for the derivation of a general factor, *gFA*, of white matter microstructure (Penke et al., 2010, Cox et al., 2016). The general factor explains almost half of variance in microstructure across major tracts, and latent variable statistical analyses show that *gFA* is predictive of information processing speed and intelligence (Penke et al., 2010, Ritchie et al., 2015b, Penke et al., 2012). The temporal emergence of *gFA* and other general factors of water diffusion biomarkers during human development is unknown, and therefore its role in the ontogeny of human cognition has not been investigated.

Probabilistic neighbourhood tractography (PNT) is an automatic segmentation technique based on single seed point tractography, that can identify the same fasciculus-of-interest across a group of subjects by modelling how individual tracts compare with a predefined reference tract in terms of length and shape (Clayden et al., 2011). The method has been optimized for use with neonatal dMRI data, which enables tract-averaged measurements of mean $\langle D \rangle$, axial (λ_{ax}) and radial (λ_{rad}) diffusivities, and FA, for the major white matter fasciculi during early brain development (corticospinal tracts, genu and splenium of corpus callosum, cingulum cingulate gyri, inferior longitudinal fasciculi) (Anblagan et al., 2015).

Early exposure to extra-uterine life by preterm birth is a leading cause of cognitive impairment in childhood and is strongly associated with a ‘disconnectivity’ phenotype that combines diffuse white matter injury and volume reduction of connected structures (Inder et al., 1999, Boardman et al., 2006, Volpe, 2009a, Ball et al., 2012). Altered development of thalamocortical networks in association with preterm birth is reported (Boardman et al., 2006, Ball et al., 2013, Ball et al., 2015, Toulmin et al., 2015,), but structural and functional connectivity analyses in the newborn period and studies of adults born preterm suggests that network disruption is more widely distributed (Pandit et al., 2013b, van den Heuvel et al., 2015, Smyser et al., 2016, Froudust-Walsh et al., 2015, Cole et al., 2015). This raises the hypothesis that disconnectivity in the context of preterm birth is a global rather than localized process.

Preterm birth is associated with an atypical social cognitive profile (Ritchie et al., 2015a). Early social cognition is also extremely tractable to measurement in infancy via measurement of gaze behaviour to social and non-social visual content. For example, visual attention is given to faces very soon after birth, with specific preference to the eye region, while at around 6 - 9 months a preference for looking at faces in multiple object arrays or animated scenes develops (Johnson et al., 1991, Farroni et al., 2002, Gliga et al., 2009). In addition, eye-movement recordings in response to social stimuli have been used to identify early behavioral trajectories associated with autism (Jones and Klin, 2013), to link emergent social cognition with white matter microstructure in specific tracts (Elison et al., 2013a), and to distinguish

between the social cognitive profiles of infants born preterm and at term (Telford et al., 2016).

We tested the following hypotheses: first, a latent measure of general white matter microstructure (g_{WM}) is present in the newborn; second, preterm birth is associated with global disconnectivity; and third, that g_{WM} measured in the newborn period is associated with emergent social cognitive function in infancy.

6.4 Materials and Methods

6.4.1 Participants

145 neonates (gestational age at birth range 23⁺² to 41⁺⁵ weeks) were recruited from the Royal Infirmary of Edinburgh between February 2013 and August 2015 to a longitudinal study of the effect of preterm birth on brain structure and long term outcome. Infants had diffusion MRI (dMRI) at term equivalent age (mean GA 40⁺⁵ weeks, range 37⁺⁵ - 47⁺¹) and 83 took part in eye-tracking assessment 6 - 12 months later (median age 7.9 months, IQR 6.8 - 8.8).

To study the effect of preterm birth on white matter microstructure the group was divided into those with GA at birth < 35 weeks (n = 109), and healthy controls recruited from postnatal wards with GA 37 - 42 weeks (n = 36). Exclusion criteria included major congenital malformations, chromosomal abnormalities, congenital infection, overt parenchymal lesions (cystic periventricular leukomalacia, hemorrhagic parenchymal infarction) or post-hemorrhagic ventricular dilatation. Demographic information is shown in Table 6.1. Ethical approval was obtained from the National Research Ethics Service (South East Scotland Research Ethics Committee 02) and informed consent was obtained from the person with parental responsibility for all individual participants included in the study.

Of the preterm group: 7% had intra-uterine growth restriction (IUGR) defined as a birth weight under the third centile for gender and gestation and 31% had bronchopulmonary dysplasia defined as need for supplementary oxygen at 36 weeks' PMA. PMA; postmenstrual age.

Table 6.1 Clinical and demographic features of the whole group, and the preterm and term controls.

	Whole sample (n = 145)	Preterm (n = 109)	Term (n = 36)
Mean PMA at birth / weeks (range)	31 ⁺⁵ (23 ⁺² - 41 ⁺⁵)	29 ⁺⁰ (23 ⁺² - 34 ⁺⁶)	39 ⁺⁶ (37 ⁺² - 41 ⁺⁵)
Mean PMA at scan / weeks (range)	40 ⁺⁵ (37 ⁺⁵ - 47 ⁺¹)	40 ⁺⁰ (37 ⁺⁵ - 44 ⁺⁰)	42 ⁺¹ (39 ⁺⁰ - 47 ⁺¹)
Mean birth weight / kg (sd)	1.72 (1.05)	1.14 (0.24)	3.46 (0.45)
Median age at eye-tracking assessment / months (IQR)	7.9 (6.8 - 8.8)	7.7 (6.7 - 8.4)	8.4 (7.7 - 9.1)
Gender (Female:Male)	69:76	54:55	15:21

6.4.2 Image acquisition

A Siemens MAGNETOM Verio 3 T MRI clinical scanner (Siemens Healthcare Erlangen, Germany) and 12-channel phased-array head coil were used to acquire: T1-weighted MPRAGE (TR = 1650 ms, TE = 2.43 ms, inversion time = 160 ms, flip angle = 9°, voxel size = 1 × 1 × 1 mm³, and acquisition time = 7 min 49 sec); T2-weighted SPACE (TR = 3800 ms, TE = 194 ms, flip angle = 120°, voxel size = 0.9 × 0.9 × 0.9 mm³, acquisition time = 4 min 32 sec); dMRI using a protocol consisting of 11 T2- and 64 diffusion-weighted (b = 750 s/mm²) single-shot spin-echo echo planar imaging (EPI) volumes acquired with 2 mm isotropic voxels (TE = 106 ms and TR = 7300 ms). Infants were scanned without sedation in natural sleep using the feed-and-wrap technique. Physiological stability was monitored using procedures described by Merchant et al. (2009) (Merchant et al., 2009). Ear protection was provided for each infant (MiniMuffs, Natus Medical Inc., San Carlos, CA).

6.4.3 Image analysis

For all four imaging biomarkers (FA, MD, λ_{ax} and λ_{rad}), tract-averaged values were derived from 8 major fasciculi segmented using probabilistic neighbourhood tractography (PNT) optimized for neonatal dMRI data (Bastin et al., 2010, Clayden et al., 2007, Anblagan et al., 2015). In summary after conversion from DICOM to NIfTI-

1 format, the dMRI data were preprocessed using FSL tools (<http://www.fmrib.ox.ac.uk/fsl>) to extract the brain and eliminate bulk patient motion and eddy current-induced artifacts by registering the diffusion-weighted to the first T2-weighted EPI volume of each subject. Using DTIFIT, MD and FA volumes were generated for each subject. From the underlying white matter connectivity data, eight major white matter fasciculi thought to be involved in cognitive functioning were segmented: genu and splenium of corpus callosum, left and right cingulum cingulate gyrus (CCG), left and right corticospinal tracts (CST), and left and right inferior longitudinal fasciculi (ILF). As described in detail in the study by Anblagan et al. (Anblagan et al., 2015), this involved using reference tracts created from a group of 20 term controls.

6.4.4 Cognitive testing

Infant social cognitive ability was assessed by tracking eye gaze in response to visual social stimuli using methods described by Telford et al. (Telford et al., 2016). Infants were positioned on the care-giver's lap 50 - 60cm from a display monitor used to present social stimuli of three levels of complexity: a static face, a face in an array of non-social objects, and a pair of naturalistic scenes with and without social content. Proportional looking time to social content relative to the overall stimulus was recorded using a Tobii© x60 eye-tracker, and Tobii Studio© (version 3.1.0) software was used for analysis. Because social preference scores that represent the distribution of fixation to social versus general image content are highly correlated across tasks, we combined social preference score from each task into a composite score per participant (Gillespie-Smith et al., 2016).

6.4.5 Statistical analysis

One principal component analysis (PCA) was conducted for each of the four water diffusion parameters (MD, FA, λ_{ax} and λ_{rad}) across the eight tracts, to quantify the proportion of shared variance between them (i.e. to determine whether a clear single-component solution was present, in line with previous reports in adults). That is, four separate data matrices (one for each DTI parameter) were separately analysed, each with dimensions $n \times m$ where $n = 145$ (number of subjects) and $m = 8$ (tract-averaged

values for eight tracts). Thus, each PCA included data from all participants, and all available tracts were included; where tract data were missing (median 3.5% of tracts, IQR 3.5 - 13.25), the mean FA, MD, λ_{ax} and λ_{rad} of the group was used to impute values for the missing tract. Next, we examined the effect of preterm birth on differences in these four general water diffusion measures. Initially, we used a dichotomous group design, comparing differences between preterm infants' and controls' white matter microstructure (corrected for age at MRI scan) using Welch's unpaired t-tests. We then applied linear regression across the entire group to quantify the dose effect of birth term on each measure of microstructure, including PMA at MRI scan and sex as covariates in the model. In order to compare tract loadings (correlations between the manifest variable and extracted component score) for each tract between preterm infants and controls, we used Fisher's test of correlation magnitude differences among independent groups (`cocor.indep.groups` in the `cocor` package in R) (Diedenhofen and Musch, 2015). Finally, we examined associations between white matter microstructure and social cognitive performance using linear regression. The MRI and cognitive variables were corrected for differences in age at their respective data collection points prior to insertion into the model, where gender and group status (preterm / control) were covariates. Statistical analyses were carried out using SPSS v 21.0 (Chicago, Il), and R (<https://www.r-project.org>) version 3.2.2 (Fire Safety).

6.5 Results

6.5.1 General component of white matter microstructure

We ran separate PCAs for each measure of white matter microstructure on all eight tracts (Fig 6.1). In each case there was a clear one component solution, denoted by its large eigenvalue, and the much lower and linearly decreasing eigenvalues of the remaining components. We extracted this first component, without rotation, which explained 49% (FA), 54% (MD), 59% (λ_{rad}), and 36% (λ_{ax}) of the variance (all loadings range between 0.409 and 0.870; Fig 6.2, Table 6.2). Thus, there is a clear tendency for white matter microstructural properties found in one part of the newborn brain to be common across all white matter tracts, and the extracted water diffusion

parameter values for each participant therefore reflect the level of white matter microstructure common across all tracts in that brain.

6.5.2 The effect of preterm birth on the general measure of white matter microstructure

There were significant differences in g for each of the four white matter water diffusion parameters between preterm and control groups: gFA ($t = -4.1367$, $p = 8.139e-05$); gMD ($t = 5.2773$, $p = 1.062e-06$); $g\lambda_{rad}$ ($t = 5.4887$, $p = 4.322e-07$); $g\lambda_{ax}$ ($t = 4.2527$, $p = 5.529e-05$), Fig 6.3.

After adjustment for age at scan and sex we found significant associations between gestational age (GA) at birth and general measures of: FA (gFA), β 0.305 ($p < 0.001$); MD (gMD), β -0.351 ($p < 0.001$), λ_{rad} ($g\lambda_{rad}$) β -0.363 ($p < 0.001$); and λ_{ax} ($g\lambda_{ax}$) β , -0.300 ($p < 0.001$) (Fig 6.4). In summary, those infants born preterm exhibited less 'mature' microstructure (less coherent water diffusion and a greater general magnitude of water molecular diffusion) across their white matter tracts than controls. Moreover, we found a dose-dependent effect of GA at birth across all general white matter indices, such that more premature birth was associated with generally less optimal white matter microstructure.

In view of variations in newborn network connectivity (van den Heuvel et al., 2015), we considered whether individual tract loading of FA might differ between preterm and term groups. In exploratory analyses we found that loadings appeared qualitatively higher in callosal and corticospinal tracts for preterm versus control infants, but there was little evidence for group difference in tract loading in association fibers (Fig 6.5). Formal tests of these differences using Fisher's Z broadly confirmed this pattern for genu ($z = 2.0593$, $p = 0.0395$) and left CST ($z = 2.3185$, $p\text{-value} = 0.0204$), though differences were not significant in the splenium ($z = 1.6072$, $p\text{-value} = 0.1080$) and right CST ($z = 1.4674$, $p\text{-value} = 0.1423$). This pattern was also present for λ_{rad} and MD, though statistical tests indicated only trend-level or weaker differences for λ_{rad} (genu: $z = 1.8146$, $p = 0.0696$; splenium: $z = 1.8551$, $p = 0.0636$; left CST: $z = 1.6845$, $p = 0.0921$; and right CST $z = 1.2033$, $p = 0.2289$) with the differences in the same direction for MD being smaller and non-significant.

Figure 6.1 Scree plot from principal component analyses for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (λ_{ax}), and radial diffusivity (λ_{rad}) of the eight white matter tracts

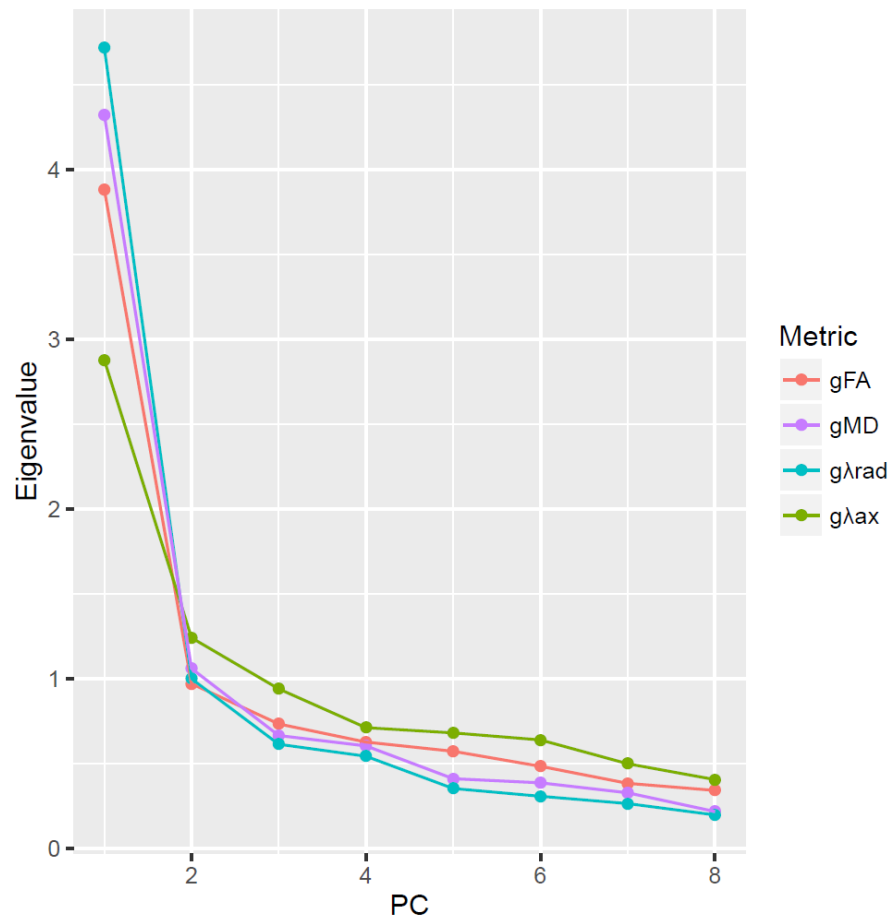


Table 6.2 Tract loadings, explained variance, and mean absolute magnitude (Pearson's r) of correlations across all tracts for the first unrotated principal component for the four water diffusion measures.

Tract	FA	MD	λ_{rad}	λ_{ax}
Genu	0.747	0.841	0.870	0.608
Splenium	0.601	0.737	0.750	0.672
L CCG	0.751	0.738	0.807	0.564
R CCG	0.619	0.783	0.808	0.639
L CST	0.803	0.739	0.812	0.409
R CST	0.722	0.768	0.784	0.652
L ILF	0.636	0.726	0.741	0.669
R ILF	0.667	0.500	0.516	0.538
Explained variance	0.485	0.540	0.589	0.360
Mean between-tract r	0.407	0.466	0.521	0.262

CCG, cingulum cingulate gyri; CST, corticospinal tract; ILF, inferior longitudinal fasciculus.

Figure 6.2 Brain images show tract segmentations obtained from one representative participant

Seed points are marked with a green cross. The statistics are factor loadings of the average FA values of each tract on the latent measure of white matter microstructure.

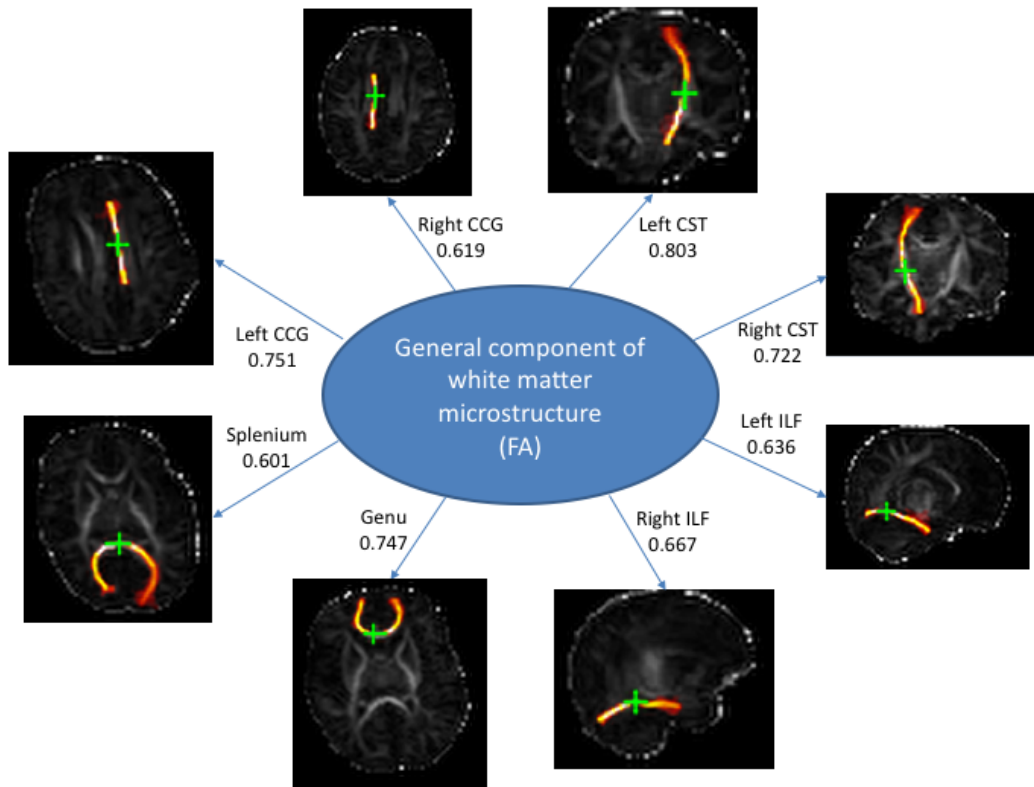


Figure 6.3 Significant group differences between preterm and controls across all four general water diffusion indices

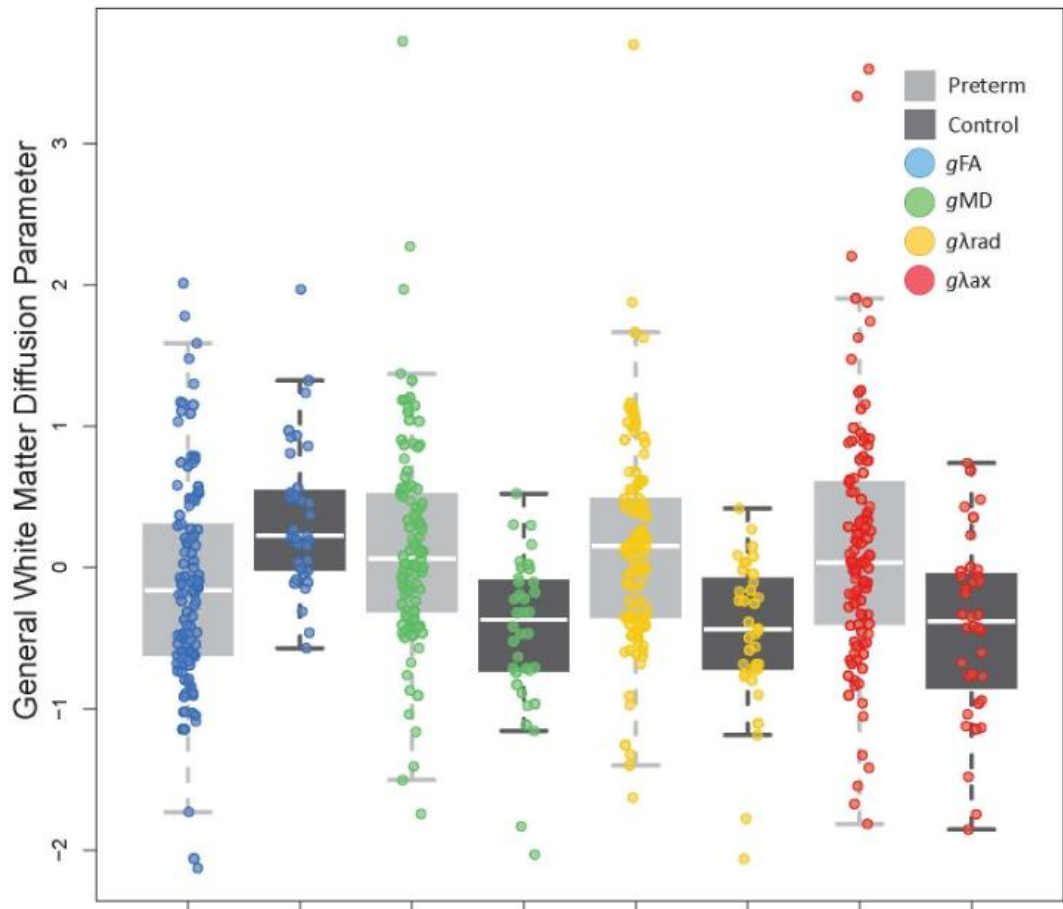


Figure 6.4 Associations between PMA birth and general measures of fractional anisotropy (gFA) mean diffusivity (gMD), radial diffusivity (g λ rad) and axial diffusivity (g λ ax).

Regression lines and 95% CIs (shaded) are shown for linear regression models between PMA at birth and white matter microstructure, corrected for age at scan and sex

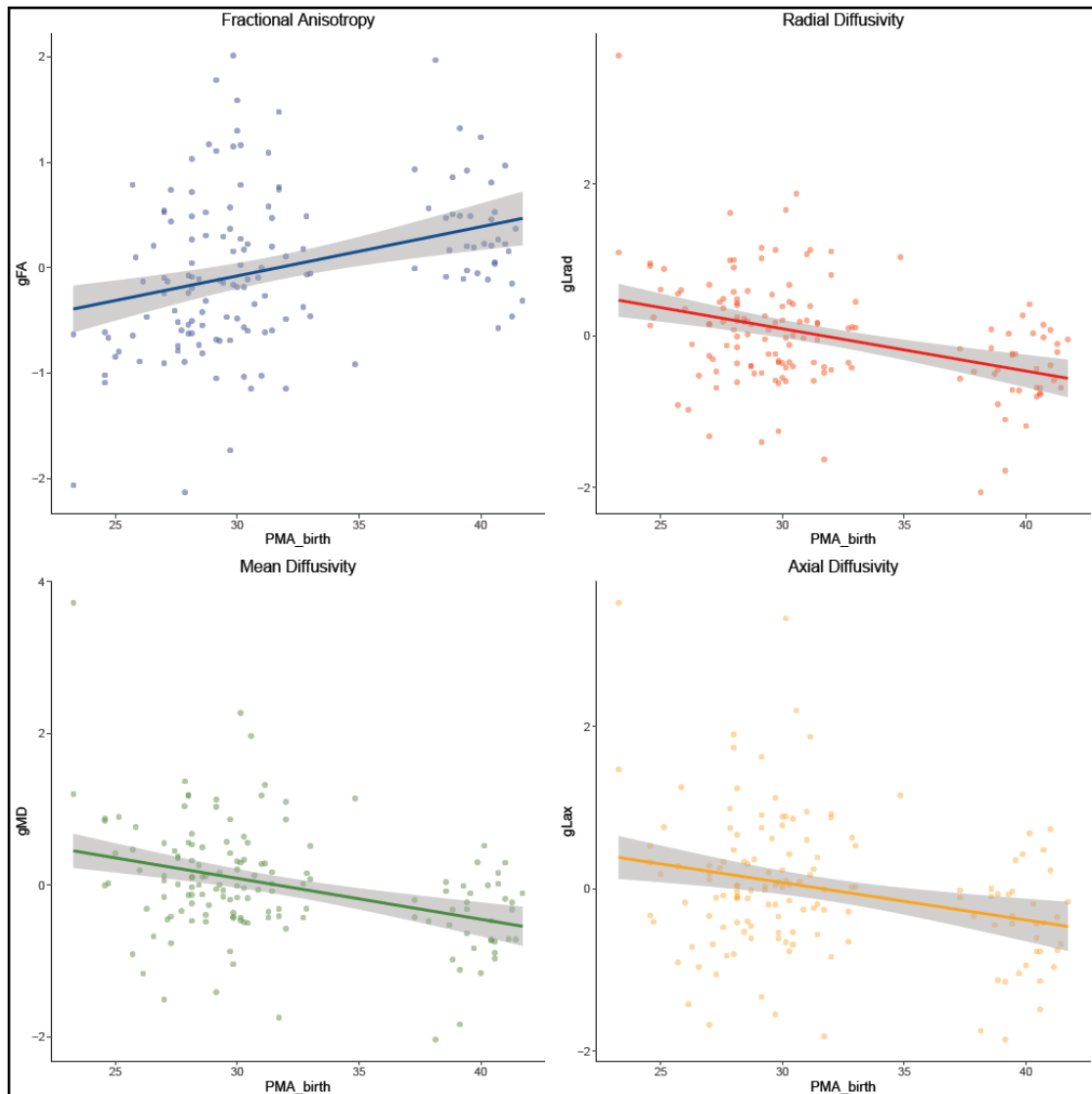
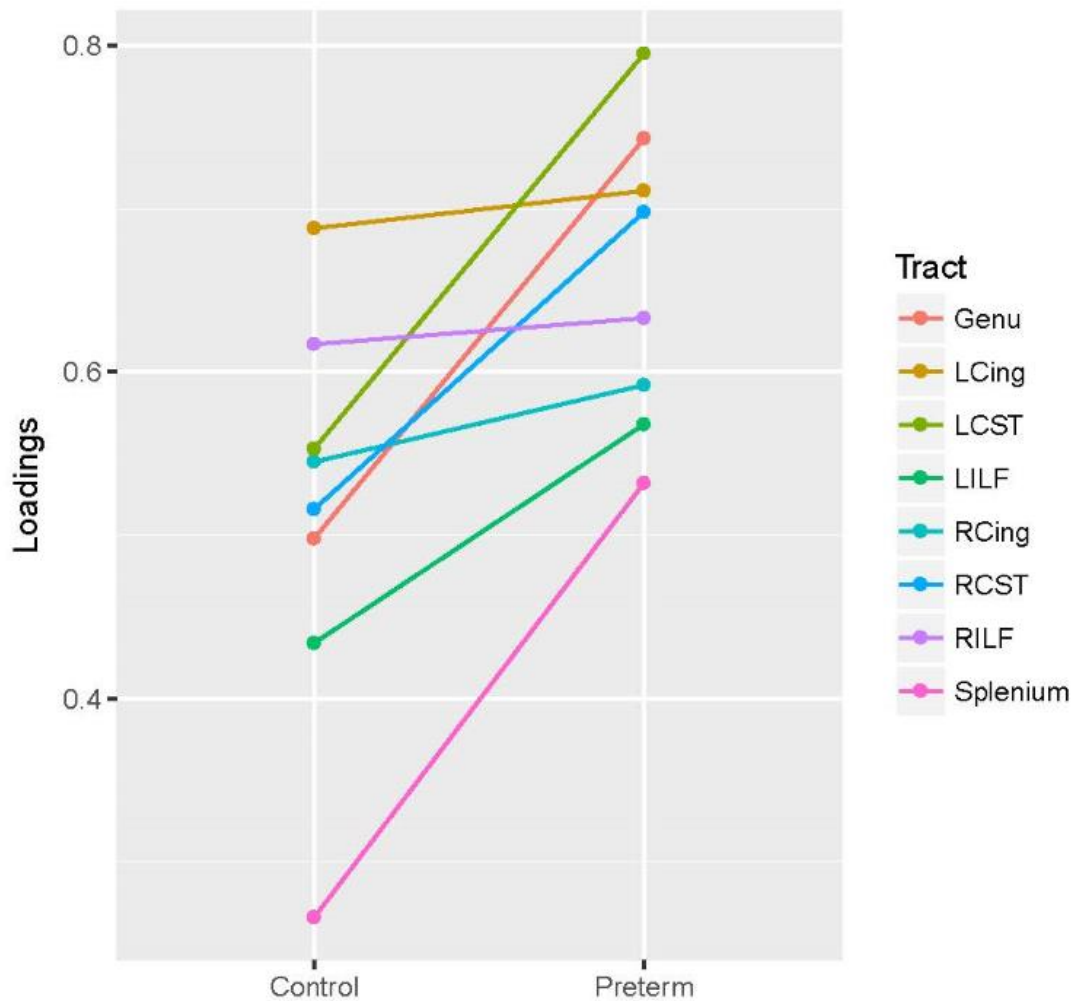


Figure 6.5 Differences in tract loadings for gFA between control and preterm, in comparison to overall loadings



6.5.3 Social cognitive ability and measures of general white matter microstructure

There were no significant associations between any general water diffusion parameter and a sensitive measure of emergent social cognition derived from an eye-tracking task battery at 7 months (all $\beta_{\text{absolute}} \leq 0.123$, all p-values ≥ 0.265), and nor were there any significant effects of group within the model (all $\beta_{\text{absolute}} \leq 0.099$, all p-values ≥ 0.378 ; Table 6.3). There was no relationship between water diffusion parameters and emergent social cognition in the genu (all p-values ≥ 0.15) or splenium (all p-values ≥ 0.064) of the corpus callosum. Social preference scores for each task (proportional

looking time at social versus general image content) are shown in Supplemental Table 6.4.

Table 6.3 Regression models of water diffusion measures and group membership on social cognitive performance

Standardized β s (p-values); imaging and cognitive variables corrected for respective age at sampling prior to being entered into the models, which included gender as a covariate. *gFA* = general component of fractional anisotropy, *gMD* = general component of mean diffusivity, *g λ rad* = general component of radial diffusivity, *g λ ax* = general component of axial diffusivity.

Diffusion parameter		Group
<i>gFA</i>	0.076 (0.551)	0.099 (0.396)
<i>gMD</i>	-0.123 (0.265)	0.081 (0.478)
<i>gλrad</i>	-0.116 (0.301)	0.080 (0.490)
<i>gλax</i>	-0.116 (0.295)	0.097 (0.378)

Table 6.4 Social preference score for each task.

	Infants born preterm (n = 59)	Infants born at term (n = 24)	Mean difference	p-value
Static face ^a	0.243	0.315	-.072	0.25
Face in array of non-social images ^b	0.437	0.477	-0.040	0.39
Naturalistic scene ^c	0.217	0.256	-0.040	0.45

^a Proportional looking time to the eye region relative to overall looking time at a static face

^bProportional looking time at an image of a face within an array of non-social images ^cProportional looking time at social content within a naturalistic scene relative to overall looking time at the stimulus

6.6 Discussion

In the human newborn brain microstructural properties of major white matter tracts are highly correlated with one another, which allows for extraction of a general

measure for each of four common water diffusion MRI parameters. This result suggests that individual differences in white matter microstructure during development are to a substantial degree common among tracts, and not a phenomenon that primarily affects specific individual tracts. Furthermore, the nature of between tract correlations is altered by the environmental exposure of preterm birth. Since global white matter microstructure contributes to the neural foundation of higher cognitive function in later life (Deary et al., 2010), and the factor loadings show remarkable similarity to those reported in adulthood (Penke et al., 2010), the data suggest that the fundamental white matter architecture required to support cognition is established as a generalized process during gestation, and that this is vulnerable to the environmental stress of preterm birth.

Inter-tract correlations were of similar strength for FA, MD and λ_{ax} but were weaker for λ_{rad} (Table 6.1). In the newborn period, before myelination is widespread, FA in white matter increases in association with maturation of axonal membrane structure, and increases in axonal caliber and oligodendrocyte number. MD in white matter is high around the time of birth but decreases over the first few months of postnatal life as brain water content lowers and localized restriction of water increases due to increased cell density and other factors (Hüppi et al., 1998, Neil et al., 1998, Wimberger et al., 1995, Nomura et al., 1994, Morriss et al., 1999). Our data suggest that these processes affect the major tracts similarly around term equivalent age. The observation that λ_{ax} was highly correlated between tracts could reflect the fact that neuronal migration has largely been completed by 24 weeks' gestation so the axonal skeleton of major tracts is established (Bystron et al., 2008). λ_{rad} was relatively weakly correlated between tracts, which could be explained by variation in myelination, which is known to be tract-specific (Kinney et al., 1988).

Having established that microstructural properties of tracts are substantially shared in the newborn, we next considered whether this relationship is modified by the environmental stress of preterm birth. After controlling for age at scan and sex, we found that the latent general measures of each of the four water diffusion parameters differed between preterm and control groups (Fig 6.3): gFA was lower and gMD higher in preterms compared with healthy infants born at term. These data are consistent with

studies that have used voxel- and tractography-based approaches to study the effect of preterm birth on the developing brain (Pannek et al., 2014, Ball et al., 2010, Anblagan et al., 2015), but methodological factors have left uncertainty about the extent to which microstructural change is a local versus a generalized process. Here, we demonstrate that preterm birth is associated with generalized differences across a functionally relevant representation of network architecture. Within this, however, we also found that group differences were most marked in projection and callosal fibers, which had higher loadings than association fibers in preterm infants compared with controls. Since neonatal water diffusion parameters are biomarkers of later neurodevelopmental function after preterm birth (Counsell et al., 2008, van Kooij et al., 2012, Boardman et al., 2010), the data presented here suggest that general properties of white matter microstructure could underlie the high prevalence of impairment seen in children and adults born preterm.

We found no relationship between general properties of any of the four water diffusion parameters and measures of infant social cognition derived from eye-tracking. The cognitive measure was selected because it discriminates between typically developing children and those with atypical cognitive trajectories, including those born preterm, and has been validated for use in infancy (Young et al., 2009, Ozonoff et al., 2010, Chawarska et al., 2013, Jones and Klin, 2013, Telford et al., 2016, Gillespie-Smith et al., 2016). There are plausible explanations for this. First, general white matter ‘integrity’ is most closely associated with information-processing speed in adulthood but it is less predictive of other aspects of cognition (Ritchie et al., 2015b). Second, although processing speed is considered to be a foundational competence for other cognitive abilities in adulthood this relation may not hold true in infancy (Salthouse, 1996, Ritchie et al., 2015b). Thus, in the infant, social cognition may develop on an independent trajectory relative to general processing abilities or emerging intelligence (Adolphs, 1999). Further study is required to determine whether g_{WM} relates to other aspects of infant cognition such as sustained attention and memory. Longitudinal study will be required to determine whether foundational general measures of neonatal white matter microstructure influence later cognitive functions that are more reliant on information transfer efficiency.

Brain structure, including dMRI measures in white matter, and intelligence are all highly heritable; twin studies suggest that up to 60% of inter-individual variation in dMRI measures are attributable to genetic factors (Thompson et al., 2001, Toga and Thompson, 2005, Geng et al., 2012, Shen et al., 2014). Common genetic variants and epigenetic modifications modify the risk of white matter disease associated with preterm birth (Boardman et al., 2014, Krishnan et al., 2016, Dutt et al., 2011, Sparrow et al., 2016), but to our knowledge these associations have not been tested using a more functionally tractable set of brain biomarkers. We speculate that considering general measures of network architecture alongside tract-specific measures in imaging genetic studies will be useful for understanding the genetic and epigenetic determinants of connectivity in the newborn.

A limitation of this study is that we were unable to investigate the relationship between dMRI parameters of tracts that serve social cognition in adulthood, such as the arcuate fasciculus and fornix, and infant social cognition. Although PNT can segment these tracts from adult data (Clayden et al., 2007), we could not identify them reliably in the training set of neonatal data because of lower image resolution inherent to neonatal dMRI acquisitions.

A second limitation is that we did not examine other factors that may have contributed to white matter injury in the preterm group, such as bronchopulmonary dysplasia or punctate white matter lesions, because a much larger sample would have been required to adjust for these factors (Ball et al., 2010, Bassi et al., 2011). In addition, group sizes were unequal in the secondary analysis of the effect of preterm birth on component loadings; the preterm group was larger and thus could have contributed more strongly to the principal component score, influencing group comparisons. Consequently, although we found a statistically significant group effect for FA, MD and λ_{rad} in the genu and CST, we cannot be certain that group differences are confined to these tracts alone. Though exploratory, these findings raise the possibility that preterm birth also subtly alters the correlational structure of infant white matter tracts with respect to specific classes of tract.

In summary, a latent general measure accounts for almost half of the variance of white matter tract microstructure in the newborn brain. Given that major white matter tracts

constitute the neuroanatomical foundation of cognitive neural systems, our study indicates that a facsimile the network architecture for intelligence is established by birth, and that is it is vulnerable to early exposure to extra-uterine life.

6.7 Acknowledgements

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Conflict of Interest: The authors declare that they have no conflict of interest.

6.8 Relationship between g_{WM} and other cognitive outcomes

Using the eye-tracking summary variables described in Chapter Four, there were no significant associations between any g_{WM} and performance at seven months' CGA in attention (switching or disengagement) or infant processing speed (as measured by the habituation score), nor were there any significant effects of group. Table 6.5 summarises the relationships between the g_{WM} of each tract-averaged dMRI parameter and the additional eye-tracking summary variables (modified table kindly generated by Dr Simon Cox) not described in the published work above. Furthermore, there were

no correlations between any g_{WM} and performance in the composite scores of cognition, language or motor development in the BSID-III, at two years' CGA in the preterm group as shown in Table 6.6.

Table 6.5 Regression models of diffusion measures and group membership on measures of cognitive performance.

Kindly produced by Dr Simon Cox. The imaging and cognitive variables were standardised prior to entering the model and gender was a co-variate. gFA = general component of fractional anisotropy, gMD = general component of mean diffusivity, $g\lambda_{rad}$ = general component of radial diffusivity, $g\lambda_{ax}$ = general component of axial diffusivity. The eye-tracking variables are defined in Chapter Four.

Cognition Test	gFA	Group
Attention Switching	0.040 (0.826)	0.034 (0.780)
Attention disengagement	-0.216 (0.225)	0.045 (0.710)
Habituation	0.179 (0.387)	-0.159 (0.211)
	gMD	
Attention Switching	0.003 (0.982)	0.045 (0.706)
Attention disengagement	-0.113 (0.459)	-0.049 (0.678)
Habituation	0.133 (0.414)	-0.077 (0.529)
	$g\lambda_{rad}$	
Attention Switching	0.010 (0.952)	0.047 (0.698)
Attention disengagement	-0.073 (0.648)	-0.038 (0.751)
Habituation	0.096 (0.577)	-0.085 (0.497)
	$g\lambda_{ax}$	
Attention Switching	0.017 (0.897)	0.048 (0.677)
Attention disengagement	-0.157 (0.243)	-0.053 (0.641)
Habituation	0.160 (0.256)	-0.081 (0.490)

Table 6.6 Association between g and BSID-III outcomes at two years' CGA in the preterm group

Composite BSID-III score	gFA <i>Pearson correlation</i>	p-value (n)
Cognition	-0.091	0.546 (46)
Language	-0.213	0.161 (45)
Motor	0.063	0.682 (45)
	gMD <i>Pearson correlation</i>	
Cognition	0.248	0.097 (46)
Language	0.259	0.086 (45)
Motor	-0.088	0.566 (45)
	gλrad <i>Pearson correlation</i>	
Cognition	0.223	0.136 (46)
Language	0.277	0.066 (45)
Motor	-0.083	0.590 (45)
	gλax <i>Pearson correlation</i>	
Cognition	0.244	0.102 (46)
Language	0.160	0.295 (45)
Motor	-0.052	0.736 (45)

6.9 Additional discussion considering the results in the context of this thesis

The degree of shared variance for each of the tract-averaged dMRI parameters demonstrated above may help explain the group-level differences observed in Chapter Five. For example, in the whole group analyses, λ rad generally had the highest loadings across all tracts and in the preterm subgroup. In Chapter Five the association between an increase in λ rad and a corresponding reduction in FA was discussed (Anjari et al., 2007, Vangberg et al., 2006). It may be hypothesised that the shared variance of λ rad may be of particular importance in driving the increase in λ rad and the reduction in FA within the raw tract-averaged values in the preterm group. It must, however, be interpreted in the context of other factors which may influence these findings such as the crossing of white matter fibres and the timing of scan acquisition in the maturational process.

In contrast to similar studies in adults (Penke et al., 2010, Penke et al., 2012), this thesis has not been able to link a shared general factor of white matter microstructure

to later cognitive function at either seven months assessed using eye-tracking or at two years' CGA assessed using the BSID-III. The lack of a relationship between a general factor of white matter microstructure at term equivalent age and an assessment of cognition at seven months of age may be attributable to many factors.

Firstly, it may simply be that the summary measures of assessing cognition (social preference score, attention switching and disengagement, or habituation score) do not fully capture the components of cognition that this study was hoping to assess. This is unlikely to be the case for the social preference score as this has previously been shown to have validity as a measure of infant social cognition (Gillespie-Smith et al., 2016). Moreover, these tasks have successfully detected group level differences between preterm and term infants at seven months' CGA (Telford et al., 2016). However other measures used here have not been formally validated – for example the habituation score, as a measure of information processing speed. As highlighted in Chapter Eight, one concern with the memory task, from which this score was extracted, was that the infants did not habituate for a long enough period of time to slide A. If that is the case, the "boredom point" the habituation score tries to capture may not be truly reflective of the infant's underlying cognitive ability and is therefore a poor measure of information processing speed.

A second possible explanation is that cognition assessed at seven months' CGA cannot be explained by g_{WM} , because, by this point in the developmental trajectory, cognitive functions are already specialised and relate to specific tracts, or to regions not assessed within the eight tracts-of-interest. Serial eye-tracking assessments in infancy may be one method to capture the developmental trajectories of different cognitive functions to determine the relationship between g_{WM} in the neonatal period and early cognition.

The lack of relationship between a general factor of white matter microstructure and the BSID-III within the preterm infants may also be attributable to confounding factors. Unlike all of the outcome variables above generated using eye-tracking, the BSID-III (or its predecessor the BSID-II) composite scores of motor, language and cognition have been widely used (Johnson and Marlow, 2006, Bode et al., 2014, Connolly et al., 2012, Duerden et al., 2015, Rose et al., 2015, De Bruine et al., 2013). Therefore, it is significantly less likely that the lack of association observed was

secondary to flaws associated with the outcome measure. A lack of power may have been a contributing factor as only a subset of preterm infants had received a BSID-III assessment. Replication within a larger cohort may overcome this problem. As eluded to previously, a lack of relationship in the general factor of white matter microstructure between the preterm group and two year outcomes may be secondary to underlying differences in cognitive development. The time lag between the scanning at term equivalent age and cognitive assessment at two years' CGA allows the possibility of significant developmental change. It may be that there is a higher degree of specialisation of neural tracts by two years of age in which function is contributed to by several white matter tracts. Furthermore, this study has not directly assessed aspects of cognition around the time of birth to explore whether this general factor of white matter microstructure relates to cognitive function within the neonatal period. Only serial scanning during the first two years of life would allow the investigation of how this general factor may change over time and concurrent assessment of cognitive function would relate this potential change to function. This, however, may prove to be technically and ethically challenging.

6.10 Conclusion

A significant amount of microstructural variance is shared between major tracts within the newborn brain in a cohort of preterm and term infants. This suggests that the general factor of white matter microstructure is also present during early stages in human development. Although g_{WM} is associated with intelligence in later life, this chapter has been unable to demonstrate the association between g_{WM} in the neonatal period and cognition in early infancy. A longitudinal study design with serial assessments will be one manner to overcome the challenges highlighted in this chapter in order to fully elucidate the relationship between g_{WM} during the neonatal period and early cognition, and in particular the cognitive deficits experienced in the preterm cohort.

CHAPTER 7 : EYE-TRACKING ASSESSMENT OF SOCIAL COGNITION

7.1 General introduction

In Chapter Two cognitive outcomes associated with preterm birth were discussed, with a focus on social cognition and executive function. The fact that preterm birth is associated with atypical social-development was highlighted, which significantly increases their risk of difficulties in childhood and beyond. Furthermore, social difficulties are part of the triad of difficulties associated with the "broader preterm phenotype" as described by Johnson and colleagues (Johnson and Marlow, 2011) and this triad of symptoms have been suggested to be unique to the preterm cohort. The fact that many of the deficits associated with preterm birth are subclinical and many problems go undetected which may impact upon the child's educational attainment were highlighted. This thesis proposes the role of eye-tracking as an early method of reliably assessing social cognition, especially based on its success in infancy in both TD infants and high-risk groups.

In this chapter, firstly the results of one hundred infants from the three social cognition tasks only, as summarised in Chapter Four, will be presented to test the following hypothesis: Infants born preterm have altered social cognition compared to term born peers assessed by eye-tracking. This chapter includes my first author publication in the *Journal of Child Psychology and Psychiatry* 2016 (Telford et al., 2016) entitled "Preterm birth is associated with atypical social orienting in infancy detected using eye tracking." The publication has been appropriately formatted for this thesis and reproduced with permission from John Wiley and Sons[§]. Within this publication, Emma Telford was involved in the recruitment of infants, undertook the majority of

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eye-tracking assessments, the analyses and first draft of the paper prior to submission. Further analyses using data from this cohort are summarised in Appendix III.

The final section of this chapter will present the results from the social composite score as described in Chapter Four and its relationship with a validated neurodevelopmental assessment at two years CGA. Please note this correlation includes all eligible infants who received an eye-tracking assessment and not just the sub-sample as described above.

7.2 Preterm birth is associated with atypical social orienting in infancy detected using eye-tracking

Background. Preterm birth is closely associated with neurocognitive impairment in childhood including increased risk for social difficulties. Eye-tracking objectively assesses eye-gaze behaviour in response to visual stimuli, which permits inference about underlying cognitive processes. We tested the hypothesis that social orienting in infancy is altered by preterm birth.

Methods. Fifty preterm infants with mean (range) gestational age (GA) at birth of 29^{+1} (23^{+2} - 33^{+0}) weeks and fifty term infants with mean (range) GA at birth 40^{+2} (37^{+0} - 42^{+3}) weeks underwent eye-tracking at median age of seven months. Infants were presented with three categories of social stimuli of increasing complexity. Time to first fixate (TFF) and looking time (LT) on areas of interest (AOIs) were recorded using remote eye-tracking.

Results. Preterm infants consistently fixated for a shorter time on social content than term infants across all three tasks: face-scanning (fixation to eyes minus mouth 0.61s versus 1.47s, $p = 0.013$); face-pop-out task (fixation to face 0.8s versus 1.34s, $p = 0.023$); and social preferential looking (1.16s versus 1.5s $p = 0.02$). Time given to AOIs containing social content as a proportion of LT at the whole stimulus was lower in preterm infants across all three tasks. These results were not explained by differences in overall looking time between the groups.

Conclusions. Eye-tracking provides early evidence of atypical cognition after preterm birth, and may be a useful tool for stratifying infants at risk of impairment for early interventions designed to improve outcome.

Key words: social orienting; development; preterm infant; eye-tracking.

Abbreviations: IQR, interquartile range; AOI, area of interest; VA, visual acuity; LT, looking time; TFF, time to first fixate; SPL, social preferential looking; GA, gestational age; SIMD, Scottish Index of Multiple Deprivation.

7.3 Introduction

Globally, preterm birth (delivery at < 37 weeks' gestational age [GA]) affects around 10% of deliveries (Blencowe et al., 2012) and is a leading cause of neurocognitive impairment and educational under-performance (Bhutta et al., 2002, Delobel-Ayoub et al., 2009, MacKay et al., 2010, Quigley et al., 2012). The preterm neurocognitive profile includes global and specific learning difficulties, executive dysfunction, inattentiveness, social difficulties, and increased likelihood of screening positive for, or receiving a diagnosis of autism spectrum disorder (ASD) (Johnson et al., 2010a, Johnson and Marlow, 2011, Gray et al., 2015, Guy et al., 2015,). Identification in infancy of children with atypical development would enable targeting of early interventions designed to improve outcome, when they are likely to be most effective (Warren et al., 2011, Wass et al., 2011, Koegel et al., 2014).

Oculomotor orienting (gaze) behaviour is a critical control point for intake of visual information and its assessment in response to visual stimuli can be used to make inferences about underlying cognitive processes including preference, memory, attention, and processing speed (Liversedge and Findlay, 2000, Fletcher-Watson et al., 2008, Fletcher-Watson et al., 2009, Johnson et al., 2015). In the developmental trajectory of social cognition visual attention is given to faces very soon after birth, with specific attention paid to the eye region; and later in infancy at around 6 to 9 months a preference for looking at faces within multiple object arrays or animated scenes develops (Johnson et al., 1991, Farroni et al., 2002, Gliga et al., 2009, Frank et al., 2009); for review see (Johnson et al., 2015). This trajectory is altered from 2 to 12

months in children who go on to receive a diagnosis of ASD, which suggests that gaze behaviour may be one of the earliest markers of atypical social cognition (Young et al., 2009, Ozonoff et al., 2010, Chawarska et al., 2012, Jones and Klin, 2013, Chawarska et al., 2013, Wass et al., 2015).

Eye tracking provides a non-biased assessment of gaze in response to visual stimuli that is highly resolved in time (milliseconds) and space, which enables calculation of time to first fixate (TFF) and looking time (LT) to pre-defined areas of interest (AoI). It is well-suited to studying gaze behaviour during infancy because it can be applied to non-verbal populations and has high test-retest reliability for individual differences in this age group (Wass and Smith, 2014, Gillespie-Smith et al., 2016).

Based on studies of the developmental trajectory of social cognition and the clinical phenotype of children and adults born preterm, we hypothesised that preterm birth would be associated with alterations in cognition detectable during infancy. We used eye-tracking to measure gaze behaviour because of its utility for assessing social phenotypes in this age group. We assessed children at a median of seven months of age, and report differences in orienting to social cues between those born preterm compared with age-matched peers born after 37 weeks of gestation.

7.4 Methods

7.4.1 Participants

Preterm infants (GA at birth $<33^{+0}$ weeks) were recruited from the Royal Infirmary of Edinburgh, and healthy term control infants (≥ 37 weeks GA) were recruited from the postnatal wards or community groups between February 2013 and April 2015. A subset of the control infants have been reported previously (Gillespie-Smith et al., 2016). The Scottish Index of Multiple Deprivation (SIMD) was used to characterise deprivation. The SIMD is the official Government tool used to identify areas of deprivation: it divides Scotland into around 6505 areas each containing around 350 households and assigns an index to each area based on multiple measures of deprivation. The data are ranked from most to least deprived and are presented as quintiles. Exclusion criteria used were major congenital malformations, chromosomal

abnormalities, congenital infection and infants with major overt parenchymal lesions (cystic periventricular leukomalacia, haemorrhagic parenchymal infarction) and post-haemorrhagic ventricular dilatation. Ethical approval was obtained from the National Research Ethics Service (South East Scotland Research Ethics Committee 02) for all participants recruited from hospital services; ethical approval for the recruitment of community participants was granted by the School of Education Ethics Sub-Committee, University of Edinburgh. Informed written parental consent was obtained.

7.4.2 Eye-tracking assessment

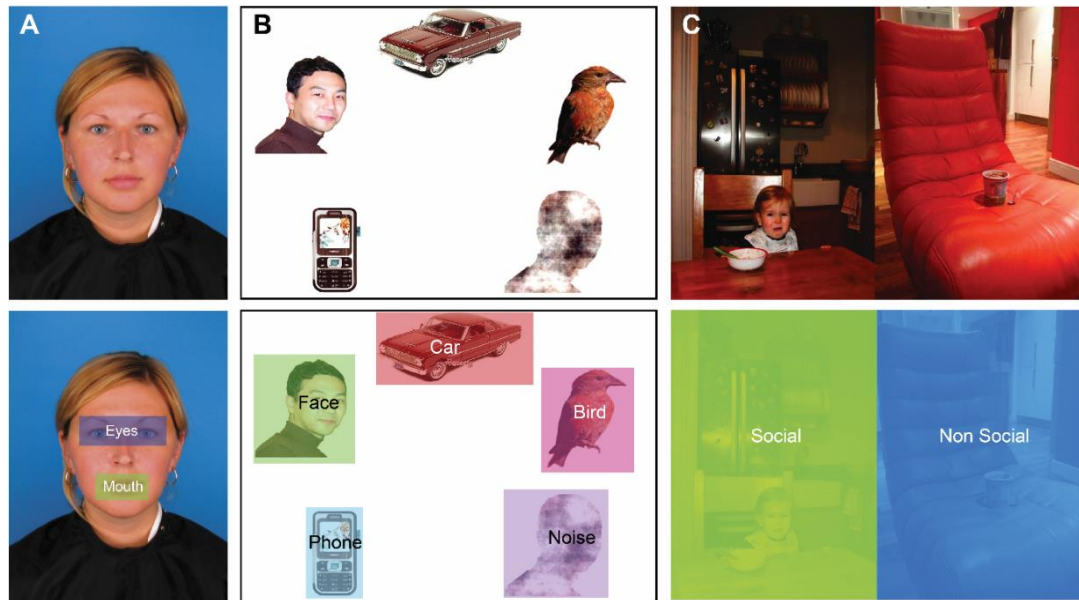
Participants were invited for assessment at 6 - 10 months (corrected gestational age was used for the preterm group because this is standard for practice for neurodevelopmental assessment of children born at less than 32 weeks until the age of two years (Johnson and Marlow, 2006)). Infants were positioned on their caregiver's lap 50 - 60cm from a display monitor used to show visual stimuli. Eye movements were detected using a Tobii© x60 eye-tracker and Tobii Studio© (version 3.1.0) software was used to present stimuli and record eye movements for analysis. Images were presented on a display monitor with a resolution of 1440 x 900 pixels. The Tobii© x60 system tracks both eyes to a rated accuracy of 0.3 degrees at a rate of 60Hz. Prior to data collection, eye-tracking calibration was performed using a five-point system. Preterm infants were screened for deficits in visual acuity (VA) using Keeler© acuity cards prior to eye-tracking, and infants were excluded if VA was below the estimated norm for age (Speedwell, 2003).

7.4.3 Tasks

We presented three tasks of increasing complexity (Fig. 7.1) that have been validated (Gliga et al., 2009, Gillespie-Smith et al., 2016). Each task contained different stimuli and these were presented in blocks with variable order. Attention grabbers (cartoon images of toys on a black background with sound effects) were presented in between each block to maintain infant attention to the screen.

Figure 7.1 Examples of stimuli for each task with accompanying areas of interest (AOI)

(A) Face-scanning; (B) Pop-out; (C) Social Preferential Looking.



7.4.3.1 Task one

Face-scanning. Photographs of natural faces with a neutral expression (three male, three female). Each stimulus measured approximately 18 x 24cm. Each stimulus was viewed for 10s and each block contained two stimuli.

7.4.3.2 Task two

Pop-out. Photographs of a natural face and a “face-noise” image alongside non-social content against a white background in a grid like array (Gliga et al., 2009). The non-social content included pictures of mobile phones, cars and birds. The “face-noise” image is an artificial scramble of the pixels in the face-stimulus, thus having the same low-level visual properties while being unrecognisable as a face. A total of seven stimuli were presented measuring between approximately 25 x 20cm. Each stimulus was viewed for 10s and each block contained two or three stimuli.

7.4.3.3 Task three

Social preferential looking task contained two neighbouring photographs with each pair consisting of a real world scene: one with social content (one or two children) and one without (no people) (Fletcher-Watson et al., 2008). A total of 12 stimuli were presented measuring approximately 27 x 19cm. Each stimulus was viewed for 5s and each block contained four stimuli.

7.4.4 Statistical analysis

LT at AOIs, LT at the whole stimulus, and TFF AOIs were analysed for each task, as measures of sustained attention and attentional priority. TFFs < 100ms were excluded: in these cases it is likely that the saccade started prior to image onset (Liversedge and Findlay, 2000). Similarly, LTs < 500ms were excluded because this was not considered a sufficient quantity of data to represent the result of a series of planned eye-movements to particular AOIs. Normality was assessed using measures of skew and by visual inspection of histograms and QQ plots. For normally distributed data, mean and standard deviation (SD) are reported and for non-normally distributed data, the median and interquartile range (IQR) are reported. For group-wise comparisons of normally distributed variables independent sample t-test was used, and for skewed data the Mann-Whitney *U* test was used. Repeated measures ANOVA and related samples Wilcoxon signed-rank test were used to investigate within-group differences for normally distributed and skewed data, respectively.

For the face-scanning task, a difference score of LT on eyes minus mouth was calculated. For all tasks, as well as analysing raw LT scores, a proportional looking score was calculated as the ratio of LT per AOI to LT at whole stimulus [proportional looking score = $LT(AOI) / LT(\text{whole stimulus})$]. Group differences in proportional looking scores were investigated using the Mann-Whitney *U* test. To investigate differences in overall attentiveness between groups, total LT to the monitor was recorded for each task. Two-tailed *p* values are reported and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 21 (Chicago, IL).

7.5 Results

7.5.1 Participant characteristics

Fifty preterm and fifty-one term eligible infants were assessed with eye-tracking. One participant born at term was excluded due to poor data acquisition, leaving 50 preterm infants and 50 term infants (Table 7.1 for participant characteristics).

Table 7.1 Demographic characteristics of participants

Characteristic	Preterm (n = 50)			Term (n = 50)		
Mean GA at birth / weeks (range)	29 ⁺¹ (23 ⁺² - 33 ⁺⁰)			40 ⁺² (37 ⁺⁰ - 42 ⁺³)		
Mean birth weight / kg (SD)	1.12 (0.26)			3.49 (0.66)		
Median age / months (IQR)*	7.72 (6.67 - 8.8)			7.85 (6.87 - 9.34)		
Gender (M:F)	22:28			26:24		
Scottish Index of Multiple Deprivation (%)	1	2 - 4	5	1	2 - 4	5
	18	68	14	8.5	40.4	51.1

IQR, interquartile range; * values for the preterm group corrected for gestational age at birth.

Of the preterm group, 94% had been exposed to antenatal steroid for threatened preterm labour and 50% had been exposed to antenatal magnesium sulphate for the purpose of neuroprotection. Thirty-six percent had bronchopulmonary dysplasia (defined as need for supplemental oxygen at 36 weeks GA), but none was oxygen dependent at the time of assessment. One preterm infant had been treated for retinopathy of prematurity. All preterm infants passed the screening test for visual acuity at time of assessment.

7.5.2 All tasks: overall eye-movement metrics

The overall proportion of trials excluded from control data because LT<500m was 6% for face-scanning, 7% for pop-out task and 8% for SPL. The same proportions for preterm infants were 4% for face-scanning, 4% for pop-out task and 9% for SPL. These

differences were not statistically significant between the groups. There was no significant group difference in raw LT to the whole stimulus for any task with all p -values ≥ 0.05 (Table 7.2).

7.5.3 Eye-gaze behaviours

7.5.3.1 Task one: Face-scanning

Both groups fixated the eyes more than the mouth (Table 7.2), but infants born at term had a significantly greater preference for looking at eyes than mouth. The mean difference score in raw LT (eyes – mouth) was 1.47s in controls (SD = 1.72) and 0.61s in the preterm group (SD = 1.68), $p = 0.013$ (Fig 7.2).

There was a group difference in proportional looking to eyes but not mouth: proportional LT eyes median = 0.31 for term infants versus 0.12 for the preterm group ($p = 0.039$). Term infants had a faster TFF to eyes than the mouth (median 1.97s vs. 4.11s, $p < 0.001$) and there was no significant difference in this comparison for preterm infants.

Table 7.2 Raw looking time, proportional looking scores, and time to first fixate to areas of interest for each task for preterm and control infants

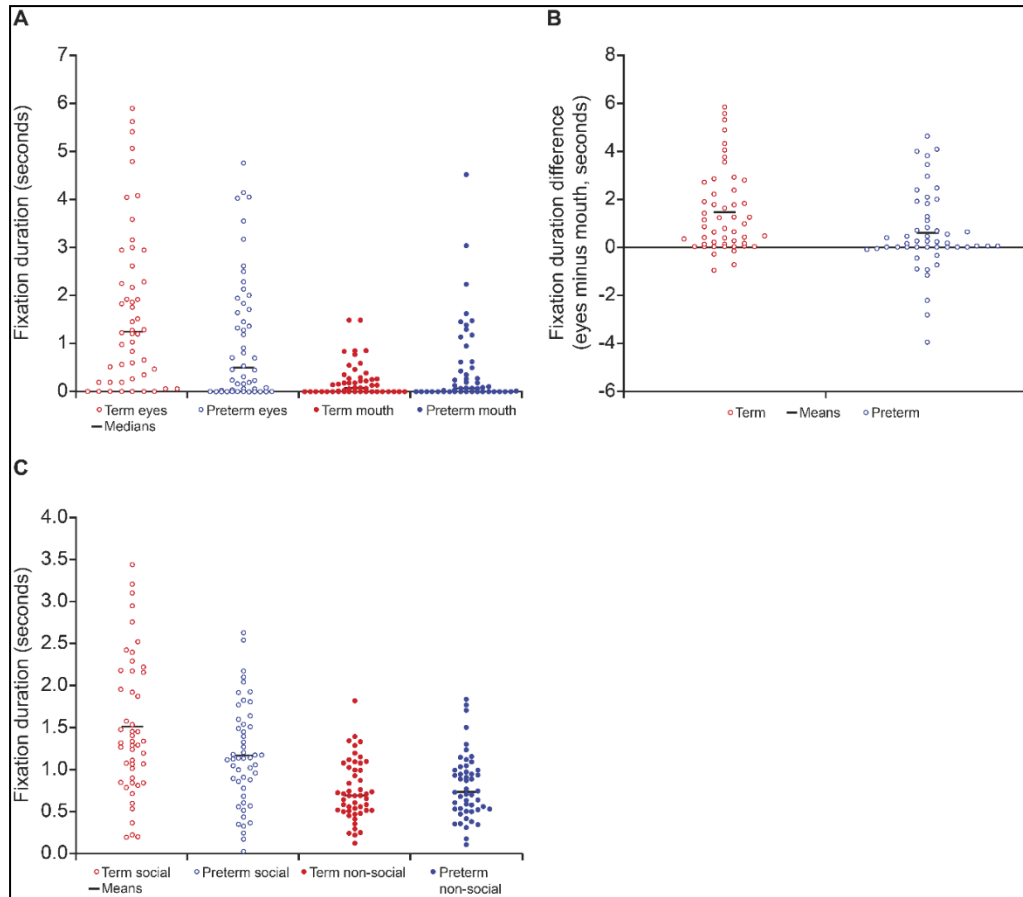
			Preterm	Term	p-value	Preterm	Term	p-value
Task	Measure	AOI	Time / s	Time / s		Proportional looking score (IQR)	Proportional looking score (IQR)	
Face-scanning	Looking Time	Eyes	0.49 (0.02 - 1.86)	1.24 (0.24 - 2.70)	0.045	0.12 (0.00 - 0.37)	0.31 (0.07 - 0.51)	0.039
		Mouth	0.07 (0.00 - 0.61)	0.06 (0.00 - 0.27)	0.479	0.02 (0.00 - 0.11)	0.01 (0.00 - 0.06)	0.388
		Whole display	5.28 (3.83 - 6.39)	4.96 (3.57 - 6.14)	0.677			
	Time to first fixate	Eyes	2.74 (1.43 - 3.92)	1.97 (1.05 - 3.35)	0.101			
		Mouth	2.66 (1.78 - 4.69)	4.11 (2.24 - 6.42)	0.058			
Pop-out	Looking Time	Face	0.80 (0.11 - 1.57)	1.34 (0.62 - 2.49)	0.023	0.16 (0.03 - 0.38)	0.34 (0.14 - 0.47)	0.036
		Face-Noise	0.13 (0.06 - 0.30)	0.26 (0.06 - 0.47)	0.170	0.03 (0.01 - 0.07)	0.04 (0.01 - 0.10)	0.294
		Bird	0.13 (0.00 - 0.24)	0.22 (0.08 - 0.36)	0.040	0.03 (0.00 - 0.05)	0.04 (0.01 - 0.08)	0.074

		Car	0.25 (0.11 - 0.57)	0.21 (0.06-0.43)	0.445	0.08 (0.02 - 0.13)	0.04 (0.02 - 0.09)	0.125	
		Phone	0.07 (0.00 - 0.14)	0.09 (0.04 - 0.21)	0.094	0.01 (0.00 - 0.03)	0.02 (0.01 - 0.04)	0.210	
		Whole display	4.49 (3.34 - 5.58)	5.28 (3.92 - 6.41)	0.063				
	Time to first fixate	Face	2.17 (1.20 - 3.35)	2.03 (1.22 - 2.97)	0.640				
		Face-Noise	4.15 (1.90 - 5.82)	2.98 (1.74 - 4.26)	0.045				
		Bird	3.46 (1.81 - 5.21)	3.59 (1.99 - 5.04)	0.908				
		Car	3.44 (1.47 - 4.95)	3.14 (2.05 - 4.79)	0.828				
		Phone	3.98 (2.17 - 6.92)	3.87 (2.54 - 7.15)	0.970				
	Social Preferential Looking	Looking Time	Social scene	1.16 (0.61)	1.50 (0.81)	0.020	0.46 (0.33 - 0.61)	0.61 (0.45 - 0.68)	0.012
			Non-social scene	0.79 (0.39)	0.74 (0.36)	0.503	0.30 (0.24 - 0.39)	0.28 (0.20 - 0.34)	0.141
		Whole display	2.46 (0.63)	2.63 (0.77)	0.225				
		Social scene	1.49	1.29	0.147				

	Time to first fixate		(0.73)	(0.61)				
		Non-social scene	1.78 (0.86)	1.63 (0.82)	0.401			

Raw values for face-scanning and pop-out task are reported as median (IQR), and raw values for social PL are reported as mean (sd). Proportional looking scores are reported as median (IQR).

Figure 7.2 (A) face-scanning looking time by group and AOI; (B) Face-scanning looking time with difference between eyes and mouth by group and AOI and (C) Social Preferential Looking, looking time by group and AOI



7.5.3.2 Task two: Pop-out

Term infants showed longer raw LT to the face compared to preterm infants (median 1.34s versus 0.8s, $p = 0.023$). This significant difference between groups was also apparent for the proportional looking score to the face (LT to Face AOI / LT to whole stimulus): median = 0.34 for term infants versus 0.16 for the preterm group, $p = 0.036$).

There was a difference in raw LT to the Bird AOI such that term infants fixated for longer than preterm (median 0.22s versus 0.13s, $p = 0.04$) but the proportional LT to the bird was not significantly different between the groups. There were no differences in looking pattern for any other AOI (Table 7.2). TFF the Face AOI did not differ between groups, however term infants fixated on the face-noise more quickly than preterm infants (median 2.98s versus 4.15s, $p = 0.045$). TFF other AOIs in the array did not differ between groups.

7.5.3.3 Task three: Social Preferential Looking

Term infants had a greater raw LT than preterm infants to the image within the stimulus that featured children: mean 1.5s versus 1.16s, $p = 0.02$ (Figure 7.2c). There were no differences between groups in raw LT to the non-social scene. Using repeated measures ANOVA, a main effect of scene was found ($F(1, 98) = 53.25, p < 0.001$) and there was a scene by group interaction ($F(1, 98) = 6.40, p = 0.013$). There was no main effect of group.

There was a significant difference between groups in proportional LT for the social scene (LT to Social Scene AOI / LT to whole stimulus): median = 0.61 for term infants versus 0.46 for the preterm group, $p = 0.012$. There was no group difference in TFF social or non-social content.

7.6 Discussion

Using eye-tracking we have demonstrated that infants born preterm have a different social orienting profile to term born peers, apparent during the first year after birth. This fixation pattern was consistently observed across three tasks of increasing stimulus complexity. In each task, the proportion of time spent looking at socially-

informative content was reduced in the preterm group compared with controls. Specifically, the raw and proportional LTs of preterm infants to social content were lower compared with values measured in the control group. Analysis of the pop-out task involves 5 simultaneous tests, which raises the possibility that shorter LT of preterm infants to the face AOI ($p = 0.023$) is a false positive result. However, we consider this is unlikely because the effect size was large, and the result is consistent with the significant difference in proportional LT to social content for this task, and with observations from other tasks. We did not apply the Bonferroni correction because test statistics are known to be correlated in this task (Gliga et al., 2009), which violates an assumption of the method and introduces the likelihood of type 2 error.

We found only one difference in time to first fixate social content: term control infants fixated eyes more rapidly than mouths when viewing a static face. Of note, term infants took less time to fixate the ‘face-noise’ AOI in the pop-out task, which could reflect a preference for social content albeit low-level, or failure to distinguish a real face from a scrambled face. While we checked that our preterm sample did not have visual acuity deficits, it is implausible to suppose that preterm infants were more capable than controls at detecting the difference between a real and scrambled face in peripheral vision. Thus we conclude that both TFF observations reflect lack of general preference for looking at social (or social-like) information in preterm infants. Elsewhere we did not find differences in time to first fixate content, or overall looking time between the groups in any task. Importantly, the proportional looking scores, which reflect attention to social content scaled by overall looking time at the stimulus was higher in term controls, and this finding was consistent across all three tasks. These scores take into account individual differences in overall looking time to the screen, which suggests that visual information processing speed and overall attentiveness do not explain the differences we observed in response to social stimuli.

The propensity to regard the mouth rather than the eyes within the static face is consistent with fixation patterns previously observed in young children either with or at risk of ASD (Chawarska and Shic, 2009) and indeed alterations in fixation to social content have been proposed as a potential early marker of later ASD (Young et al., 2009, Ozonoff et al., 2010, Jones and Klin, 2013, Chawarska et al., 2013). The

prevalence of ASD in preterm infants is estimated at 4% - 8% (Hack et al., 2009, Johnson et al., 2010a) therefore it is statistically unlikely that our sample contains a large number of infants who will later be diagnosed with ASD. Furthermore we found no evidence of a split distribution or other evidence suggesting our results were driven by a sub-group within the preterm sample. Therefore we hypothesise that the social cognitive patterns seen in this sample may point to a lack of specificity of early social attention atypicalities for ASD. This interpretation is consistent with the observation that early atypical eye-movement behaviour initially associated with ASD diagnostic status is eliminated after adjustment for development level scores (Wass et al., 2015). In other words, some early signs of ASD may not be specific to ASD and could instead be markers of developmental delay.

It is possible that the data presented here reflect the early emergence of impaired social function, which has been described in children with very low birth weight (<1500g) despite normal IQ (Williamson and Jakobson, 2014), or they may herald atypical social traits that are reported in adults born preterm who do not reach diagnostic criteria for ASD (Pyhälä et al., 2014). Such traits include difficulties in processing biological motion, facial expressions or social perception (Pavlova et al., 2006, Wocadlo, 2006, Indredavik et al., 2008, Taylor et al., 2009). The significance of an early preference to the mouth within the preterm group requires further investigation. Previous studies have suggested that attention to the mouth region is a predictor of normal language development, but the association is less clear in high-risk groups (Young et al., 2009, Lewkowicz and Hansen-Tift, 2012).

These data show that social orienting in late infancy differs between children born preterm and those born at term. Long-term follow-up of the cohort is planned, which will enable investigation of the place of atypical social orienting infancy in the development of language, and the ontogenesis of the broader preterm neurocognitive phenotype. Future research could focus on determining the sensitivity, specificity and predictive values of these measures for clinically important outcomes such as cognitive impairment or ASD. If measures of early social cognitive impairment are found to have high positive or negative predictive values for important clinical outcomes then they could have a role in diagnostic pathways, or be used to stratify risk status and

provide a basis for targeting early interventions designed to improve outcome. Inattention and distractibility are two common features also associated with preterm birth (Hille et al., 2001) and success has been previously demonstrated in improving attentional control among infants under 12 month using eye-tracking (Wass et al., 2011). This raises a potential use of eye-tracking not just in risk stratification for early intervention trials, but also as an intervention delivery route.

7.7 Conclusion

Eye-gaze behaviours in response to stimuli depicting social content differ in infants born preterm compared with healthy term controls. These data suggest the development of social cognition is altered by preterm birth, and that eye-tracking may be a useful tool for very early stratification of infants who might benefit from early interventions designed to improve neurocognitive outcome.

7.8 Acknowledgements

The authors are grateful for the provision of stimuli from the University of Stirling (<http://pics.psych.stir.ac.uk>), and the British Autism Study of Infant Siblings Network (<http://www.basisnetwork.org>).

The study was funded by Theirworld, (<http://www.theirworld.org>), and EJT received fellowship support from the same organisation. The study was sponsored by the University of Edinburgh.

7.9 Linkage of the social composite score to outcome measures at two years in the preterm group

As described in Chapter Four, the social composite score is generated from a mean of the proportional fixation to social content across three tasks: the static face, the pop-out task and social preferential looking group. There was no correlation between the social composite score and the composite scores within the BSID-III for motor (-0.042, $p = 0.838$, $n = 26$), language (-0.147, $p = 0.474$, $n = 26$) or cognition (0.072, $p = 0.728$, $n = 26$) at two years' CGA within the preterm group.

7.10 Additional discussion considering social cognition in the context of this thesis

This chapter has shown that the development of social cognition is altered by preterm birth and provides preliminary evidence that eye-tracking may prove itself to have clinical utility.

In addition to the analyses within the paper above, a small number of other analyses were also undertaken, and are summarised in Appendix III. An image-wise analysis for the Social PL task for each group was undertaken to check for systematic variability between stimuli (as described in appendix III). The proportion of fixation to the face and the bodies was calculated relative to the size of the stimulus. A one-sample t-test showed that both group means differed significantly from one (where a value of one indicates a random looking pattern) for the faces and not the bodies. Both groups were therefore fixating on the faces more than would be predicted by a random looking pattern. The social and non-social difference observed in the TFD above was also reinforced by the fact the image-wise score for the faces also significantly differed between the groups, being higher in the terms than the preterm infants, indicating more substantial face-preference in term than preterm infants.

Further to early identifiable social difficulties in preterm infants highlighted in Chapter Two, the current finding is consistent with more recent evidence. Frie et al (2016) showed different cortical facial recognition to their mother's face when compared to their term peers at six to ten months' CGA. This study, however had a small sample size of preterm and term infants (26 and 27 infants respectively) when compared to the current study (Frie et al., 2016).

As with the other eye-tracking variables discussed in Chapter Eight, the social composite score did not correlate with the BSID-III at two years' CGA. Unlike the executive function eye-tracking tasks, group level differences have consistently been identified for the social cognition tasks. A plausible explanation for the lack of association between the social composite score at 6 – 9 months and the composite scores two years' CGA is that social outcomes specifically were not assessed as part of the BSID-III. However, due to the overlap between social development and

language development, a relationship between the social preference variable and later language development at two years would be plausible (Young et al., 2009, Wetherby et al., 2008).

In summary, group-level differences in the response to social stimuli are identifiable at between seven and eight months' CGA in preterm infants, when compared to infants born at term using eye-tracking. The clinical long-term consequences of these early differences require further study, especially as there was no correlation between early eye-tracking measures and the BSID-III. Chapter Eight will now examine if there are differences between term and preterm infants in another domain of cognition: executive function.

CHAPTER 8 : EYE-TRACKING ASSESSMENT OF EXECUTIVE FUNCTION

In Chapter Two a second area of cognition in which preterm infants frequently perform poorly was highlighted - executive function, including (I) memory (recognition and object permanence as a measure of complex memory) and (II) attention switching. In this chapter, the results of executive function tasks for all participants who had an eye-tracking assessment will be presented, and the following hypothesis will be tested: infants born preterm have altered executive function compared to term born peers assessed by eye-tracking.

This chapter will also link three of the four eye-tracking summary variables (related to executive function tasks: habituation score and attention switching and disengagement) in the preterm group described in Chapter Four to a validated neurodevelopmental assessment (BSID-III) at two years' CGA. The results from correlations with the composite social score are described in Chapter Seven.

Dr Mark Bastin generated the values for the habituation score used in this chapter from the raw data generated from the eye-tracking assessments.

8.1 Whole eye-tracking sample demographics

Seventy-three preterm and sixty-one term eligible infants undertook an eye-tracking assessment in late infancy. One term infant was excluded due to difficulties in data acquisition. The final sample for analysis included 73 preterm and 60 term infants (see Table 8.1 for participant characteristics).

Table 8.1 Whole sample eye-tracking participant characteristics

Characteristic	Preterm (n= 73)			Term (n = 60)			P-value
Mean GA at birth / weeks (range)	29 ⁺⁰ (23 ⁺² - 34 ⁺⁶)			40 ⁺¹ (37 ⁺⁰ - 42 ⁺³)			Not tested
Mean birth weight / kg (sd)	1.12 (0.25)			3.52 (0.44)			Not tested
Median age / months (IQR)	7.93 (6.77 - 8.72)			8.25 (7.23 - 9.29)			*0.356
Gender (M:F)	34:39			33:27			-
Scottish Index of Multiple Deprivation (%)	1	2-4	5	1	2-4	5	-
	15.5	67.6	16.9	7.0	40.4	52.6	-
Mean IBQ questionnaire scores (sd)	169.27 (22.67)			160.73 (20.18)			Not tested

*Tested using Mann-Whitney *U* test

8.2 Attention switching paradigm: switching and disengagement

Hypothesis: preterm infants would be slower to both switch and disengage attention than their term peers.

In measures of infant attention switching and disengagement, there was no significant difference between the groups for either measurement using Mann-Whitney *U* tests (Table 8.2).

8.2.1 Attention switching paradigm: linkage to outcome measures at two years in the preterm group

The measures of attention switching and disengagement discussed above will be used without modification as measures of attention. The attention switching scores did not correlate with the BSID-III composite scores for motor (0.00, $p = 0.999$, $n = 19$), language (-0.191, $p = 0.433$, $n = 19$) or cognition (-0.280, $p = 0.246$, $n = 19$) at two years' CGA. The disengagement scores also did not correlate with any of the composite scores: motor (-0.121, $p = 0.603$, $n = 21$); language (-0.155, $p = 0.503$, $n = 21$) or cognition (-0.173, $p = 0.454$, $n = 21$).

Neither the (I) attention switching or (II) disengagement scores correlated with the composite scores within the BSID-III (for motor, language or cognition) assessment at two years' CGA in the preterm group.

Table 8.2 Time to first fixate the peripheral stimulus in attention switching and disengagement tasks

	Preterm	Term	Mann-Whitney <i>U</i> test statistic p-value
Attention switching <i>median (IQR), number</i>	0.69 (0.48 - 0.91) n = 66	0.69 (0.47 - 0.82) n = 54	0.481
Disengagement <i>median (IQR), number</i>	0.78 (0.57 - 1.1) n = 64	0.77 (0.54 - 0.98) n = 53	0.837

A related sample within group Wilcoxon-signed rank test showed that both preterm ($p = 0.012$) and term infants ($p = 0.016$) are significantly faster at switching than disengaging attention. This difference, however, does not differ significantly between groups.

8.3 Object permanence as a complex measure of memory

Hypothesis: term infants would show object permanence, and definitely by nine months, however this would not be observed in the preterm group.

There was no significant difference between groups using Fisher's exact test for object permanence demonstrated in fifty percent of the trials, $p = 0.463$. There was no significant difference in object permanence being demonstrated in at least two trials between both groups, $p = 0.467$ (Tables 8.3 and 8.4). The same analysis was repeated separately for a sub-sample of infants aged over nine months at the date of assessment, but this did not reveal differences by gestation at birth group.

Table 8.3 Numbers of infants demonstrating rated evidence of object permanence on 50% or more of trials

		Object permanence <i>n</i> (%)	No object permanence <i>n</i> (%)	Total number of infants
Preterm	All infants	23 (39)	36 (61)	59
	Over 9 months	6 (46)	7 (54)	13
	Under 9 months	17 (37)	29 (63)	46
Term	All infants	12 (50)	12 (50)	24
	Over 9 months	3 (50)	3 (50)	6
	Under 9 months	9 (50)	9 (50)	18
Total	All infants	35 (42)	48 (58)	83
	Over 9 months	9 (47)	10 (53)	19
	Under 9 months	26 (41)	38 (59)	64

Table 8.4 Numbers of infants demonstrating rated evidence of object permanence on a minimum of two trials

		Object permanence shown: in a minimum of two trials <i>n (%)</i>	Object permanence not shown: in a minimum of two trials <i>n (%)</i>	Total number of infants
Preterm	All infants	30 (51)	29 (49)	59
	Over 9 months	9 (69)	4 (31)	13
	Under 9 months	21 (46)	25 (54)	46
Term	All infants	15 (63)	9 (37)	24
	Over 9 months	4 (67)	2 (33)	6
	Under 9 months	11 (61)	7 (39)	18
Total	All infants	45 (54)	38 (46)	83
	Over 9 months	13 (68)	6 (32)	19
	Under 9 months	32 (50)	32 (50)	64

8.4 Recognition memory: assessed by memory task

Hypothesis: at two seconds ISI, both preterm and term infants will recognise the familiar shapes from slide A and show a preference in the form of increased looking to either familiar, or novel, stimulus regions. At five seconds ISI, differences between term and preterm groups may emerge, such that preterm infants show reduced group mean preference score, indicating smaller numbers of infants with intact recognition. At eight seconds ISI, infants from both groups may start to show impaired recognition, reflected in reduced preference scores for both groups. However, unless performance is at floor, group-differences may still be apparent.

8.4.1 Stimulus A

Attentiveness was measured by total fixation duration to the screen during presentation of the whole A stimulus (pre-ISI) - please refer to Chapter Four, Sections 4.4.3.3 and 4.4.3.4. Differences in total fixation duration between groups were non-significant for each separate ISI (Table 8.5).

Table 8.5 Between group comparisons: memory task

Mean and sd are shown for normally distributed data and median and IQR for skewed data. Significant differences in bold.

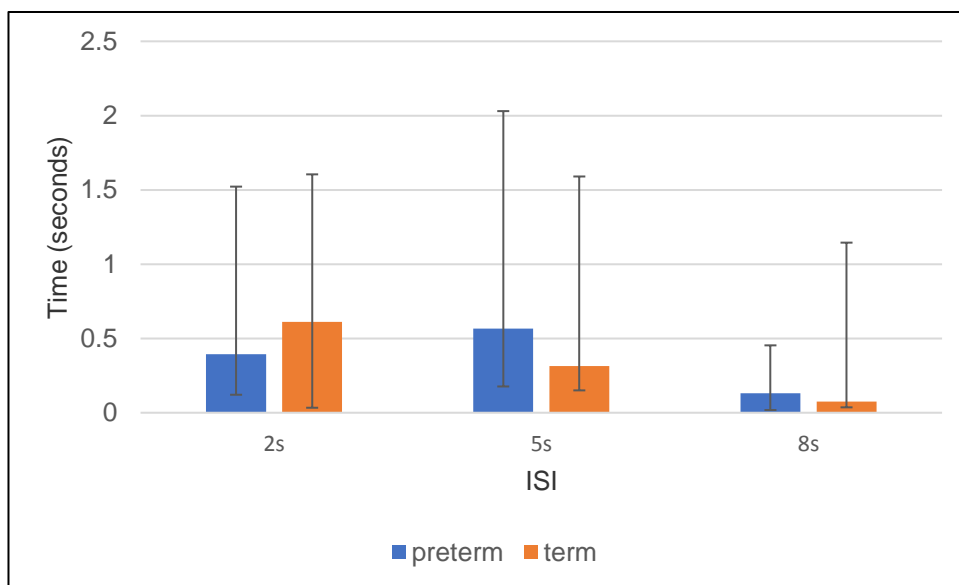
		Preterm	Term	
Measure	ISI	Time / s	Time / s	p-value
LT to screen: whole stimulus A <i>Mean (sd) number</i>	2s	8.85 (2.97) n = 59	9.63 (2.36) n = 24	0.255
	5s	7.44 (3.20) n = 59	8.71 (3.10) n = 24	0.101
	8s	6.28 (2.51) n = 59	7.16 (2.93) n = 24	0.175
Fixation / visits for familiar shapes in stimulus B <i>Median (IQR) number</i>	2s	2.50 (1.94 - 3.42) n = 57	2.14 (2.00 - 2.67) n = 23	0.278
	5s	2.25 (1.58 - 4.00) n = 54	1.67 (1.33 - 3.00) n = 23	0.096
	8s	2.00 (1.40 - 2.63) n = 56	2.20 (1.33 - 2.83) n = 21	0.696
Fixation / visits for novel shapes in stimulus B <i>Median (IQR) number</i>	2s	2.10 (1.67 - 4.00) n = 47	2.67 (1.75 - 3.40) n = 20	0.810
	5s	3.61 (2.42 - 5.08) n = 54	2.40 (1.95 - 3.25) n = 22	0.006
	8s	2.16 (1.60 - 2.73) n = 56	1.80 (1.42 - 2.11) n = 21	0.085

8.4.2 Stimulus B

A difference variable was created (total fixation duration to familiar AOI minus total fixation duration to novel AOI) and converted into an absolute value by squaring the original value. The new variable represents absolute size of preference in either direction (familiarity or novelty). This variable was normally distributed apart from some evidence of kurtosis in the preterm sample at the eight seconds ISI (Figure 8.1). This kurtosis was significantly reduced by exclusion of a single outlier (> 15 sd from the subgroup mean) from the data set, but not completely eliminated. Non-parametric testing revealed no differences between groups on the absolute preference score for any ISI (all $p > 0.60$).

Figure 8.1 Memory preference difference score absolute values

The memory preference difference score absolute values with the single outlier excluded across all ISI timings: median and IQR shown.



Using Fagan's cut off reference value of 54%, proposed to be the minimum threshold to indicate preference (Fagan, 1974), chi-square analyses demonstrated no significant differences between groups in the numbers of infants falling into each preference category (see Table 8.6). The pattern observed within the frequency table is surprising as a preference would be expected at 2s ISI, moving towards no preference by 8s ISI.

Table 8.6 Frequency table for infants in each preference category by inter-stimulus interval

	Novelty		Familiarity		No preference		Total
	Term n (%)	Preterm n (%)	Term n (%)	Preterm n (%)	Term n (%)	Preterm n (%)	All infants, n
2s ISI	23 (30)	51 (66)	0 (0)	1 (1)	0 (0)	2 (3)	77
5s ISI	3 (4)	8 (10)	17 (21)	33 (41)	4 (5)	16 (20)	81 ^h
8s ISI	20 (24)	49 (60)	0 (0)	4 (5)	4 (5)	5 (6)	82

8.4.3 Summary variable generated from memory task: linkage to outcome measures at two years in the preterm group

Habituation can be used as a measure of underlying processing speed. This is of particular interest as it has been proposed that slower processing speed in middle childhood results in the deficits seen in executive function (Mulder et al., 2011b). The variable described in Chapter Four is termed the "fixation index." This score (please see Section 4.4.3.4) did not correlate with the composite scores within the BSID-III for motor (0.453, $p = 0.09$, $n = 15$), language (0.501, $p = 0.057$, $n = 15$) or cognition (0.465, $p = 0.081$, $n = 15$) assessment at two years' CGA in the preterm group.

8.5 Discussion

This chapter set out to test the hypothesis that infants born preterm have altered executive function compared to term born peers assessed by eye-tracking. This chapter tested this hypothesis in the context of an over-arching goal of the thesis to test the potential of eye-tracking as a marker of early cognition in at-risk groups with evidence of neurological damage. Group level differences however were not detectable in any of the executive function tasks. Here, we will address each of the tasks in turn before also discussing demographic differences, summary variables generated from the executive function tasks and their relationship to outcomes at two years' CGA.

^h This row sums to 101% due to rounding

In the attention switching paradigm, the null hypothesis was found to be true, that there is no difference in the assessment of attention in term and preterm infants. In contrast to our findings, previous studies have identified preterm infants as having slower disengagement and attention shift in infancy (Rose et al., 2001, Rose et al., 2002, Ricci et al., 2010). These studies, however, have employed methodological differences (and non-eye-tracking assessment methods) and at times differing inclusion criteria to the current study design which may in part explain the contradictory findings. For example, Rose et al. (2001) used nine-paired comparison problems consisting of faces and patterns assessed by observations of the participants' corneal reflections (Rose et al., 2001), while Rose et al. (2002) used observations of eye-gaze to paired faces (Rose et al., 2002). Comparable similarities exist between the present study and those described above: both studies had a similar inclusion criteria to the present study (birth weight < 1750g) with a comparable number of preterm infants and assessments were carried out at a similar age (5, 7, and 12 months CGA). However, in these two studies the gestation at birth was < 37 weeks, which may have allowed the inclusion of a large subset of IUGR or small for gestational age infants and subsequently skewed performance in the assessment. In a more directly comparable cohort of preterm infants (< 31 weeks' GA at birth, and all birth weights under 1750g), Ricci et al. (2010) undertook a set of visual assessments including the fixation shift test and found that more than 25% of infants failed at three months, with a higher proportion failing at five and twelve months (Ricci et al., 2010). This preterm cohort also had a similar sample size of preterm infants, were at a similar age at assessment and medically comparable (low-risk) to the current cohort. It therefore seems unlikely that the lack of difference in performance in our cohort is due to different participant characteristics, but due to the use of eye-tracking methodology. Eye-tracking is a more reliable assessment method and it may be capturing a more accurate representation of group-level differences between term and preterm infants in the current study. The conflicting results in our study compared to those in the literature are also likely to be influenced by task design. De Schuymer et al. (2012) found preterm infants to be slower to disengage and shift attention in a non-social context at four and six months' CGA using infant-mother interaction and eye-tracking task (non-competition / competition paradigm) (De Schuymer et al., 2012). It may be the task in the current study was not sensitive

enough to detect group level differences in disengagement and attention switching. The preterm cohort in the De Schuymer et al. study was, however, relatively small. Replication of the current task design in a larger cohort would address these potential methodological differences.

The underlying origins of no difference in attention switching or disengagement in the preterm group when compared to term infants should be considered. During infancy, the overlap condition within the gap-overlap task (attention disengagement) has been suggested to assess the orienting attention network (Nakagawa and Sukigara, 2013). One interpretation of the current finding is that in fact the maturational process involving this neural network is comparable between preterm and term infants in infancy and divergence occurs later in childhood. Supporting this view is the finding that in early development low risk preterm infants have a quicker disengagement and attention shift than their term peers until about four months post-term (Hunnius et al., 2008), which is suggested to be secondary to additional postnatal visual exposure by preterm infants (Hunnius et al., 2008). Opposing this developmental theory was a small study by Hitzert et al. (Hitzert et al., 2014) who assessed seventeen term and ten low risk term infants in a gaze-shifting task every four weeks until six months of age. Gaze-shifting behaviour was linked to later cognitive outcomes and they showed a slower disengagement in both groups related to a worse performance in the outcome measures. Hitzert et al. concluded that the preterm infants did not seem to benefit from extra visual exposure secondary to the fact they were chronologically older at the time of testing when compared to their term peers. Early measures of attention in the VLBW remain inconclusive and require further investigation.

No difference was found between the two groups in the assessment of recognition memory, at any of the three inter-stimulus intervals tested. Using Fagan's published preference cut off, we found high rates of novelty preference in both groups for the shortest and longest intervals. However, at the five second interval, there was an unexpectedly large variability in size and type of preference shown. One interpretation of this finding could be that the infants did not habituate properly when they were initially presented with slide A: familiarisation durations of 6 – 9 seconds at the eight month age are relatively short as a basis for assessing memory (Fagan, 1974). However

we did see evidence of a preference in the shortest and longest intervals, and this explanation cannot account for the difference in data patterns between intervals tested. Infant memory is notoriously challenging to capture (*Teodora Gliga, personal communication*) and it may be that human-coding methods as used by Rose and colleagues (Rose et al., 2002, Rose et al., 2001) are more able to capture behaviour than automated processes as used here.

Another interpretation of findings in the current cohort, is that recognition memory is not impaired within the preterm cohort at this developmental stage. This would be unexpected, as deficits in memory would plausibly be expected as a result of damage to white matter and neural areas involved in memory (Woodward et al., 2005, Woodward et al., 2011). Certainly, without a reliable measure of infant recognition memory it would be premature to draw strong conclusions from these data.

In the current study, object permanence has been used as a complex measure of memory in infants. Object permanence has previously been considered the earliest way to assess memory (Lowe et al., 2009b). As stated in Chapter Two, memory is necessary but not a sufficient function to pass this task. Previous groups have found preterm infants perform worse in memory tasks in preterm infants as young as 12 months of age (Rose et al., 1991), and more recently at 18 - 22 months (Lowe et al., 2009a) when compared to term infants. Furthermore, group level differences have been identified between preterm and term infants at two years' CGA using an object working memory task (Woodward et al., 2005). The lack of difference observed between groups and the subgroups older than nine months may be secondary to the task being too complex for infants at the age of assessment. The pattern of results, however, would suggest this to be less likely. The non-significant pattern in the predicted direction is indicative of less consistent evidence of object permanence in preterm infants when compared to term infants. Future work may include repeating the task in a larger cohort and correlations with real-world object permanence such as the A-not-B task to determine if the lack of significant differences is secondary to being under-powered or design. With a larger sample, age effects not seen in the current study may then be observed.

In Chapter Two, three neural networks which underpin several aspects of cognition were identified: the alerting, orienting and executive control network (Keehn et al.,

2013). Given the lack of group difference observed in the executive function tasks, it is plausible there is no identifiable deficit in the first few months of life, or perhaps the preterm infants go through a period of faster, almost compensatory, rate of development.

The differences between the groups for socio-economic status requires acknowledgement. As discussed in Chapter Seven, the analyses were not corrected for socio-economic status. In the case of the executive function tasks, there was no difference in cognition despite a larger percentage of infants in the preterm group being in a lower socio-economic group. Consequentially, it was not felt to be such that it would be clinically significant. Attempts were made during the recruitment process to address this, however challenges associated with term recruitment limited attempts to balance the groups on this factor.

Three summary eye-tracking variables relating to executive function (attention switching, disengagement or habituation score) did not relate to any of the composite scores for the Bayley Scales of Infant and Toddler Development, Third Edition (cognition, language or motor). One possible explanation may be that the summary variables do not capture early deficits within the preterm group at the single point of testing. This may be overcome by repeating the tasks in a cohort with a longitudinal design with serial testing intervals such as in the study design by Jones and Klin (Jones and Klin, 2013). It may be that changes in a developmental trajectory identifiable in a serial testing design are the first indication of deficits in executive function in preterm infants. A second possible reason for the lack of relationship between the summary eye-tracking variables and BSID-III composite scores is the time point was too early for deficits to be detected within an at-risk group. Using individuals who later receive a diagnosis of ASD as an example, Elsabbagh and colleagues were not able to relate disengagement at seven months with later outcomes, however by fourteen months, performance was predictive of a later diagnosis of ASD (Elsabbagh et al., 2013a). Similarly, repeat assessments at different time points along the developmental trajectory may highlight an age at which a single assessment would be able to identify group level differences and relate to outcomes. Although it is known that processing speed (measured using the habituation score) can be impaired within the first year of

life in preterm infants, further longitudinal studies are required to examine how this impacts on specific aspects of later development (Rose et al., 2002). The habituation score was the only summary eye-tracking variable relating to EF which is not directly measuring components of a task. The lack of association for the habituation score may be acting as a poor summary variable. One final consideration may be the sample size was too small to detect an association as data was only available on a subset of preterm participants.

8.6 Conclusions

Eye-tracking in infancy has been unable to detect group-level differences in executive function tasks between preterm and term infants. A lack of difference in switching and disengaging of attention may be secondary to three reasons. Firstly, it may be too early in development to accurately detect any difference. Secondly, it may be that changes within the developmental trajectory need to be observed over time and cannot be captured in a single assessment. Thirdly, the additional visual exposure preterm infants have when assessed based on their CGA when compared to their term peers is under debate and requires further investigation.

The assessment of memory using the object permanence task and recognition memory has also given conflicting results. The object permanence task is most likely under-powered and requires re-administration to a larger cohort especially as the distribution of results suggests that differences would be significant in a larger cohort. Finally, the memory task and its results have proved the most challenging to interpret due to a lack of consistent patterns in the data. Predominantly, this is most likely to be secondary to the infants having too short a familiarisation period. It may be that there is no detectable deficit in memory in preterm infants, however it is impossible to draw that as a conclusion without significant further work. It is worth administering this task to an older cohort to ensure that it is not just a case of the infants being too young for differences to be detected.

A longitudinal study design with serial assessments may address many of the difficulties highlighted across all tasks. This may also then assist in attempts to relate eye-tracking

data with later outcomes at two years and beyond. In Chapter Nine, a final overall discussion of the findings of this thesis will be presented.

CHAPTER 9 : DISCUSSION

In this final chapter, the study findings will be discussed in a broader context to explore how current gaps in the literature have been addressed. The study's strengths and limitations will be addressed, before closing with suggestions for future direction.

9.1 Summary of key study findings

A summary of the key findings are summarised below:

- FA, MD, λ_{ax} , λ_{rad} and R in eight major white matter tracts are altered in association with preterm birth, measured using Probabilistic Neighbourhood Tractography (Chapter Five).
- There is a general factor of white matter microstructure that explained around half the variance of white matter microstructure in the newborn brain, and is altered by preterm birth (Chapter Six).
- A general factor of white matter microstructure does not relate to summary eye-tracking measures at six to nine months' CGA or to the composite scores of the Bayley Scales of Infant and Toddler Development, Third Edition at two years' CGA (Chapter Six).
- Eye-gaze behaviours in response to stimuli depicting social content differ between infants born prematurely and at term (Chapter Seven).
- Using three eye-tracking tasks to assess executive function in infancy, there appears to be no group-level difference in performance between preterm and term infants (Chapter Eight).
- Summary variables generated from eye-tracking metrics as measures of social cognition, attention and information processing speed do not relate to composite scores of the Bayley Scales of Infant and Toddler Development, Third Edition (Chapters Seven and Eight).

9.2 Characterisation of white matter in the neonatal brain

This thesis attempted to address inconsistencies in the literature related to the characterisation of microstructural white matter changes in the preterm brain using dMRI metrics and PNT. The pattern of reduced FA and increased MD after adjustment for age and multiple comparisons in four tracts-of-interest, and increased MD in a further tract are not novel in isolation, however it highlights reduced white matter microstructural integrity and diffuse vulnerability within the white matter tracts secondary to stressors associated with prematurity. This thesis was able to simultaneously examine eight tracts-of-interest in the preterm brain in a larger cohort than has previously been attempted (Anblagan et al., 2015). For the first time, a high degree of shared variance between white matter tracts is identifiable in the neonatal period, which allows neural changes that underpin cognition in both typical and atypical development to be examined in early life. Furthermore, in the case of prematurity, it suggests that brain development and injury is a generalised process. This finding may focus research away from the more traditional study design investigating specific tracts or regions and later patterns of impairment (Roze et al., 2015). The identification of an imaging target in the preterm brain allows the potential for dMRI to be further developed as a biomarker for preterm brain injury.

Although this study has demonstrated a general factor of white matter microstructure, this only accounts for 50% of the variance between the eight tracts-of-interest. It is therefore possible that tract-specific abnormalities exist and contribute to infant cognition. This has certainly been proposed in the adult literature where a general factor was also identified (Penke et al., 2010). Within the context of prematurity, the functional activity of localised processes will be dependent on the maturational processes, the connectivity within networks and the degree to which they are impaired. Research examining thalamocortical connectivity have demonstrated localised regional differences at term equivalent age in preterm infants. Toulmin et al. (2015) used fMRI to assess 19 term and 47 preterm infants. Increased functional connectivity in the preterm group was shown between the thalamus and lateral primary sensory cortex and decreased between the thalamus and cortex in prefrontal, insular and anterior cingulate regions (Toulmin et al., 2015). Ball et al. (2013) demonstrated

reduced structural connectivity between the thalamus, frontal cortices, supplementary motor areas, occipital lobe and temporal gyri in preterm infants (Ball et al., 2013). Furthermore, Ball et al. (2015) were able to relate their findings to neurocognitive outcome at two years using the BSID-III (Ball et al., 2015). In the context of the current study, the impact of regional variation as observed in the different loading patterns in the preterm brain described in Chapter Six is worthy of further study to assess its influence upon cognition.

Although beyond the scope of this study, one method of addressing the impact of localised tracts on outcome may be to correlate raw diffusion metrics for specific tracts with different outcome measures. It can be hypothesised what implications microstructural differences observed in the preterm group may have on later function. The corticospinal tracts connect the motor cortex within the brain to the brainstem via the posterior limb of the internal capsule (Pannek et al., 2014). Myelination can be detected around term-equivalent age (Counsell et al., 2002), and based on previous work, one may expect a decrease in FA to be associated with motor deficits (De Bruïne et al., 2013). The corpus callosum is another commonly studied tract, especially as it is thinned in preterm birth (Pannek et al., 2014). It is the largest interhemispheric structure and it is paramount in the transfer of information between the right and left hemispheres (Pannek et al., 2014). Myelination occurs caudo-cranially, and reaches the genu during the third trimester (Deoni et al., 2011), however both the genu and splenium show microstructural alterations associated with preterm birth (Thompson et al., 2012). Microstructural alterations in the corpus callosum have been related to performance with hand eye-coordination or on a developmental quotient (Counsell et al., 2008) and psychomotor development (De Bruïne et al., 2013). It would be expected to be one of the more significant tracts to be associated with later impairments in cognition. Microstructural changes in the cingula have been less commonly linked to developmental outcomes (Counsell et al., 2008), however, reductions in FA in both cingula have been related to eye-hand co-ordination, and in the right cingulum to performance on neurodevelopmental testing (using practical reasoning for infants achieving an age equivalent of over two years on assessment) (Counsell et al., 2008). Microstructural changes in adults with particular diagnoses such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and

schizophrenia have been linked to deficits in executive function (O'Sullivan et al., 2005) or attention and working memory respectively (Kubicki et al., 2005). This certainly appears to be a plausible early marker of impairments in memory. The inferior longitudinal fasciculi are involved in visual function (Akazawa et al., 2016). Impairments in the inferior longitudinal fasciculi have been linked to deficits in visual perception (Ortibus et al., 2012) and a wide range of clinical diagnoses, and it has therefore been proposed as a likely candidate of the source of a wide range of impairments (Akazawa et al., 2016). In the case of the current study, specific correlations between the tract-averaged measures and eye-tracking metrics beyond those tested in Chapter Eight would address this hypothesis. Finally, in the case of the bilateral tracts, hemispheric differences should be further explored to understand the contribution of individual tracts to later function in preterm infants. This study did not test the significance of different hemispheric tract-averaged dMRI parameters in either the preterm or term group. It would therefore be impossible to draw conclusions from the seemingly higher FA values in the left cingulum and corticospinal tract and the right inferior longitudinal fasciculi in both groups. Hemispheric microstructural differences have previously been identified in the preterm brain (Liu et al., 2010) and these have been related to outcome at two years (van Kooij et al., 2011).

9.3 Social cognition is altered in preterm infants, assessed using eye-tracking

This study is novel in its use of eye-tracking as a tool to measure social cognition within the preterm cohort during infancy. Eye-tracking as an assessment tool in this cohort has shown itself to be an acceptable method, and it is able to detect group level differences in social cognition between preterm and term infants before a year of age. The combination of the three social tasks (as described in Chapter Seven), have shown themselves to be a reliable measure of social cognition in an at-risk group in addition to TD infants as previously shown (Gillespie-Smith et al., 2016). The consistently poorer performance across all three tasks in the preterm group increase the reliability of the results.

When considering the implications of the group level differences, it is important to ascertain to what degree the differences are due to prematurity itself, or indeed the

impact of other factors. To date, studies have focused on a combination of neural changes associated with preterm birth, stress in the immediate postnatal period and the relationship between them (Montagna and Nosarti, 2016). In keeping with previous work showing adverse changes in corticostriatal and thalamocortical pathways (Karolis et al., 2016, Ball et al., 2015), it is plausible that the generalised neural changes observed in the current cohort contribute to the difficulties seen in early infancy. Alternatively, it is plausible that specific structural changes (not all directly measured in the current study) between preterm and term infants underpin the differences observed (cross reference Chapter Two), for example differences in subcortical regions (Johnson, 2005). Without further investigation, it is not possible to determine if this would be secondary to maturational delay or secondary to white matter damage associated with prematurity. It is impossible to quantify the impact of perinatal stress in the current cohort, and the post-discharge environment is unknown. The altered pattern of fixation observed in the preterm group is most likely combination of all of these factors and the underlying relationship between these remains inconclusive (Montagna and Nosarti, 2016).

In Chapter Two, this thesis showed the increased risk of early detectable difficulties in aspects of social cognition and an overall increased risk of ASD in childhood in the preterm cohort. Therefore, it is likely that a proportion of the preterm infants within our cohort will develop later difficulties, but what remains unclear if this will be in the social or another cognitive domain. The lack of group differences in the attention switching paradigm described in Chapter Eight, in addition to the early social differences, may support a hypothesis of later social difficulties (cross reference Chapter Seven). For example ASD-siblings do not show any difference in disengagement at seven months between those who do and do not later develop ASD (Elsabbagh et al., 2013a).

To further develop eye-tracking as an assessment tool in this cognitive domain and determine the clinical implications of these deficits, further work would be required. Firstly, the study should be repeated in a larger cohort, with serial measurements and as part of a longitudinal study with a longer period of clinical follow up. Furthermore, an extension of the small test-retest subsample would act as measure of internal

validation. Serial assessments would allow the determination of when group level differences are first detectable and determine if there is a specific atypical preterm developmental trajectory, such as used by Klin et al. in infants at risk of ASD (Jones and Klin, 2013). At present, the single time point assessment and the lack of designated follow up to assess social outcomes is unable to give sensitivity or specificity for the development of social cognitive impairment in preterm infants.

The hypothesis that eye-tracking metrics could link to the composite measures in the BSID-III acted as a measure of external validation for the eye-tracking metrics. It could, however, be proposed that the BSID-III may not be the ideal choice of external validation tool. The cognitive score is a composite and it may not be sensitive enough to correlate with isolated components of executive function which were assessed in the eye-tracking tasks. Furthermore, concerns have arisen that the BSID-III assessment over-estimates performance (Vohr et al., 2012, Anderson et al., 2010) and therefore is less sensitive in detecting cognitive delay in the children it assesses. The social-emotional questionnaire within the BSID-III was not available for the infants in this study, however such information is required to investigate the predictive value of infant eye-tracking and social cognition.

In summary, this study has shown that eye-tracking can be used in the assessment of infant cognition. Future work could focus on the positive and negative predictive value of eye-tracking to assess the relationship with later outcomes.

9.4 The relationship between dMRI and outcomes in this cohort

Finally, the relationship between dMRI and later outcomes will be addressed. In Chapter Two, the wide range of microstructural changes throughout many neural structures and the associated functional outcome were discussed. As highlighted in Section 9.2 above, this strategy was not replicated by comprehensively linking dMRI metrics of tracts-of-interest to later outcomes. From the perspective of this thesis, associations remain speculative rather than secondary to causal relationships within the current cohort.

The relationship between white matter changes observed on conventional imaging seen in approximately 50% of the preterm infants and later functional outcomes has not been fully explored. This specifically would require correlation with the dMRI metrics and further longitudinal follow up. This study was unable to reliably determine the percentage of infants who demonstrate deficits based on the BSID-III due to the low number preterm infants who completed the assessment at time of writing. Throughout this general discussion and in previously chapters, reasons which may explain a lack of relationship between the general factor of white matter microstructure and cognitive outcomes assessed by eye-tracking and the BSID-III assessment have been discussed. Furthermore, the dual contribution of shared variance and the likelihood of the importance of individual tracts for the development of cognition has been put forward. Further work would need to link the specific microstructural metrics for individual tracts (e.g. FA or MD of the genu of the corpus callosum) to specific eye-tracking metrics (e.g. the looking time to an AOI in particular task) rather than using the summary variables. Further hypothesis-driven analyses (out with the scope of the current thesis) may result in associations between structure and function.

9.5 Clinical implications of this study

The over-arching reasons for undertaking this study were: (i) determine if it were possible to predict those preterm infants who would later develop neurocognitive impairment by undertaking MRI at term equivalent age and (ii) assess what those impairments were. This study has given rise to invaluable foundational work required to identify potential imaging and eye-tracking targets worthy of further evaluation as biomarkers of preterm brain injury or outcome respectively.

At present, routine clinical practice advocates the use of cranial ultrasound scanning for screening of IVH or other cranial pathologies in VLBW infants. It should also be noted that in contrast to the universal acceptability associated with the eye-tracking assessment, a few parents found the degree of uncertainty which persisted with the diffuse white matter abnormalities reported in the structural scans difficult to comprehend. This may be reconsidered if the potential imaging target (g_{WM}) reliably related to outcome measures. Eye-tracking has shown its potential to be further developed. However, its sensitivity and specificity (for example for ASD in infants

who show early deficits in social cognition) would require to be robust before its role could be expanded out with the research setting. The BSID-III assessment is a commonly used follow up modality for VLBW infants, certainly within the local clinical network. This has significant benefits of being a standardised method of assessing outcome at a single time point, even if limitations exist. It is certainly worth considering adjusting cut-off scores at a network level to ensure that infants with delay do not over-perform (Johnson et al., 2014) and therefore are discharged from further follow-up without identification of their deficits.

9.6 Study strengths

One of this study's greatest strengths is the assessment of preterm brain injury using quantitative dMRI measures and analysis techniques. Using this the current study has been able to demonstrate the novel finding of the existence of a general factor of white matter microstructure within the neonate brain as discussed in Chapter Six. Furthermore, the use of eye-tracking has shown partial success as an assessment tool with the identification of altered social cognition in preterm infants. Attempts were made to overcome the broad diagnostic outcomes often used in the literature in the outcome measures by examining different areas of cognition independently.

This study has demonstrated strengths in many areas including patient selection, design and analysis. One strength of this study which contributed to its success, was the longitudinal nature of the overall study design which allowed two points of follow up at six to twelve months and two years' CGA. The study population is well defined in that infants were under 1500 g or under 32 weeks' PMA at birth, and in the absence of HPI or cystic PVL, conditions which may have skewed the interpretation of the MRI findings. The preterm cohort was representative as having received contemporary neonatal intensive care. The experimental approach was rigid in the exclusion criteria following an MRI scan in the event of the identification of an incidental finding which would invalidate the inclusion criteria. Three preterm infants were excluded for this reason, therefore ensuring the study focused on diffuse patterns of preterm brain injury. Furthermore, very few of the preterm infants were older at birth and born with IUGR. Both prematurity and IUGR are independently associated with an increased risk of adverse neurocognitive outcome (Fischi-Gomez et al., 2016) and this risk is not

increased when both risk factors simultaneously occur (Fischi-Gomez et al., 2016), therefore the small subset within the preterm group (6.5% of the total sample size), are unlikely to be sufficient to drive an overall effect within either the MRI or eye-tracking parameters assessed. The preterm neonatal complications or outcomes within the preterm group such as bronchopulmonary dysplasia, late onset sepsis and chorioamnionitis were also comparable to other studies (Horbar et al., 2012, Yoon et al., 2001, Moore and Boardman, 2014). As each of these complications are associated with an adverse neurological outcome or cerebral damage (Ball et al., 2010, Mitha et al., 2013, Shatrov et al., 2010), it was important that this study did not have an over-representation of a particular complication that may have acted as a confounder in the interpretation of the results. These results are therefore generalisable and representative of the preterm group. This study was also sufficiently powered, particularly within the preterm group. Using PNT, group sizes of approximately 30 should be sufficient to detect group level differences and any larger number should detect a smaller effect size. Both the preterm and term groups were balanced in patient demographic factors as far as possible, with similar patterns of gender distribution.

This study also ensured optimisation of data acquisition and analysis (in terms of imaging protocols and analysis techniques). Attempts were made to address common problems associated with diffusion MRI data acquisition in neonates (Heemskerk et al., 2013). For consistency, all scans were acquired on the same 3T scanner over a three year period from 2012 - 2015. An optimised bipolar gradient pulse scheme was selected with a manually selected shim box covering a region extending from the top of the head to several centimetres below the chin to minimise the effect of eddy current induced artefacts and shimming errors. Two layers of ear protection for the infants were also used to minimise response to noise and subsequent motion artefact. Sedation would have eliminated this further, however in keeping with recent preferences to avoid this (Tocchio et al., 2015), it would have been less ethical and less acceptable to parents than to scan in natural sleep. During the image analysis phase, a rigorous process of image processing involving a minimum of two raters to ensure agreement of what were anatomically acceptable tracts was in place.

Conditions for data acquisition from the eye-tracking assessments were optimised. In order to minimise the risk of bias, eye-tracking assessments were largely performed by a single assessor (Dr Telford). Dr Gillespie-Smith also collected the data for term infants recruited from the community and a single preterm infant. All preterm infants underwent visual screening to ensure they were not disadvantaged by complications associated with preterm birth. No preterm infant was excluded based upon this assessment, and it is worth noting that only 4.1% of preterm infants received laser treatment for retinopathy of prematurity. The design of the eye-tracking tasks assessing social cognition were validated (Gillespie-Smith et al., 2016, Telford et al., 2016) and provided a sound basis for the summary variable used as an outcome measure. Discussion surrounding the design of the executive function tasks and the generation of summary variables can be found in Chapters Six and Eight. The automated generation of raw variables from the Tobii x60 tracker and software reduce the risk of subjectivity. Rigorous data cleaning principles were also uniformly applied to ensure consistency across all data sets.

The two-year BSID-III was undertaken by a small number of professionals who adhered to the marking schedule, ensuring the validity of the results. The relatively small number at follow up within this thesis can be explained by the longitudinal nature of the study and that a relatively smaller proportion of infants were old enough to receive an assessment at the time of writing. A small proportion of infants were also discharged to follow up at their local hospital and therefore clinical follow up practices of VLBW infants differs. Alternatively, a formal assessment was not performed as it was not deemed to be clinically necessary as there was no clinical concern regarding the child. Data collection of remaining study participants continues.

9.7 Study limitations

Design limitations within the context of this study should also be considered. Most noticeably, are the challenges associated with interpreting the lack of difference observed in the executive function tasks in the eye-tracking assessment. It remains unclear if the lack of effect of prematurity is secondary to there being no detectable difference, or indeed the task is insensitive to detecting true differences. This is discussed in more detail in Chapter Eight.

The clinical implications of group-level differences between preterm and term infants described in Chapter Seven at even the single time-point assessment are made more challenging by the lack of validated social outcome measures in this study as longitudinal information on social function was unavailable. In addition to the clinical implications of eye-tracking measures, a longer follow up period will allow a more accurate prediction of dMRI metrics and how these relate to functional outcomes. As discussed above, the relationship between neural structures and later cognitive function require further study, especially the investigation of the relationship between more localised areas of the brain and later function. Finally, a longer follow up period within a longitudinal study may see the emergence of specific difficulties within the preterm group that would appear after two years' CGA.

Other possible limitations exist especially with regards to the differences in demographic factors as described in Chapter Four. In Section 9.6 above, the generalisability of the preterm group in relation to their associated complications was highlighted. Most noticeable is the imbalance in socio-economic groups between the preterm and term infants. In keeping with this group difference, is the higher maternal educational level in the term infants. Attempts were made to address this imbalance at the time of recruitment, however this was with limited success. Socio-economic status is a potential confounder for neonatal MRI and infant social cognition. The impact of socio-economic status on neonatal MRI and later outcomes requires further examination.

The challenges associated with term recruitment were also evident within the sample size difference. This may have hindered further exploration of the general factor of white matter microstructure between groups in Chapter Six as demonstrated in in the secondary analysis of the effect of preterm birth on component loadings. At present, there is no agreed or predetermined power calculation methodology for neuroimaging studies and our sample size for the MRI component of the study was comparable to or exceeded others (Thompson et al., 2012, Boardman et al., 2006, Boardman et al., 2010). Similarly, eye-tracking power calculations are not established and precedence was taken from previous studies involving group level comparisons (Elsabbagh et al., 2013a, Elsabbagh et al., 2013b). Although type one error was controlled in all

experiments that were susceptible to this error type, within the imaging component of the study it is possible that type two error exists in the negative findings.

The method of scoring the object permanence task was subjective when compared to the automated generation of data using the Tobii software and pre-defined areas of interest. However, as discussed in Chapter Eight, the fixation patterns on the objects reappearance was indicative that the lack of group differences was associated with a lack of power rather than the assessment method. The high inter-rater agreement between the two scorers also indicated the scoring method was reliable.

In the context of image processing, although every attempt was made to ensure the visual inspection of images was a rigorous process, accuracy could have been further improved by using automatic outlier detection as a measure of quality assessment. This is of particular importance, as individual tract data will be influenced by the “tensor estimation method,” and its accuracy is improved by the accurate handling of data outliers (Plaisier et al, 2014b).

Finally, potential factors which may impact on later outcomes were not explored, for example the role of environmental or genetic factors. Environmental factors such as parental mental health (Montagna and Nosarti, 2016) and maternal attachment (Korja et al., 2012) are important factors in an infant’s development. Mothers of preterm infants are at an increased risk of anxiety and depression (Davis et al., 2003, Singer et al., 1999), however the net effect of early maternal-factors on the preterm infant’s development remains unclear (Korja et al., 2009). The influence of parental factors was addressed in part by asking parents if there was a history of postnatal depression, however this was used as descriptive information in the current study. Furthermore, the parent-infant interaction are factors which are out with experimental control. The home environment and family are important area to assess as these are areas through which home-based interventions have been successfully applied in order to improve cognitive and behavioural outcomes at two years’ CGA (Poggioli et al., 2016). Common genetic variations have been shown to modulate white matter injury after preterm birth (Boardman et al., 2014, Sparrow et al., 2016), however the effect on long-term cognition remains unclear. The impact of this and the concurrent role of environmental factors are worthy of further study.

9.8 Future directions: a summary

Before concluding, this thesis will now highlight how this study should shape the direction of future investigation. Firstly, in order to understand the neural structural and functional correlates associated with prematurity, the absolute contribution of both the general factor of white matter microstructure and that of the specialisation of individual white matter tracts require to be determined. This will aid the understanding of the significance of white matter on different aspects of cognition in early infancy. Further examination of the impact of specific neonatal complications upon this relationship will also help guide prognostic information.

Many of the discussion points in Chapters Five to Nine would be addressed by a longitudinal study with serial assessments. In terms of current findings, this would certainly determine if the differences in social cognition assessed using eye-tracking between preterm and term infants was an early marker of general delay or specifically, social difficulties or even a later diagnosis of ASD. A longitudinal approach may also highlight an optimal timing for intervention, depending on the nature or the severity of the impairment identified. At present, given the diversity of later difficulties it would potentially be very difficult to have a targeted approach. Other factors such as the interplay between genetic and environmental factors could also be explored.

Finally, it would be an ultimate goal to be able to provide an individualised and early approach in prognostication of outcomes associated with prematurity and the ability to intervene early in order to optimise outcome.

9.9 Conclusions

This thesis has furthered the understanding of preterm brain injury detectable using dMRI. It has shown that disturbance to brain microstructural development occurs as a mainly generalised process. This indicates that the network basis for intelligence is established by birth.

Furthermore, this thesis has also revealed evidence of atypical social cognition is identifiable in infancy. This is one of the earliest indicators of deviation from a typical developmental trajectory in an important cognitive domain.

Collectively these findings have enhanced current knowledge of the neural components which underpin cognition in the first few months of life. It also provides a platform for future research to exploring the implication of this relationship further, with the aim of optimising the outcome for each preterm infant.

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APPENDIX I: VISUAL ACUITY CALCULATIONS

Using the Keeler© acuity cards, the approximate visual acuity was calculated using a reference distance of 38 cm. Each visual acuity card corresponds to cycles per cm and cycles per degree at 38 cm which then equates to an approximate Snellen equivalence. In order to engage the infants, the assessment was carried out at a distance of 1.25m. The Snellen approximate value was calculated using the following equation with a reference distance of 38cm:

Cycles per degree: $(\text{Distance in cm} / 38 \text{ cm}) \times \text{cycles per cm}$

This was then compared to the mean age-appropriate norm.

APPENDIX II: ADDITIONAL METHODOLOGY INFORMATION

II.1 AOI timing and sizes

The following pages show the detailed sizing of each AOI as calculated within Tobii software. The timing is also shown for the attention switching paradigm task.

II.1.1 Static face

Table II.1 Static Face

All AOIs were present for the duration each stimulus was shown to the infant.

AOI	Female 1	Female 2	Female 3	Male 1	Male 2	Male 3
Bottom half of face	246 x 179	288 x 191	282 x 175	260 x 195	280 x 208	305 x 218
Top half of face	261 x 213	299 x 167	303 x 216	268 x 214	293 x 229	317 x 249
Mouth	156 x 76	181 x 80	168 x 7 8	192 x 72	202 x 74	214 x 101
Eyes	230 x 107	268 x 84	287 x 118	250 x 109	266 x 100	307 x 116

II.1.2 Attention switching paradigm

Tables II.2 and 3 show the AOI timings and sizing respectively for the attention switching paradigm stimuli included in the analysis.

Table II.2 Attention switching paradigm timings

Video name	Central stimulus on time (s)	Central stimulus off time (s)	Peripheral stimulus on time (s)	Peripheral stimulus off time (s)	Peripheral stimulus duration (s)	Gap or Overlap + / -	Condition
Clock_CloudRight_NoOverlap	0	2.972	3.269	5.348	2.079	-0.297	GAP
Clock_CloudRight_Overlap	0.1	5.45	3.368	5.45	2.082	2.082	OVERLAP
Planet_CloudLeft_NoOverlap	0.197	3.219	3.416	5.454	2.038	-0.197	GAP
Planet_CloudLeft_Overlap	0.264	6.7	4.592	6.7	2.108	2.108	OVERLAP
Planet_CloudRight_NoOverlap	0.263	3.298	3.496	5.598	2.102	-0.198	GAP
Planet_CloudRight_Overlap	0.461	5.784	3.681	5.784	2.103	2.103	OVERLAP

Table II.3 Attention switching paradigm AOI size and location

The AOIs in this task are dynamic, dependent on the visualisation timing of each of the central (C) and peripheral (P) stimuli.

	Clock cloud right overlap	Clock cloud right no overlap	Planet cloud left no overlap	Planet cloud right no overlap	Planet cloud right overlap	Planet cloud left overlap
C stimulus	400 x 350	400 x 350	450 x 400	450 x 400	450 x 400	450 x 400
Location	390 x 275	390 x 275	512 x 350	512 x 350	512 x 350	512 x 350
P stimulus	400 x 350	400 x 350	450 x 400	450 x 400	450 x 400	450 x 400
Location	790 x 275	790 x 275	60 x 350	966 x 350	966 x 350	60 x 350

II.1.3 Memory task

Table II.4 shows the sizes for each AOI in the memory task.

Table II.4 Memory task AOI sizes

All AOIs were present for the duration each stimulus was shown to the infant.

AOI	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Pair 6	Pair 7	Pair 8	Pair 9	Pair 10	Pair 11	Pair 12
Familiar shapes (a)	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632	420 x 632
Familiar shapes (b)	420 x 632	420 x 632	420 x 632	420 x 632	492 x 740	492 x 740	420 x 632	492 x 740	420 x 632	420 x 632	420 x 632	492 x 740
Novel shapes (b)	420 x 632	420 x 632	420 x 632	420 x 632	492 x 740	492 x 740	420 x 632	492 x 740	420 x 632	420 x 632	420 x 632	492 x 740

II.1.4 Pop-out task

Table II.5 shows the size and location of each AOI for the Pop-out task.

II.1.5 Social Preferential Looking

Table II.6 shows the AOI sizing and location for each AOI in the social preferential looking task.

Table II.5 Pop-out task AOI size and location

All AOIs were present for the duration each stimulus was shown to the infant. The top figure indicates the size and the bottom figure indicates the location of the AOI.

AOI	Slide 1	Slide 2	Slide 3	Slide 4	Slide 5	Slide 6	Slide 7
Face: size	198 x 248	235 x 269	184 x 197	168 x 181	165 x 161	168 x 174	246 x 255
location	716 x 328	26 x 123	73 x 343	468 x 0	282 x 7	272 x 363	102 x 8
Face-noise: size	209 x 245	251 x 274	177 x 194	151 x 186	152 x 153	174 x 173	237 x 263
location	118 x 14	630x478	503 x 100	45 x 230	66 x 386	492 x 22	385 x 490
Car: size	289 x 166	389 x 197	245 x 164	241 x 143	200 x 143	206 x 144	284 x 146
location	346 x 592	308 x 3	425 x 375	40 x 16	30 x 180	47 x 24	692 x 420
Phone: size	117 x 277	144 x 228	235 x 119	250 x 142	124 x 175	126 x 173	112x 265
location	120 x 377	155 x 516	220 x -1	232x395	505 x 162	81 x 249	72 4x 13
Bird: size	130 x 250	214 x 270	228 x 163	156 x 209	218 x 143	207 x 141	267 x 190
location	692 x 12	722 x 151	18 x 121	521 x 226	430 x 398	478 x 279	21 x 406

Table II.6 Social Preferential Looking AOI size and location

AOIs were present for the duration each stimulus was shown to the infant.

AOI	Slide 1	Slide 2	Slide 3	Slide 4	Slide 5	Slide 6	Slide 7	Slide 8	Slide 9	Slide 10	Slide 11	Slide 12
Social	431 x 610	442 x 612	439 x 610	438 x 612	436 x 610	432 x 612	436 x 612	431 x 612	434 x 612	426 x 610	437 x 612	436 x 612
Location	0 x 0	44 x 0	439 x 0	440 x 0	428 x 0	0 x 0	0 x 0	0 x 0	0 x 0	438 x 0	0 x 0	424 x 0
Non-social	431 x 610	442 x 612	439 x 610	440 x 612	428 x 610	437 x 612	436 x 612	445 x 612	437 x 612	438 x 610	433 x 612	424 x 612
Location	431 x 0	0 x 0	0 x 0	0 x 0	0 x 0	432 x 0	436 x 0	431 x 0	434 x 0	0 x 0	437 x 0	0 x 0
Faces		130 x 156	120 x 158	52 x 82	68 x 84	72 x 111		94 x 134	38 x 47	35 x 41	46 x 79	33 x 42
Location		635 x 38	712 x 320	682 x 303	713 x 246	184 x 376		137 x 144	272 x 131	669 x 310	318 x 206	616 x 113
Faces					70 x 91				31 x 54			
Location					78 x 236				208 x 139			
Bodies	73 x 160	381 x 589	181 x 88	136 x 138	172 x 193	127 x 45	182 x 423	318 x 251	122 x 273	86 x 132	129 x 215	76 x 61
Location	36 x 194	481 x 8	680 x 445	585 x 365	654 x 310	147 x 466	154 x 118	103 x 239	247 x 166	655 x 342	287 x 241	580 x 147
Bodies					203 x 228				127 x 253	88 x 195		
Location					498 x 313				174 x 179	566 x 290		

APPENDIX III SOCIAL TASKS: ADDITIONAL ANALYSES

III.1 Sub-sample analyses

In this section, further analyses are described for both the pop-out and social preferential looking tasks based upon the sub-sample described in Chapter Seven.

III.1.1 Pop-out task

First fixation data in the pop-out task were subject to a data cleaning procedure in which first fixation times were excluded if less than 100ms. This was to eliminate first fixations which were anticipatory – i.e. planned in advance of stimulus onset. This process entails a risk, in cases where the second fixation (i.e. the first *planned* fixation) is in the same AOI as the first *anticipatory* fixation, that the true TTF is not recorded. Therefore, a validity check was carried out on TTF data, in which the location of the first fixation was also identified from visual inspection of the gaze plot. Using this method, there was no significant difference in the mean percentages of first fixations to each AOI between groups. This means that differences / lack of differences in *timing* of first fixations between the two infant groups cannot be explained by differences in *apparent location* of first fixations between the two groups. This was calculated as the mean percentage of first fixations to that AOI as a percentage of the total number shown. There was no significant difference between groups for any of the five AOIs using Mann-Whitney *U* tests as shown in Table III.1.

III.1.2 Social Preferential Looking

In the social preferential looking task, an image wise analysis was undertaken examining the proportion of fixation to the face and bodies within the social half of the image relative to the size of the AOI. A one-sample t-test showed that both groups differed significantly from one (which indicates a random looking pattern) for the faces and not the bodies: preterm fixation to bodies ($p = 0.307$) and faces ($p = 0.023$) and term fixation to bodies ($p = 0.06$) and faces ($p = 0.002$). Furthermore, fixations differed significantly between groups for the faces ($p = 0.003$) but not the bodies ($p = 0.498$) using a paired sample t-test.

Table III.1 First fixation location by AOI, medians and IQR shown with the corresponding p-value.

	Preterm <i>Median % (IQR)</i>	Term <i>Median % (IQR)</i>	p-value
Car	14 (0 - 29)	14 (0 - 29)	0.80
Face	29 (14 - 43)	29 (14 - 44.75)	0.403
Bird	7 (0 - 14)	14 (0 - 14)	0.569
Face-Noise	14 (0 - 26)	14 (0 - 14)	0.445
Phone	0 (0 - 14)	7 (0 - 14)	0.293

APPENDIX IV: ORIGINAL COPIES OF PUBLISHED AND ACCEPTED PAPERS

The original format of the following first author papers are shown in this appendix. Moore et al. (2014) is reproduced from Elsevier with permission and Telford et al (2016) is reproduced from John Wiley and Sons under the Creative Commons Attribution License.

1. Moore EJ and Boardman JP. Modifiable risk factors for preterm brain injury. *Paediatrics and Child Health*, 2014, 24 (9), 401 - 406.
2. Telford EJ, Fletcher-Watson S, Gillespie-Smith K, Pataky R, Sparrow S, Murray IC, O'Hare A, Boardman JP. Preterm birth is associated with atypical social orienting in infancy detected using eye tracking. *Journal of Child Psychology and Psychiatry*, 2016, 57 (7), 861 - 868.
3. Telford EJ, Cox SR, Fletcher-Watson S, Anblagan D, Sparrow S, Pataky R, Quigley A, Semple SI, Bastin ME, Boardman JP. A latent measure explains substantial variance in white matter microstructure across the newborn human brain. *Brain Structure and Function*, 2017, *in press*.

Modifiable risk factors for preterm brain injury

Emma J Moore
James P Boardman

Abstract

The prevalence of preterm birth is increasing globally and it is a leading cause of neurodevelopmental impairment in childhood. Preterm brain injury consists predominantly of: white matter disease, which may be diffuse or cystic and is usually accompanied by grey matter alterations; and haemorrhagic lesions (germinal matrix haemorrhage–intraventricular haemorrhage).

The evidence base for neuroprotective strategies has grown in recent years. Antenatal interventions include the use of corticosteroids and magnesium sulphate, and organisation of maternity services so that early postnatal transfer is avoided. Postnatal interventions associated with improved neurological outcome include delayed clamping of the umbilical cord, respiratory management strategies that reduce the incidence of pneumothorax and bronchopulmonary dysplasia, avoidance of hypotension and hypocarbia, feeding practices that promote human milk intake, caffeine therapy, avoidance of early relatively high dose postnatal dexamethasone, and minimising the incidence of postnatal sepsis. In this review, we describe the predominant forms of preterm brain injury in the current era and consider the evidence base for clinical practices designed to reduce brain injury and adverse outcome after preterm birth.

Keywords brain; magnetic resonance image; neonatal; neonate; preterm; white matter

Introduction

Fifteen million children are born at less than 37 weeks' of gestation around the world each year and this number is rising. The rate of preterm birth ranges from 5 to 18% by country; in the United Kingdom the figure is 7–8% of all deliveries. Globally, preterm birth is a leading cause of death, and among survivors the rates of disability are high.

The most informative UK data about the survival and later health of extremely premature infants comes from the EPICure studies: EPICure 1 collected data on all deliveries in the UK and Ireland between 20 and 25⁺⁶ weeks' gestation over a 10 month period in 1995, and the EPICure 2 study collected perinatal data for babies born between 22 and 26⁺⁶ weeks in England during 2006. Overall, rates of survival to hospital discharge increased

from 40% in 1995 to 53% in 2006, but the risk of disability is high: 14% of the 2006 cohort had cerebral palsy when assessed at 3 years and developmental quotients were lower than those of the general population. These data are consistent with observations from other countries, which report that 5–10% of all very low birth weight (VLBW, less than 1500 g) infants develop cerebral palsy and 25–50% develop cognitive, behavioural, attentional, and/or social difficulties.

Here, we will review the common forms of preterm brain injury and consider the factors that promote resilience to injury and improve long-term outcome.

Types of preterm brain injury

White matter disease of prematurity

Over the past 15 years there has been a paradigm shift in understanding of the importance of white matter disease of prematurity, with greater appreciation of diffuse white matter disease as well as the focal cystic form of periventricular leukomalacia (PVL) (Figure 1). The focal form represents the classic description of coagulation necrosis of all cellular elements leading to cystic degeneration in a periventricular distribution. This pattern of injury is strongly associated with cerebral palsy (usually spastic diplegia), cerebral visual impairment, and cognitive impairment. The prevalence of cystic PVL has declined over the past twenty years, and now affects 2–5% of VLBW children.

Diffuse white matter disease is characterized by loss of premyelinating oligodendrocytes (pre-OLs) and subsequent hypomyelination with astrogliosis and microgliosis. The neuropathological description has come from experimental models and the post-mortem study of human tissue. It is thought that the diffuse abnormality in signal intensity on magnetic resonance imaging (MRI) commonly seen among preterm infants at term equivalent age (and quantifiable using diffusion tensor imaging, DTI) may be an image marker of diffuse white matter disease (Figure 1). MRI evidence of diffuse white matter disease is seen in around one half to two thirds of preterm infants at term equivalent age, and because this is similar to the prevalence of later cognitive impairment, this pattern of injury is now a focus of research attention as a neural substrate for impairment.

The pathogenesis of white matter disease of prematurity centres on the vulnerability of the pre-OL and involves two upstream processes – cerebral ischaemia and systemic infection/inflammation – which activate three downstream mechanisms to converge on pre-OL injury: microglial activation, glutamate-mediated excitotoxicity, and release of reactive oxygen and nitrogen species (see review by Volpe in further reading list).

Punctate white matter lesions

These are small areas of increased signal intensity on T1 weighted MRI, usually situated in the corona radiata, the posterior periventricular white matter, and the optic radiation. They occur in around one quarter of very preterm infants and are seen more frequently in the preterm period than at term equivalent age, which suggests a transitory course. The aetiology is uncertain. Although they are not known to predict poor outcome, they are associated with altered DTI measures, and further follow-up studies are required to assess their clinical significance.

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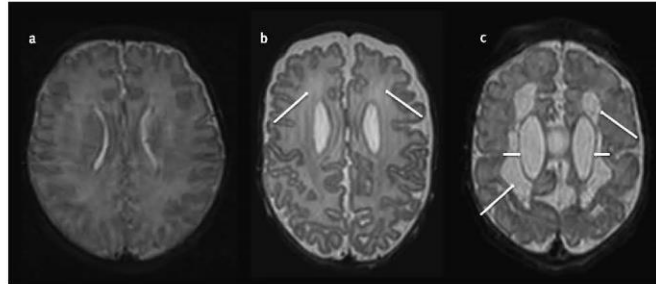


Figure 1 T2 weighted axial images at the level of the lateral ventricles from: (a) a healthy infant born at 39⁺¹ weeks with images acquired on day 16 after birth; (b) an infant born at 25⁺³ weeks with image acquisition at 42⁺¹ weeks' PMA; and (c) an infant born at 26⁺⁰ weeks, with images acquired at 39⁺³ weeks PMA. Figure (b) shows features that are common among preterm infants at term equivalent age including enlargement of the ventricular system and extracerebral space and diffuse excessive high signal intensity in the white matter (arrows) compared with (a). Figure (c) shows areas of cystic periventricular leucomalacia (long arrows) distinct from the lateral ventricles (short arrows).

Evidence from experimental, pathological and neuroimaging studies shows that white matter disease is not limited to the pre-OL population but that injury to the white matter also affects neurons and is associated with structural alterations in cortical grey matter, the deep grey matter nuclei, the brainstem and the cerebellum. These observations suggest that preterm brain injury disturbs the *connectivity* of developing neural systems.

Haemorrhagic lesions

Germinal matrix – intraventricular haemorrhage (GMH-IVH): GMH-IVH describes the spectrum of haemorrhagic lesions that originate with a bleed in the subependymal germinal matrix, a structure that lies over the head of the caudate nucleus predominantly, but also in the periventricular zone. It is most prominent between 24 and 34 weeks' gestation, with almost complete regression by term. It is populated with neuroblasts and glioblasts and contains a capillary bed that is supported by stromal tissue. Haemorrhage at this site can be limited to the germinal matrix ('grade 1' according to the Papile classification), or extend into the lateral ventricle without causing distension (uncomplicated GMH-IVH/Papile grade 2), or extend into the ventricle leading to enlargement (complicated GMH-IVH/Papile grade 3). If GMH-IVH leads to a progressive enlargement of the ventricles over time so that the ventricular index exceeds 97th centile for gestation, then the term post-haemorrhagic ventricular dilatation is used.

Venous drainage of the deep white matter converges on the terminal vein, which runs through the germinal matrix. If haemorrhage in the germinal matrix disrupts venous return through the terminal vein, this can lead to obstruction of the medullary veins of the deep white matter leading to venous infarction of parenchymal tissue with or without a haemorrhagic component. Typically this occurs in a characteristic distribution, which can be visualized on ultrasound as a 'wedge-shape' adjacent to the lateral ventricle in the coronal plane. Although the term grade 4 IVH has been applied to this lesion in the past, it is important to recognize that this is not an extension of an IVH, but rather the consequence of venous infarction, and the term haemorrhagic parenchymal infarction (HPI) is a more suitable description if

imaging or post-mortem examination confirms haemorrhage in the affected area.

Most GMH-IVH occurs in the first 72 hours after birth and is strongly associated with younger gestational age. There is evidence of a decline in the prevalence of GMH-IVH over the past two decades. Uncomplicated GMH-IVH is not usually associated with significant impairment, however the risk of neurodevelopmental impairment increases to around 50% if ventricular dilatation develops and is around 80% if a shunt is required. Outcome following HPI is determined by site and size of the lesion: frontal lesions anterior to the trigone may not lead to significant motor impairment, whereas lesions posterior to the trigone are associated with hemiplegic cerebral palsy. HPIs that degenerate into porencephalic cysts are associated with seizures and cognitive impairment as well as motor impairment.

Cerebellar haemorrhage

MRI allows improved visualisation of the posterior fossa compared with conventional ultrasound approaches through the anterior fontanelle, and this has led to greater appreciation of the prevalence of cerebellar haemorrhage as a complication of preterm birth. It is seen in 10–15% of preterm infants and is specifically associated with motor and cognitive deficits.

Modifiable risk factors for preterm brain injury

Antenatal and intra-partum factors

Place of delivery: delivery of preterm infants in centres that deliver a high volume of neonatal intensive care activity is associated with improved outcomes. This has been one of the leading drivers for the reorganization of neonatal care into managed clinical networks (MCNs) in the UK. In the MCN model groups of hospitals work collaboratively to deliver different levels of specialist care, ensuring that intensive care is delivered in centres with the greatest experience, and that transfer back to the local hospital for ongoing care after the period of intensive care is over is facilitated. One of the outcomes that is improved by avoiding early postnatal transfer of VLBWs is IVH. The National Audit Office and the National Institute for Health and

Clinical Excellence suggest that maternity and neonatal services should work together to ensure that *in utero* transfer takes place before delivery if it is safe for the mother so that acute postnatal transfer of infants of low gestational ages can be avoided.

Antenatal corticosteroids: antenatal corticosteroids given to women at risk of threatened preterm labour are associated with reductions in neonatal death, respiratory distress syndrome (RDS) and IVH, and are safe for the mother. A Cochrane review of 21 studies (3885 women and 4269 infants) found that antenatal steroids reduced the risk of death by 31% (95% CI 19–42%), of IVH by 46% (95% CI 31–67%), and of RDS by 44% (95% CI 31–57%). Other neonatal benefits include reductions in necrotizing enterocolitis, need for respiratory support, and early-onset infection. Therefore the Royal College of Obstetricians and Gynaecologists (RCOG) recommend that all women who present with threatened preterm labour between 24⁺⁰ and 34⁺⁶ weeks' should receive antenatal corticosteroids.

There are likely survival benefits to the neonate born at 23 weeks who has been exposed to antenatal steroids, so if following discussion with obstetric colleagues and parents, a decision has been made to offer intensive care to a baby born at this gestation then our practice is to counsel in favour of giving the mother corticosteroids prior to delivery.

Antenatal magnesium sulphate (MgSO₄): a number of case-control studies describe an association between exposure to antenatal MgSO₄, given for maternal reasons, and a reduction in the risk of cerebral palsy. The apparent neuroprotective effects seen in the early observational studies have been tested in randomized controlled trials where antenatal MgSO₄ versus placebo is given for the purpose of fetal neuroprotection. There is unequivocal evidence of benefit when given to mothers who are at risk of preterm labour at less than 30 weeks' gestation. An updated Cochrane systematic review included five trials (6145 babies) and showed that 63 mothers (95% CI 43–155) need to be treated with MgSO₄ for one baby to avoid cerebral palsy.

Based on these figures, and with no evidence of long-term harm to mother or infant, several countries have developed clinical practice guidelines that endorse or support the use of antenatal MgSO₄ for fetal neuroprotection in women who are at risk of preterm delivery. A Scientific Impact Paper (No.29) from the RCOG concludes that if clinicians plan to use antenatal MgSO₄ for fetal neuroprotection then they should base local guidelines on the National Clinical Practice Guideline published by the University of Adelaide in 2010. This recommends use of antenatal MgSO₄ in women at risk of early preterm (GA less than 30 weeks), imminent birth (early preterm birth is planned or definitely expected within 24 hours). The guideline recommends an intravenous 4 g loading dose over 20–30 minutes followed by a 1 g/hour maintenance infusion to continue for 24 hours or until birth, whichever occurs soonest.

Trials and follow-up studies are ongoing to determine whether antenatal MgSO₄ is protective at later gestations and whether it confers benefit for long-term cognitive function.

Placental transfusion: increasing the volume of placental transfusion to the newborn by delayed clamping of the umbilical cord is associated with a number of health benefits to the preterm neonate. A recently updated Cochrane review of fifteen studies

(738 infants aged between 24 and 36 weeks' gestation at birth) found that delayed cord clamping was associated with a significant risk reduction for all grades of IVH with RR 0.59 (95% CI 0.41–0.85), as well as reducing the number of transfusions required for anaemia (RR 0.61, 95% CI 0.46–0.81) and the risk of necrotizing enterocolitis (RR 0.62, 95% CI 0.43–0.90), when compared with immediate clamping of the cord. Although there is a slight increase in the peak bilirubin in infants who have experienced delayed cord clamping (mean difference 15.01 micromol/litre, 95% CI 5.62–24.40), it is unlikely that this will lead to harm in settings where accurate and regular surveillance of hyperbilirubinaemia is carried out, and where there is access to effective phototherapy if levels exceed gestational age appropriate thresholds.

Neonatal factors

General neonatal care: survival rates after birth at young gestational ages have improved between 1996 and 2006. During this time period there have been changes to the way services are organized, and a number of evidence based practice changes have occurred or become embedded over this time period: more widespread use of antenatal steroids; occlusive wrapping to prevent hypothermia immediately after birth, earlier and more frequent use of surfactant replacement treatment, and a reduction in the use of postnatal dexamethasone to wean babies from mechanical ventilation. It is plausible that some of these measures have also had a positive effect on the rates of preterm brain injury, since some are known to be associated with specific adverse outcomes: lack of antenatal steroids, postnatal transfer and respiratory distress syndrome (especially if complicated by pneumothorax) are all associated with GMH-IVH; and relatively high dose dexamethasone early in the postnatal period, is associated with cerebral palsy.

Other general measures are important for protecting the preterm brain including ventilation strategies that minimize risk of pneumothorax and bronchopulmonary dysplasia, and the avoidance of hypoglycaemia, hypothermia, hypotension and hypocarbia.

Feeding: the benefits of breast feeding term infants are unequivocal and underpin the World Health Organisation recommendation that all infants should be exclusively breast fed from birth until 6 months. Optimal enteral feeding of the VLBW infant is challenging because unmodified human milk does not meet the VLBW infant's requirements for protein, energy, sodium, calcium, phosphorus and magnesium, trace elements and vitamins.

The physician has a number of options to help deliver nutrient requirements including human milk (mother's own preterm milk; donor milk; fortified human milk; and human milk formulas), and term and preterm infant formulas. The advantages of using human milk include reduced risk of necrotizing enterocolitis, improving gastrointestinal tolerance, and possible long-term modulating effects on cardiovascular, metabolic health and immune modulation.

There is also evidence that human milk feeds are neuroprotective for preterm infants. In early seminal studies, preterm infants fed with maternal expressed breast milk had higher developmental quotients at 18 months and higher IQs at 7 years compared to infants fed on other diets, and in sophisticated MRI studies of adolescents born preterm white matter volume in

males correlates positively with neonatal human milk exposure. Many questions remain about the optimal timing of introducing enteral feeds, the pace of increase, the role of fortification, the macronutrient components of early parenteral nutrition, and the role of donor milk in supporting the preterm infant and optimising brain outcomes, but the evidence of neurodevelopmental benefit for infants fed human milk is compelling, and mothers should be made aware of this during postnatal counseling after preterm delivery.

Caffeine: caffeine is widely used for the treatment of apnoea of prematurity and because it reduces the rate of bronchopulmonary dysplasia (BPD) in VLBW infants. The CAP (Caffeine for Apnoea of Prematurity) study, which randomly assigned 2006 infants with birth weights of 500–1250 g during the first 10 days after birth to receive either caffeine or placebo, found a reduction in BPD in the intervention group, but also showed that the intervention group were less likely to have cerebral palsy (OR 0.58, 95% CI 0.39–0.87) or cognitive delay (OR 0.81, 95% CI 0.66–0.99) at 18–21 months, and improvements in some aspects motor function and visual perception were sustained at 5 years. In the original CAP trial, caffeine was continued to a median age of 34 weeks' postmenstrual age, so it seems prudent to continue

caffeine therapy until this age if the neuroprotective effects are to be realized.

Minimise exposure to infection/inflammation: perinatal infection, including chorioamnionitis and early-onset (less than 72 hours after birth) and late-onset (more than 72 hours after birth) sepsis are risk factors for white matter disease, and are closely associated with neurodevelopmental impairment. In a meta-analysis by Wu and colleagues, clinical chorioamnionitis was associated with cerebral palsy (RR 1.9, 95% CI 1.4–2.5) and cystic PVL (RR 3.0, 95% CI 2.2–4.0) in preterm infants.

Postnatal sepsis is very common among VLBWs, with rates of early-onset sepsis around 2–5% and late-onset around 20–40%. The National Institute of Child Health and Human Development Neonatal Research Network in the United States assigned 6093 ELBW infants to one of five groups: uninfected; clinical evidence of sepsis; blood culture positive sepsis; sepsis and necrotizing enterocolitis; and meningitis with or without sepsis. When compared with uninfected infants those in the four sepsis groups had significantly increased odds of neurodevelopmental impairments including cerebral palsy (range of significant ORs 1.4–1.7), low Bayley Scales of Infant Development II scores on the mental development index (ORs 1.3–1.6) and psychomotor development

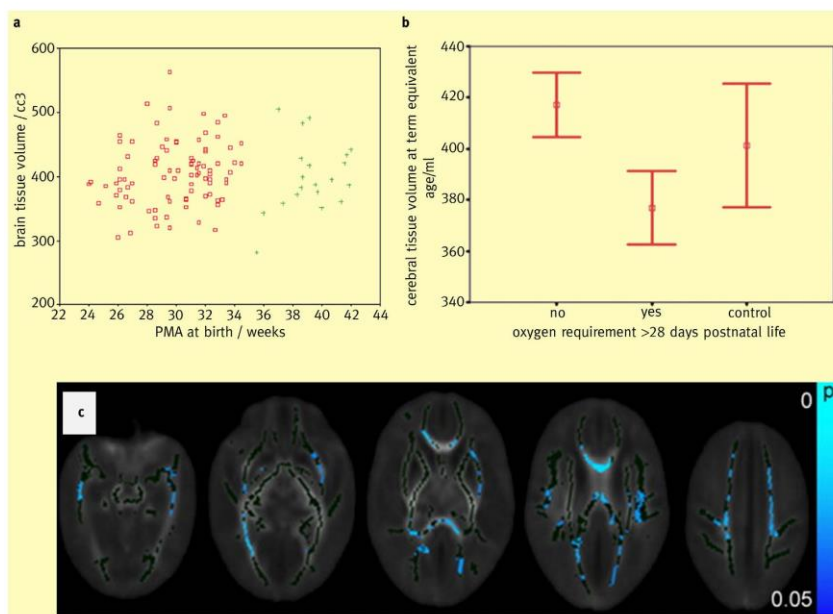


Figure 2 Association between respiratory morbidity and cerebral development. Whole brain volume is preserved in the majority of preterm infants at term equivalent age, and does not differ significantly from brain volumes of healthy term controls (a). However preterm infants with prolonged need for supplemental oxygen have lower brain volumes than preterm infants without this complication (b). In a two group comparison of preterm neonates with and without BPD, there were significant alterations in white matter microstructure associated with BPD. Areas of blue show regions at the centre of white matter tracts where fractional anisotropy, a measure of tract integrity, is reduced in association with BPD (c). Figures (a) and (b) are from Boardman et al. *Ann Neurol* 2007, reproduced with permission from John Wiley and Sons. Figure (c) is from Ball et al. *Neuroimage* 2010, reproduced with permission from Elsevier.

index (ORs 1.5–2.4), and vision impairment (ORs, 1.3–2.2). Data from the Epipage study group show that the effects of neonatal sepsis exposures are cumulative for cerebral palsy and persist to 5 years of age.

Although the mechanistic link between perinatal inflammation or sepsis and cerebral injury is a subject of ongoing research and may yield new treatment strategies, there is little doubt that prevention is vitally important. Intra-partum antibiotic prophylaxis is effective at reducing early-onset infection with Group B streptococcus in women whose infants are known to be at risk, and local systems should be in place to ensure eligible women are identified and offered this treatment in labour.

Quality improvement initiatives can be highly effective at reducing the prevalence of late-onset sepsis among VLBWs. A detailed description of the care bundles and practices that are effective is beyond the scope of this review, but in summary the following strategies should be considered: systematic collection of high quality sepsis data and benchmarking; rigorous attention to hand hygiene including the use of gloves for handling VLBWs; care bundles for central and peripheral line insertion and maintenance; chlorhexidine solution for skin antisepsis; promotion of human milk feeds; bathing protocols; implement strategies for preventing ventilator (including nasal CPAP) associated pneumonia; use antifungal prophylaxis; improve antibiotic stewardship; avoid over-crowding and provide staff with education and feedback.

Minimise respiratory morbidity: bronchopulmonary dysplasia is an independent predictor of poor neurodevelopmental outcome, and in a primate model of premature birth, prolonged exposure to ventilation is associated with adverse cerebral outcomes including reduced oligodendroglia number, volume loss and white matter injury. We have shown that brain volumes are reduced in preterm infants with an oxygen requirement that persists beyond 28 days and that white matter microstructure is altered in preterm infants with bronchopulmonary dysplasia (Figure 2). The mechanistic link between lung and brain injury is uncertain, and could include factors related to nutrition, inflammation, or fluctuating hyperoxia; but the associations described suggest that interventions designed to improve respiratory outcomes should also be assessed for neuroprotective effects.

Future directions

Advances in perinatal medicine have improved the survival of VLBWs, and understanding about how to protect the preterm brain has increased. It is important that evidence based strategies are translated into clinical practice. Basic research in to the neurobiology of preterm brain injury has led to the development of new therapeutic strategies. Some of these are already at the stage of clinical trial, including melatonin, erythropoietin, IGF-1, optimal management of the umbilical cord at birth, nutrition, tissue perfusion, and transfusion practice. It is likely that technical advances in the acute assessment of the cerebral perfusion, and quantitative high resolution MRI and DTI will play significant roles in assessing the effect of interventions on the developing brain and so expedite the translation of new neuroprotective strategies to the bedside.

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Practice points to minimize the risk of preterm brain injury among very low birth weight infants

- Antenatal
 - Antenatal steroids for eligible women
 - Antenatal magnesium sulphate for eligible women
 - Ensure that women who are eligible for intra-partum antibiotic prophylaxis against neonatal group B streptococcus infection are identified and offered the intervention
 - Organise for delivery of very preterm infants in a facility with a level 3 NICU
 - Neonatal
 - Prevent hypothermia at delivery through use of occlusive wrap for all infants less than 30 weeks
 - Delay clamping of the umbilical cord after preterm birth
 - Early surfactant therapy
 - Routine use of caffeine
- Use a low dose regimen if postnatal dexamethasone is considered necessary
 - Avoid acute postnatal transfer when possible
 - Avoid hypocarbia
 - Avoid hypoglycaemia
 - Avoid hypotension
 - Avoid postnatal sepsis
 - Promote use of human milk feeds
 - Take measures to reduce the prevalence of bronchopulmonary dysplasia

Preterm birth is associated with atypical social orienting in infancy detected using eye tracking

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Background: Preterm birth is closely associated with neurocognitive impairment in childhood including increased risk for social difficulties. Eye tracking objectively assesses eye-gaze behaviour in response to visual stimuli, which permits inference about underlying cognitive processes. We tested the hypothesis that social orienting in infancy is altered by preterm birth. **Methods:** Fifty preterm infants with mean (range) gestational age (GA) at birth of 29⁺¹ (23⁺²–33⁺⁰) weeks and 50 term infants with mean (range) GA at birth 40⁺² (37⁺⁰–42⁺³) weeks underwent eye tracking at median age of 7 months. Infants were presented with three categories of social stimuli of increasing complexity. Time to first fixate (TFF) and looking time (LT) on areas of interest (AoIs) were recorded using remote eye tracking. **Results:** Preterm infants consistently fixated for a shorter time on social content than term infants across all three tasks: face-scanning (fixation to eyes minus mouth 0.61 s vs. 1.47 s, $p = .013$); face pop-out task (fixation to face 0.8 s vs. 1.34 s, $p = .023$); and social preferential looking (1.16 s vs. 1.5 s $p = .02$). Time given to AoIs containing social content as a proportion of LT at the whole stimulus was lower in preterm infants across all three tasks. These results were not explained by differences in overall looking time between the groups. **Conclusions:** Eye tracking provides early evidence of atypical cognition after preterm birth, and may be a useful tool for stratifying infants at risk of impairment for early interventions designed to improve outcome. **Keywords:** Social orienting; development; preterm infant; eye tracking.

Introduction

Globally, preterm birth [delivery at <37 weeks' gestational age (GA)] affects around 10% of deliveries (Blencowe et al., 2012) and is a leading cause of neurocognitive impairment and educational underperformance (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Delobel-Ayoub et al., 2009; MacKay, Smith, Dobbie, & Pell, 2010; Quigley et al., 2012). The preterm neurocognitive profile includes global and specific learning difficulties, executive dysfunction, inattentiveness, social difficulties and increased likelihood of screening positive for, or receiving a diagnosis of autism spectrum disorder (ASD; Johnson et al., 2010; Johnson & Marlow, 2011; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Guy et al., 2015). Identification in infancy of children with atypical development would enable targeting of early interventions designed to improve outcome, when they are likely to be most effective (Warren et al., 2011; Wass, Porayska-Pomsta, & Johnson, 2011; Koegel, Koegel, Ashbaugh, & Bradshaw, 2014).

Oculomotor orienting (gaze) behaviour is a critical control point for intake of visual information and its assessment in response to visual stimuli can be used to make inferences about underlying cognitive processes including preference, memory, attention and processing speed (Liversedge & Findlay, 2000; Fletcher-Watson, Findlay, Leekam, & Benson, 2008; Fletcher-Watson, Leekam, Benson, Frank, &

Findlay, 2009; Johnson, Senju, & Tomalski, 2015). In the developmental trajectory of social cognition visual attention is given to faces very soon after birth, with specific attention paid to the eye region; and later in infancy at around 6–9 months a preference for looking at faces within multiple object arrays or animated scenes develops (Johnson, Dziurawiec, Ellis, & Morton, 1991; Farroni, Csibra, Simion, & Johnson, 2002; Gliga, Elsabbagh, Andravizou, & Johnson, 2009; Frank, Vul, & Johnson, 2009); for review see (Johnson et al., 2015). This trajectory is altered from 2 to 12 months in children who go on to receive a diagnosis of ASD, which suggests that gaze behaviour may be one of the earliest markers of atypical social cognition (Young, Merin, Rogers, & Ozonoff, 2009; Ozonoff et al., 2010; Chawarska, Macari, & Shic, 2012; Jones & Klin, 2013; Chawarska, Macari, & Shic, 2013; Wass et al., 2015).

Eye-tracking provides a nonbiased assessment of gaze in response to visual stimuli that is highly resolved in time (milliseconds) and space, which enables calculation of time to first fixate (TFF) and looking time (LT) to predefined areas of interest (AoI). It is well suited to studying gaze behaviour during infancy because it can be applied to nonverbal populations and has high test-retest reliability for individual differences in this age group (Wass & Smith, 2014; Gillespie-Smith et al., 2015).

Based on studies of the developmental trajectory of social cognition and the clinical phenotype of children and adults born preterm, we hypothesised that preterm birth would be associated with alterations in

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cognition detectable during infancy. We used eye tracking to measure gaze behaviour because of its utility for assessing social phenotypes in this age group. We assessed children at a median of 7 months of age, and report differences in orienting to social cues between those born preterm compared with age-matched peers born after 37 weeks' gestation.

Methods

Participants

Preterm infants (GA at birth <33⁺0 weeks) were recruited from the Royal Infirmary of Edinburgh, and healthy term control infants (≥37 weeks' GA) were recruited from the postnatal wards or community groups between February 2013 and April 2015. A subset of the control infants have been reported previously (Gillespie-Smith et al., 2015). The Scottish Index of Multiple Deprivation (SIMD) was used to characterise deprivation. The SIMD is the official Government tool used to identify areas of deprivation: it divides Scotland into around 6,505 areas each containing around 350 households and assigns an index to each area based on multiple measures of deprivation. The data are ranked from most to least deprived and are presented as quintiles. Exclusion criteria: major congenital malformations, chromosomal abnormalities, congenital infection and infants with major overt parenchymal lesions (cystic periventricular leukomalacia, haemorrhagic parenchymal infarction) and posthaemorrhagic ventricular dilatation. Ethical approval was obtained from the National Research Ethics Service (South East Scotland Research Ethics Committee 02) for all participants recruited from hospital services; ethical approval for the recruitment of community participants was granted by the School of Education Ethics Sub-Committee, University of Edinburgh. Informed written parental consent was obtained.

Eye-tracking assessment

Participants were invited for assessment at 6–10 months (corrected gestational age was used for the preterm group because this is the standard practice for neurodevelopmental assessment of children born at <32 weeks until the age of two years (Johnson & Marlow, 2006)). Infants were positioned on their caregiver's lap 50–60 cm from a display monitor used to show visual stimuli. Eye movements were detected using a Tobii® x60 eye-tracker and Tobii Studio® (version 3.1.0) software was used to present stimuli and record eye movements for analysis. Images were presented on a display monitor with a resolution of 1,440 × 900 pixels. The Tobii® x60 system tracks both eyes to a rated accuracy of 0.3 degrees at a rate of 60 Hz. Prior to data collection, eye-tracking calibration was performed using a five-point system. Preterm infants were screened for deficits in visual acuity (VA) using Keeler® acuity cards prior to eye tracking, and infants were excluded if VA was below the estimated norm for age (Speedwell, 2003).

Tasks

We presented three tasks of increasing complexity (Figure 1) that have been validated (Gliga et al., 2009; Gillespie-Smith et al., 2015). Each task contained different stimuli and these were presented in blocks with variable order. Attention grabbers (cartoon images of toys on a black background with sound effects) were presented in between each block to maintain infant attention to the screen.

Task 1: Face Scanning. Photographs of natural faces with a neutral expression (three male, three female). Each stimulus

measured approximately 18 × 24 cm. Each stimulus was viewed for 10s and each block contained two stimuli.

Task 2: Pop-out. Photographs of a natural face and a 'face-noise' image alongside nonsocial content against a white background in a grid-like array (Gliga et al., 2009). The nonsocial content included pictures of mobile phones, cars and birds. The 'face-noise' image is an artificial scramble of the pixels in the face-stimulus, thus having the same low-level visual properties while being unrecognisable as a face. A total of seven stimuli were presented measuring between approximately 25 × 20 cm. Each stimulus was viewed for 10s and each block contained two or three stimuli.

Task 3: Social preferential looking task contained two neighbouring photographs with each pair consisting of a real-world scene: one with social content (one or two children) and one without (no people) (Fletcher-Watson et al., 2008). A total of 12 stimuli were presented measuring approximately 27 × 19 cm. Each stimulus was viewed for 5s and each block contained four stimuli.

Statistical analysis

Looking time at Aols, LT at the whole stimulus and TFF Aofs were analysed for each task, as measures of sustained attention and attentional priority. TFFs <100 ms were excluded: in these cases it is likely that the saccade started prior to image onset (Liversedge & Findlay, 2000). Similarly, LTs <500 ms were excluded because this was not considered a sufficient quantity of data to represent the result of a series of planned eye movements to particular Aols. Normality was assessed using measures of skew and by visual inspection of histograms and QQ plots. For normally distributed data, mean and standard deviation (*SD*) are reported and for non-normally distributed data, the median and interquartile range (*IQR*) are reported. For group-wise comparisons of normally distributed variables independent sample *t*-test was used, and for skewed data the Mann-Whitney *U* test was used. Repeated measures ANOVA and related samples Wilcoxon signed-rank test were used to investigate within-group differences in normally distributed and skewed data, respectively.

For the face-scanning task, a difference score of LT on eyes minus mouth was calculated. For all tasks, as well as analysing raw LT scores, a proportional looking score was calculated as the ratio of LT per Aol to LT at whole stimulus [proportional looking score = LT (Aol)/LT(whole stimulus)]. Group differences in proportional looking scores were investigated using the Mann-Whitney *U* test. To investigate differences in overall attentiveness between groups, total LT to the monitor was recorded for each task. Two-tailed *p*-values are reported and *p* < .05 was considered statistically significant. Statistical analyses were performed using SPSS version 21 (Chicago, IL).

Results

Participant characteristics

Fifty preterm and 51 term eligible infants were assessed with eye tracking. One participant born at term was excluded due to poor data acquisition, leaving 50 preterm infants and 50 term infants (Table 1 for participant characteristics).

Of the preterm group, 94% had been exposed to antenatal steroid for threatened preterm labour and 50% had been exposed to antenatal magnesium sulphate for neuroprotection. A total of 36% had bronchopulmonary dysplasia (defined as need for supplemental oxygen at 36 weeks' GA), but none was

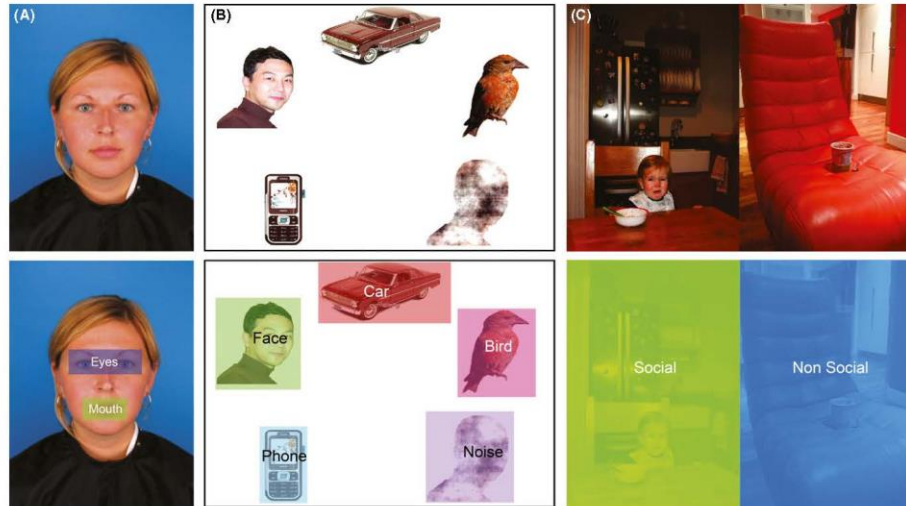


Figure 1 Examples of stimuli for each task with accompanying areas of interest (AoI): (A) Face Scanning; (B) Pop-out; (C) Social Preferential Looking

Table 1 Demographic characteristics of participants

Characteristic	Preterm (n = 50)	Term (n = 50)
Mean gestational age at birth/weeks (range)	29 ⁺¹ (23 ⁺² –33 ⁺⁶)	40 ⁺² (37 ⁺⁰ –42 ⁺³)
Mean birth weight /kg (SD)	1.12 (0.26)	3.49 (0.66)
Median age/ months (IQR)*	7.72 (6.67–8.8)	7.85 (6.87–9.34)
Gender (M:F)	22:28	26:24
Scottish Index of Multiple Deprivation (%)	1 2–4 5 18 68 14	1 2–4 5 8.5 40.4 51.1

IQR, interquartile range.

*Values for the preterm group corrected for gestational age at birth.

oxygen dependent at the time of assessment. One preterm infant had been treated for retinopathy of prematurity. All preterm infants passed the screening test for visual acuity at the time of assessment.

All tasks: overall eye-movement metrics

The overall proportion of trials excluded from control data because LT < 500 ms was 6% for face scanning, 7% for pop-out task and 8% for SPL. The same proportions for preterm infants were 4% for face scanning, 4% for pop-out task and 9% for SPL. These differences were not statistically significant between the groups.

There was no significant group difference in raw LT to the whole stimulus for any task with all *p*-values $\geq .05$ (Table 2).

Eye-gaze behaviours

Task 1: Face scanning. Both groups fixated the eyes more than the mouth (Table 2), but infants born at term had a significantly greater preference for looking at eyes than mouth. The mean difference score in raw LT (eyes – mouth) was 1.47s in controls (*SD* = 1.72) and 0.61s in the preterm group (*SD* = 1.68), *p* = .013 (Figure 2).

There was a group difference in proportional looking to eyes but not mouth: proportional LT eyes median = 0.31 for term infants versus 0.12 for the preterm group (*p* = .039). Term infants had a faster TFF the eyes than the mouth (median 1.97s vs. 4.11s, *p* < .001); and there was no significant difference in this comparison for preterm infants.

Task 2: Pop-out. Term infants showed longer raw LT to the face compared to preterm infants (median 1.34s vs. 0.8s, *p* = .023). This significant difference between groups was also apparent for the proportional looking score to the face (LT to Face AoI / LT to whole stimulus): median = 0.34 for term infants versus 0.16 for the preterm group, *p* = .036).

There was a difference in raw LT to the Bird AoI such that term infants fixated for longer than preterm (median 0.22s vs. 0.13s, *p* = .04), but the proportional LT to the bird was not significantly different between the groups. There were no differences in looking pattern for any other AoI (Table 2).

TFF the Face AoI did not differ between groups, however term infants fixated on the face-noise more quickly than preterm infants (median 2.98s vs.

Table 2 Raw looking time, proportional looking scores and time to first fixate areas of interest for each task for preterm and control infants

Task	Measure	AOI	Preterm Time/s	Term Time/s	p-value	Preterm Proportional looking score (IQR)	Term Proportional looking score (IQR)	p-value
Face-scanning	Looking Time	Eyes	0.49 (0.02-1.86)	1.24 (0.24-2.70)	.045	0.12 (0.00-0.37)	0.31 (0.07-0.51)	.039
		Mouth	0.07 (0.00-0.61)	0.06 (0.00-0.27)	.479	0.02 (0.00-0.11)	0.01 (0.00-0.06)	.388
		Whole display	5.28 (3.83-6.39)	4.96 (3.57-6.14)	.677			
Pop-out	Time to first fixate	Eyes	2.74 (1.43-3.92)	1.97 (1.05-3.35)	.101			
		Mouth	2.66 (1.78-4.69)	4.11 (2.24-6.42)	.058			
		Face	0.80 (0.11-1.57)	1.34 (0.62-2.49)	.023	0.16 (0.03-0.38)	0.34 (0.14-0.47)	.036
Pop-out	Looking Time	Face-Noise	0.13 (0.06-0.30)	0.26 (0.06-0.47)	.170	0.03 (0.01-0.07)	0.04 (0.01-0.10)	.294
		Bird	0.13 (0.00-0.24)	0.22 (0.08-0.36)	.040	0.03 (0.00-0.05)	0.04 (0.01-0.08)	.074
		Car	0.25 (0.11-0.57)	0.21 (0.06-0.43)	.445	0.08 (0.02-0.13)	0.04 (0.02-0.09)	.125
Social Preferential Looking	Looking Time	Phone	0.07 (0.00-0.14)	0.09 (0.04-0.21)	.094	0.01 (0.00-0.03)	0.02 (0.01-0.04)	.210
		Whole display	4.49 (3.34-5.58)	5.28 (3.92-6.41)	.063			
		Face	2.17 (1.20-3.35)	2.03 (1.22-2.97)	.640			
Social Preferential Looking	Time to first fixate	Face-Noise	4.15 (1.90-5.82)	2.98 (1.74-4.26)	.045			
		Bird	3.46 (1.81-5.21)	3.59 (1.99-5.04)	.908			
		Car	3.44 (1.47-4.95)	3.14 (2.05-4.79)	.828			
Social Preferential Looking	Time to first fixate	Phone	3.98 (2.17-6.92)	3.87 (2.54-7.15)	.970			
		Social scene	1.16 (0.61)	1.50 (0.81)	.020	0.46 (0.33-0.61)	0.61 (0.45-0.68)	.012
		Nonsocial scene	0.79 (0.39)	0.74 (0.36)	.503	0.30 (0.24-0.39)	0.28 (0.20-0.34)	.141
Social Preferential Looking	Time to first fixate	Whole display	2.46 (0.63)	2.63 (0.77)	.225			
		Social scene	1.49 (0.73)	1.29 (0.61)	.147			
		Nonsocial scene	1.78 (0.86)	1.63 (0.82)	.401			

Raw values for face scanning and pop-out task are reported as median (IQR), and raw values for social PL are reported as mean (SD). Proportional looking scores are reported as median (IQR). Values in bold indicate $p < 0.05$

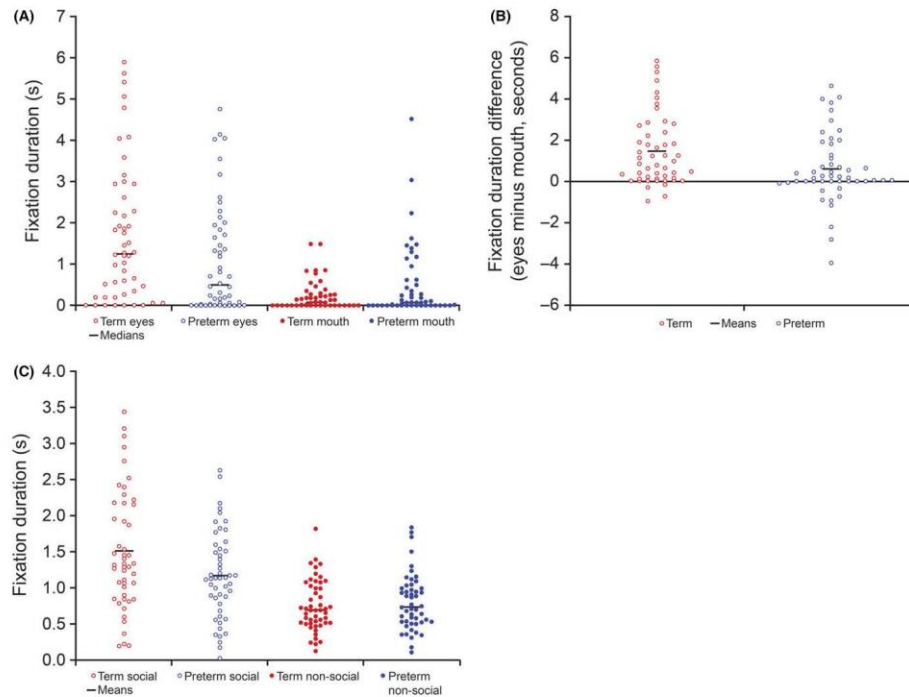


Figure 2 (A) Face scanning looking time by group and Aol; (B) Face scanning looking time with difference between eyes and mouth by group and Aol and (C) social preferential looking, looking time by group and Aol

4.15s, $p = .045$). TFF other Aols in the array did not differ between groups.

Task 3: Social preferential looking. Term infants had a greater raw LT than preterm infants to the image within the stimulus that featured children: mean 1.5s versus 1.16s, $p = .02$ (Figure 2c). There were no differences between groups in raw LT to the nonsocial scene. Using repeated measures ANOVA, a main effect of scene was found ($F(1, 98) = 53.25$, $p < .001$) and there was a scene by group interaction ($F(1,98) = 6.40$, $p = .013$). There was no main effect of group.

There was a significant difference between groups in proportional LT for the social scene (LT to Social Scene Aol / LT to whole stimulus): median = 0.61 for term infants versus 0.46 for the preterm group, $p = .012$.

There was no group difference in TFF social or nonsocial content.

Discussion

Using eye tracking we have demonstrated that infants born preterm have a different social orienting profile to term-born peers, apparent during the first year after

birth. This fixation pattern was consistently observed across three tasks of increasing stimulus complexity. In each task, the proportion of time spent looking at socially informative content was reduced in the preterm group compared with controls. Specifically, the raw and proportional LTs of preterm infants to social content were lower compared with values measured in the control group. Analysis of the pop-out task involves five simultaneous tests, which raises the possibility that shorter LT of preterm infants to the face Aol ($p = .023$) is a false positive result. However, we consider this is unlikely because the effect size was large, and the result is consistent with the significant difference in proportional LT to social content for this task, and with observations from other tasks. We did not apply the Bonferroni correction because test statistics are known to be correlated in this task (Gliga et al., 2009), which violates an assumption of the method and introduces the likelihood of type 2 error.

We found only one difference in time to first fixate social content: term control infants fixated eyes more rapidly than mouths when viewing a static face. Of note, term infants took less time to fixate the 'face-noise' Aol in the pop-out task, which could reflect a preference for social content albeit low-level, or

failure to distinguish a real face from a scrambled face. While we checked that our preterm sample did not have visual acuity deficits, it is implausible to suppose that preterm infants were more capable than controls at detecting the difference between a real and scrambled face in peripheral vision. Thus, we conclude that both TFF observations reflect lack of general preference for looking at social (or social-like) information in preterm infants. Elsewhere, we did not find differences in time to first fixate content, or overall looking time between the groups in any task. Importantly, the proportional looking scores, which reflect attention to social content scaled by overall looking time at the stimulus was higher in term controls, and this finding was consistent across all three tasks. These scores take into account individual differences in overall looking time to the screen, which suggests that visual information processing speed and overall attentiveness do not explain the differences we observed in response to social stimuli.

The propensity to regard the mouth rather than the eyes within the static face is consistent with fixation patterns previously observed in young children either with or at risk of ASD (Chawarska & Shic, 2009) and indeed atypicalities in fixation to social content have been proposed as a potential early marker of later ASD (Young et al., 2009; Ozonoff et al., 2010; Jones & Klin, 2013; Chawarska et al., 2013). The prevalence of ASD in preterm infants is estimated at 4–8% (Hack et al., 2009; Johnson et al., 2010) therefore it is statistically unlikely that our sample contains a large number of infants who will later be diagnosed with ASD. Furthermore, we found no evidence of a split distribution or other evidence suggesting that our results were driven by a subgroup within the preterm sample. Therefore, we hypothesise that the social cognitive patterns seen in this sample may point to a lack of specificity of early social attention atypicalities for ASD. This interpretation is consistent with the observation that early atypical eye-movement behaviour initially associated with ASD diagnostic status is eliminated after adjustment for development level scores (Wass et al., 2015). In other words, some early signs of ASD may not be specific to ASD and could instead be markers of developmental delay.

It is possible that the data presented here reflect the early emergence of impaired social function, which has been described in children with very low birth weight (<1,500 g) despite normal IQ (Williamson & Jakobson, 2014), or they may herald atypical social traits that are reported in adults born preterm who do not reach diagnostic criteria for ASD (Pyhälä et al., 2014). Such traits include difficulties in processing biological motion, facial expressions or social perception (Pavlova, Sokolov, Birbaumer, & Krageloh-Mann, 2006; Wocadlo & Rieger, 2006; Indredavik, Vik, Skranes, & Brubakk, 2008; Taylor, Jakobson, Maurer, & Lewis, 2009). The significance of an early

preference to the mouth within the preterm group requires further investigation. Previous studies have suggested that attention to the mouth region is a predictor of normal language development, but the association is less clear in high-risk groups (Young et al., 2009; Lewkowicz & Hansen-Tift, 2012).

These data show that social orienting in late infancy differs between children born preterm and those born at term. Long-term follow-up of the cohort is planned, which will enable investigation of the place of atypical social orienting in the development of language, and the ontogenesis of the broader preterm neurocognitive phenotype. Future research could focus on determining the sensitivity, specificity and predictive values of these measures for clinically important outcomes such as cognitive impairment or ASD. If measures of early social cognitive impairment are found to have high positive or negative predictive values for important clinical outcomes then they could have a role in diagnostic pathways, or be used to stratify risk status and provide a basis for targeting early interventions designed to improve outcome. Inattention and distractibility are two common features also associated with preterm birth (Hille et al., 2001) and success has been previously demonstrated in improving attentional control among infants under 12 months using eye tracking (Wass et al., 2011). This raises a potential use of eye tracking not just in risk stratification for early intervention trials, but also as an intervention delivery route.

Conclusion

Eye-gaze behaviours in response to stimuli depicting social content differ in infants born preterm compared with healthy term controls. These data suggest the development of social cognition is altered by preterm birth, and that eye tracking may be a useful tool for very early stratification of infants who might benefit from early interventions designed to improve neurocognitive outcome.

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Key points

- Preterm birth is a leading cause of neurocognitive impairment but early diagnosis of difficulty is limited by imprecise diagnostic tools.
- Remote eye tracking in response to visual stimuli can be used to make inference about cognitive processes in preverbal populations.
- Preterm infants have an atypical social phenotype that is present in infancy.
- Eye tracking may be valuable for early stratification of preterm infants at risk of impairment who may benefit from early interventions designed to improve outcome.

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A latent measure explains substantial variance in white matter microstructure across the newborn human brain

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Abstract

A latent measure of white matter microstructure (g_{WM}) provides a neural basis for information processing speed and intelligence in adults, but the temporal emergence of g_{WM} during human development is unknown. We provide evidence that substantial variance in white matter microstructure is shared across a range of major tracts in the newborn brain. Based on diffusion MRI scans from 145 neonates (gestational age [GA] at birth range 23⁺² to 41⁺⁵ weeks), the microstructural properties of eight major white matter tracts were calculated using probabilistic neighborhood tractography. Principal component analyses (PCAs) were carried out on the correlations between the eight tracts, separately for four tract-averaged water diffusion parameters: fractional anisotropy, and mean, radial and axial diffusivities. For all four parameters, PCAs revealed a single latent variable that explained around half of the variance across all eight tracts, and all tracts showed positive loadings. We considered the impact of early

environment on general microstructural properties, by comparing term-born infants with preterm infants at term equivalent age. We found significant associations between GA at birth and the latent measure for each water diffusion measure; this effect was most apparent in projection and commissural fibers. These data show that a latent measure of white matter microstructure is present in very early life, well before myelination is widespread. Early exposure to extra-uterine life is associated with altered general properties of white matter microstructure, which could explain the high prevalence of cognitive impairment experienced by children born preterm.

Introduction

White matter tracts connecting cortical networks are fundamental substrates of higher cognitive function in humans. ‘Disconnection’ of networks, which can be inferred from the microstructural properties of tracts, characterizes a number of diseases and contributes to functional impairment through reduced information transfer efficiency (Bartzokis et al. 2004; Penke et al. 2010; Ritchie et al. 2015b; Ball et al. 2015; Uddin et al. 2013; Liston et al. 2011). Tract connectivity has been widely investigated *in vivo* using diffusion magnetic resonance imaging (dMRI) which is a non-invasive method that provides voxel-wise measures of water molecule diffusion. Since the molecular motion of water in the brain is influenced by biological factors including macromolecules, axonal diameter, membrane thickness and myelination, dMRI enables inference about underlying tract microstructure (LeBihan et al. 1986; Basser and Pierpaoli 1996).

In adulthood, microstructural properties of white matter are shared among major tracts (for example, an adult individual with high fractional anisotropy (FA) in one tract is likely to have high FA in all other tracts in the brain). This property allows for the derivation of a general factor, *gFA*, of white matter microstructure (Penke et al. 2010; Cox et al. 2016). The general factor explains almost half of variance in microstructure across major tracts, and latent variable statistical analyses show that *gFA* is predictive of information processing speed and intelligence (Penke et al. 2010; Ritchie et al. 2015b; Penke et al. 2012). The temporal emergence of *gFA* and other general factors of water diffusion biomarkers during human development is unknown, and therefore its role in the ontogeny of human cognition has not been investigated.

Probabilistic neighbourhood tractography (PNT) is an automatic segmentation technique based on single seed point tractography, that can identify the same fasciculus-of-interest across a group of subjects by modelling how individual tracts compare with a predefined reference tract in terms of length and shape (Clayden 2011). The method has been optimized for use with neonatal dMRI data, which enables tract-averaged measurements of mean D , axial (λ_{ax}) and radial (λ_{rad}) diffusivities, and FA, for the major white matter fasciculi during early brain development (corticospinal tracts, genu and splenium of corpus callosum, cingulum cingulate gyri, inferior longitudinal fasciculi) (Anblagan et al. 2015).

Early exposure to extra-uterine life by preterm birth is a leading cause of cognitive impairment in childhood and is strongly associated with a ‘disconnectivity’ phenotype that combines diffuse white matter injury and volume reduction of connected structures (Inder et al. 1999; Boardman et al. 2006; Volpe 2009; Ball et al. 2012). Altered development of thalamocortical networks in association with preterm birth is reported (Boardman et al. 2006; Ball et al. 2013; Ball et al. 2015; Toulmin et al. 2015), but structural and functional connectivity analyses in the newborn period and studies of adults born preterm suggests that network disruption is more widely distributed (Pandit et al. 2013; van den Heuvel et al. 2015; Smyser et al. 2016; Froudast-Walsh et al. 2015; Cole et al. 2015). This raises the hypothesis that disconnectivity in the context of preterm birth is a global rather than localized process.

Preterm birth is associated with an atypical social cognitive profile (Ritchie et al. 2015a). Early social cognition is also extremely tractable to measurement in infancy via measurement of gaze behaviour to social and non-social visual content. For example, visual attention is given to faces very soon after birth, with specific preference to the eye region, while at around 6 - 9 months a preference for looking at faces in multiple object arrays or animated scenes develops (Johnson et al. 1991; Farroni et al. 2002; Gliga et al. 2009). In addition, eye-movement recordings in response to social stimuli have been used to identify early behavioral trajectories associated with autism (Jones and Klin 2013), to link emergent social cognition with white matter microstructure in specific tracts (Elison et al. 2013), and to distinguish

between the social cognitive profiles of infants born preterm and at term (Telford et al. 2016).

We tested the following hypotheses: first, a latent measure of general white matter microstructure (g_{WM}) is present in the newborn; second, preterm birth is associated with global disconnectivity; and third, that g measured in the newborn period is associated with emergent social cognitive function in infancy.

Materials and Methods

Participants

145 neonates (gestational age at birth range 23⁺² to 41⁺⁵ weeks) were recruited from the Royal Infirmary of Edinburgh between February 2013 and August 2015 to a longitudinal study of the effect of preterm birth on brain structure and long term outcome. Infants had diffusion MRI (dMRI) at term equivalent age (mean GA 40⁺⁵ weeks, range 37⁺⁵ - 47⁺¹) and 83 took part in eye-tracking assessment 6 - 12 months later (median age 7.9 months, IQR 6.8 -8.8).

To study the effect of preterm birth on white matter microstructure the group was divided into those with GA at birth <35 weeks (n = 109), and healthy controls recruited from postnatal wards with GA 37 - 42 weeks (n = 36). Exclusion criteria included major congenital malformations, chromosomal abnormalities, congenital infection, overt parenchymal lesions (cystic periventricular leukomalacia, hemorrhagic parenchymal infarction) or post-hemorrhagic ventricular dilatation. Demographic information is shown in Table 1. Ethical approval was obtained from the National Research Ethics Service (South East Scotland Research Ethics Committee 02) and informed consent was obtained from the person with parental responsibility for all individual participants included in the study.

Of the preterm group: 7% had intra-uterine growth restriction (IUGR) defined as a birth weight under the third centile for gender and gestation and 31% had bronchopulmonary dysplasia defined as need for supplementary oxygen at 36 weeks' PMA. PMA; postmenstrual age.

Image acquisition

A Siemens MAGNETOM Verio 3 T MRI clinical scanner (Siemens Healthcare Erlangen, Germany) and 12-channel phased-array head coil were used to acquire: T1-weighted MPRAGE (TR = 1650 ms, TE = 2.43 ms, inversion time = 160 ms, flip angle = 9°, voxel size = 1 × 1 × 1 mm³, and acquisition time = 7 min 49 sec); T2-weighted SPACE (TR = 3800 ms, TE = 194 ms, flip angle = 120°, voxel size = 0.9 × 0.9 × 0.9 mm³, acquisition time = 4 min 32 sec); dMRI using a protocol consisting of 11 T2- and 64 diffusion-weighted (b = 750 s/mm²) single-shot spin-echo echo planar imaging (EPI) volumes acquired with 2 mm isotropic voxels (TE = 106 ms and TR = 7300 ms). Infants were scanned without sedation in natural sleep using the feed-and-wrap technique. Physiological stability was monitored using procedures described by Merchant et al. (2009) (Merchant et al. 2009). Ear protection was provided for each infant (MiniMuffs, Natus Medical Inc., San Carlos, CA).

Image analysis

For all four imaging biomarkers (FA, MD, λ_{ax} and λ_{rad}), tract-averaged values were derived from 8 major fasciculi segmented using probabilistic neighbourhood tractography (PNT) optimized for neonatal dMRI data (Bastin et al. 2010; Clayden et al. 2007; Anblagan et al. 2015). In summary after conversion from DICOM to NIfTI-1 format, the dMRI data were preprocessed using FSL tools (<http://www.fmrib.ox.ac.uk/fsl>) to extract the brain and eliminate bulk patient motion and eddy current-induced artifacts by registering the diffusion-weighted to the first T2-weighted EPI volume of each subject. Using DTIFIT, MD and FA volumes were generated for each subject. From the underlying white matter connectivity data, eight major white matter fasciculi thought to be involved in cognitive functioning were segmented: genu and splenium of corpus callosum, left and right cingulum cingulate gyrus (CCG), left and right corticospinal tracts (CST), and left and right inferior longitudinal fasciculi (ILF). As described in detail in the study by Anblagan et al. (Anblagan et al. 2015), this involved using reference tracts created from a group of 20 term controls.

Cognitive testing

Infant social cognitive ability was assessed by tracking eye gaze in response to visual social stimuli using methods described by Telford et al. (Telford et al. 2016). Infants were positioned on the care-giver's lap 50 - 60cm from a display monitor used to present social stimuli of three levels of complexity: a static face, a face in an array of non-social objects, and a pair of naturalistic scenes with and without social content. Proportional looking time to social content relative to the overall stimulus was recorded using a Tobii© x60 eye-tracker, and Tobii Studio© (version 3.1.0) software was used for analysis. Because social preference scores that represent the distribution of fixation to social versus general image content are highly correlated across tasks, we combined social preference score from each task into a composite score per participant (Gillespie-Smith et al. 2016).

Statistical analysis

One principal component analysis (PCA) was conducted for each of the four water diffusion parameters (MD, FA, λ_{ax} and λ_{rad}) across the eight tracts, to quantify the proportion of shared variance between them (i.e. to determine whether a clear single-component solution was present, in line with previous reports in adults). That is, four separate data matrices (one for each DTI parameter) were separately analysed, each with dimensions $n \times m$ where $n = 145$ (number of subjects) and $m = 8$ (tract-averaged values for eight tracts). Thus, each PCA included data from all participants, and all available tracts were included; where tract data were missing (median 3.5% of tracts, IQR 3.5-13.25), the mean FA, MD, λ_{ax} and λ_{rad} of the group was used to impute values for the missing tract. Next, we examined the effect of preterm birth on differences in these four general water diffusion measures. Initially, we used a dichotomous group design, comparing differences between preterm infants' and controls' white matter microstructure (corrected for age at MRI scan) using Welch's unpaired t-tests. We then applied linear regression across the entire group to quantify the dose effect of birth term on each measure of microstructure, including PMA at MRI scan and sex as covariates in the model. In order to compare tract loadings (correlations between the manifest variable and extracted component score) for each tract between preterm infants and controls, we used Fisher's test of correlation

magnitude differences among independent groups (cocor.indep.groups in the cocor package in R)(Diedenhofen and Musch 2015). Finally, we examined associations between white matter microstructure and social cognitive performance using linear regression. The MRI and cognitive variables were corrected for differences in age at their respective data collection points prior to insertion into the model, where gender and group status (preterm / control) were covariates. Statistical analyses were carried out using SPSS v 21.0 (Chicago, Il), and R (<https://www.r-project.org>) version 3.2.2 (Fire Safety).

Results

1. General component of white matter microstructure

We ran separate PCAs for each measure of white matter microstructure on all eight tracts (Fig 1). In each case there was a clear one component solution, denoted by its large eigenvalue, and the much lower and linearly decreasing eigenvalues of the remaining components. We extracted this first component, without rotation, which explained 49% (FA), 54% (MD), 59% (λ_{rad}), and 36% (λ_{ax}) of the variance (all loadings range between 0.409 and 0.870; Fig 2, Table 2). Thus, there is a clear tendency for white matter microstructural properties found in one part of the newborn brain to be common across all white matter tracts, and the extracted water diffusion parameter values for each participant therefore reflect the level of white matter microstructure common across all tracts in that brain.

2. The effect of preterm birth on the general measure of white matter microstructure

There were significant differences in g for each of the four white matter water diffusion parameters between preterm and control groups: gFA ($t = -4.1367$, $p = 8.139e-05$); gMD ($t = 5.2773$, $p = 1.062e-06$); $g\lambda_{rad}$ ($t = 5.4887$, $p = 4.322e-07$); $g\lambda_{ax}$ ($t = 4.2527$, $p = 5.529e-05$), Fig 3.

After adjustment for age at scan and sex we found significant associations between gestational age (GA) at birth and general measures of: FA (gFA), β 0.305 ($p < 0.001$); MD (gMD), β -0.351 ($p < 0.001$), λ_{rad} ($g\lambda_{rad}$) β -0.363 ($p < 0.001$); and λ_{ax} ($g\lambda_{ax}$) β ,

-0.300 ($p < 0.001$) (Fig 4). In summary, those infants born preterm exhibited less 'mature' microstructure (less coherent water diffusion and a greater general magnitude of water molecular diffusion) across their white matter tracts than controls. Moreover, we found a dose-dependent effect of GA at birth across all general white matter indices, such that more premature birth was associated with generally less optimal white matter microstructure.

In view of variations in newborn network connectivity (van den Heuvel et al. 2015), we considered whether individual tract loading of FA might differ between preterm and term groups. In exploratory analyses we found that loadings appeared qualitatively higher in callosal and corticospinal tracts for preterm versus control infants, but there was little evidence for group difference in tract loading in association fibers (Fig 5). Formal tests of these differences using Fisher's Z broadly confirmed this pattern for genu ($z = 2.0593$, $p = 0.0395$) and left CST ($z = 2.3185$, $p\text{-value} = 0.0204$), though differences were not significant in the splenium ($z = 1.6072$, $p\text{-value} = 0.1080$) and right CST ($z = 1.4674$, $p\text{-value} = 0.1423$). This pattern was also present for λ_{rad} and MD, though statistical tests indicated only trend-level or weaker differences for λ_{rad} (genu: $z = 1.8146$, $p = 0.0696$; splenium: $z = 1.8551$, $p = 0.0636$; left CST: $z = 1.6845$, $p = 0.0921$; and right CST $z = 1.2033$, $p = 0.2289$) with the differences in the same direction for MD being smaller and non-significant.

3. Social cognitive ability and measures of general white matter microstructure

There were no significant associations between any general water diffusion parameter and a sensitive measure of emergent social cognition derived from an eye-tracking task battery at 7 months (all $\beta_{\text{absolute}} \leq 0.123$, all $p\text{-values} \geq 0.265$), and nor were there any significant effects of group within the model (all $\beta_{\text{absolute}} \leq 0.099$, all $p\text{-values} \geq 0.378$; Table 3). There was no relationship between water diffusion parameters and emergent social cognition in the genu (all $p\text{-values} \geq 0.15$) or splenium (all $p\text{-values} \geq 0.064$) of the corpus callosum. Social preference scores for each task (proportional looking time at social versus general image content) are shown in Supplemental Table 1.

Discussion

In the human newborn brain microstructural properties of major white matter tracts are highly correlated with one another, which allows for extraction of a general measure for each of four common water diffusion MRI parameters. This result suggests that individual differences in white matter microstructure during development are to a substantial degree common among tracts, and not a phenomenon that primarily affects specific individual tracts. Furthermore, the nature of between tract correlations is altered by the environmental exposure of preterm birth. Since global white matter microstructure contributes to the neural foundation of higher cognitive function in later life (Deary et al. 2010), and the factor loadings show remarkable similarity to those reported in adulthood (Penke et al. 2010), the data suggest that the fundamental white matter architecture required to support cognition is established as a generalized process during gestation, and that this is vulnerable to the environmental stress of preterm birth.

Inter-tract correlations were of similar strength for FA, MD and λ_{ax} but were weaker for λ_{rad} (Table 1). In the newborn period, before myelination is widespread, FA in white matter increases in association with maturation of axonal membrane structure, and increases in axonal caliber and oligodendrocyte number. MD in white matter is high around the time of birth but decreases over the first few months of postnatal life as brain water content lowers and localized restriction of water increases due to increased cell density and other factors (Huppi et al. 1998; Neil et al. 1998; Wimberger et al. 1995; Nomura et al. 1994; Morriss et al. 1999). Our data suggest that these processes affect the major tracts similarly around term equivalent age. The observation that λ_{ax} was highly correlated between tracts could reflect the fact that neuronal migration has largely been completed by 24 weeks' gestation so the axonal skeleton of major tracts is established (Bystron et al. 2008). λ_{rad} was relatively weakly correlated between tracts, which could be explained by variation in myelination, which is known to be tract-specific (Kinney et al. 1988).

Having established that microstructural properties of tracts are substantially shared in the newborn, we next considered whether this relationship is modified by the environmental stress of preterm birth. After controlling for age at scan and sex, we

found that the latent general measures of each of the four water diffusion parameters differed between preterm and control groups (Figure 3): *gFA* was lower and *gMD* higher in preterms compared with healthy infants born at term. These data are consistent with studies that have used voxel- and tractography-based approaches to study the effect of preterm birth on the developing brain (Pannek et al. 2014; Ball et al. 2010; Anblagan et al. 2015), but methodological factors have left uncertainty about the extent to which microstructural change is a local versus a generalized process. Here, we demonstrate that preterm birth is associated with generalized differences across a functionally relevant representation of network architecture. Within this, however, we also found that group differences were most marked in projection and callosal fibers, which had higher loadings than association fibers in preterm infants compared with controls. Since neonatal water diffusion parameters are biomarkers of later neurodevelopmental function after preterm birth (Counsell et al. 2008; van Kooij et al. 2012; Boardman et al. 2010), the data presented here suggest that general properties of white matter microstructure could underlie the high prevalence of impairment seen in children and adults born preterm.

We found no relationship between general properties of any of the four water diffusion parameters and measures of infant social cognition derived from eye-tracking. The cognitive measure was selected because it discriminates between typically developing children and those with atypical cognitive trajectories, including those born preterm, and has been validated for use in infancy (Young et al. 2009; Ozonoff et al. 2010; Chawarska et al. 2013; Jones and Klin 2013; Telford et al. 2016; Gillespie-Smith et al. 2016). There are plausible explanations for this. First, general white matter ‘integrity’ is most closely associated with information-processing speed in adulthood but it is less predictive of other aspects of cognition (Ritchie et al. 2015b). Second, although processing speed is considered to be a foundational competence for other cognitive abilities in adulthood this relation may not hold true in infancy (Salthouse 1996; Ritchie et al. 2015b). Thus, in the infant, social cognition may develop on an independent trajectory relative to general processing abilities or emerging intelligence (Adolphs 1999). Further study is required to determine whether *g_{WM}* relates to other aspects of infant cognition such as sustained attention and memory. Longitudinal study will be required to determine whether foundational general measures of neonatal white

matter microstructure influence later cognitive functions that are more reliant on information transfer efficiency.

Brain structure, including dMRI measures in white matter, and intelligence are all highly heritable; twin studies suggest that up to 60% of inter-individual variation in dMRI measures are attributable to genetic factors (Thompson et al. 2001; Toga and Thompson 2005; Geng et al. 2012; Shen et al. 2014). Common genetic variants and epigenetic modifications modify the risk of white matter disease associated with preterm birth (Boardman et al. 2014; Krishnan et al. 2016; Dutt et al. 2011; Sparrow et al. 2016), but to our knowledge these associations have not been tested using a more functionally tractable set of brain biomarkers. We speculate that considering general measures of network architecture alongside tract-specific measures in imaging genetic studies will be useful for understanding the genetic and epigenetic determinants of connectivity in the newborn.

A limitation of this study is that we were unable to investigate the relationship between dMRI parameters of tracts that serve social cognition in adulthood, such as the arcuate fasciculus and fornix, and infant social cognition. Although PNT can segment these tracts from adult data (Clayden et al. 2007), we could not identify them reliably in the training set of neonatal data because of lower image resolution inherent to neonatal dMRI acquisitions.

A second limitation is that we did not examine other factors that may have contributed to white matter injury in the preterm group, such as bronchopulmonary dysplasia or punctate white matter lesions, because a much larger sample would have been required to adjust for these factors (Ball et al. 2010; Bassi et al. 2011). In addition, group sizes were unequal in the secondary analysis of the effect of preterm birth on component loadings; the preterm group was larger and thus could have contributed more strongly to the principal component score, influencing group comparisons. Consequently, although we found a statistically significant group effect for FA, MD and λ_{rad} in the genu and CST, we cannot be certain that group differences are confined to these tracts alone. Though exploratory, these findings raise the possibility that preterm birth also subtly alters the correlational structure of infant white matter tracts with respect to specific classes of tract.

In summary, a latent general measure accounts for almost half of the variance of white matter tract microstructure in the newborn brain. Given that major white matter tracts constitute the neuroanatomical foundation of cognitive neural systems, our study indicates that a facsimile the network architecture for intelligence is established by birth, and that it is vulnerable to early exposure to extra-uterine life.

Table 1 Clinical and demographic features of the whole group, and the preterm and term controls

	Whole sample (n = 145)	Preterm (n = 109)	Term (n = 36)
Mean PMA at birth / weeks (range)	31 ⁺⁵ (23 ⁺² - 41 ⁺⁵)	29 ⁺⁰ (23 ⁺² - 34 ⁺⁶)	39 ⁺⁶ (37 ⁺² - 41 ⁺⁵)
Mean PMA at scan / weeks (range)	40 ⁺⁵ (37 ⁺⁵ - 47 ⁺¹)	40 ⁺⁰ (37 ⁺⁵ - 44 ⁺⁰)	42 ⁺¹ (39 ⁺⁰ - 47 ⁺¹)
Mean birth weight / kg (sd)	1.72 (1.05)	1.14 (0.24)	3.46 (0.45)
Median age at eye-tracking assessment / months (IQR)	7.9 (6.8 - 8.8)	7.7 (6.7 - 8.4)	8.4 (7.7 - 9.1)
Gender (Female:Male)	69:76	54:55	15:21

Table 2 Tract loadings, explained variance, and mean absolute magnitude (Pearson's *r*) of correlations across all tracts for the first unrotated principal component for the four water diffusion measures.

Tract	FA	MD	λ_{rad}	λ_{ax}
Genu	0.747	0.841	0.870	0.608
Splenium	0.601	0.737	0.750	0.672
L CCG	0.751	0.738	0.807	0.564
R CCG	0.619	0.783	0.808	0.639
L CST	0.803	0.739	0.812	0.409
R CST	0.722	0.768	0.784	0.652
L ILF	0.636	0.726	0.741	0.669
R ILF	0.667	0.500	0.516	0.538
Explained variance	0.485	0.540	0.589	0.360
Mean between-tract <i>r</i>	0.407	0.466	0.521	0.262

CCG, cingulum cingulate gyri; CST, corticospinal tract; ILF, inferior longitudinal fasciculus.

Table 3. Regression models of water diffusion measures and group membership on social cognitive performance

Standardized β s (p-values); imaging and cognitive variables corrected for respective age at sampling prior to being entered into the models, which included gender as a covariate. gFA = general component of fractional anisotropy, gMD = general component of mean diffusivity, $g\lambda_{rad}$ = general component of radial diffusivity, $g\lambda_{ax}$ = general component of axial diffusivity.

Diffusion parameter		Group
gFA	0.076 (0.551)	0.099 (0.396)
gMD	-0.123 (0.265)	0.081 (0.478)
$g\lambda_{rad}$	-0.116 (0.301)	0.080 (0.490)
$g\lambda_{ax}$	-0.116 (0.295)	0.097 (0.378)

Supplemental table 1. Social preference score for each task.

	Infants born preterm (n = 59)	Infants born at term (n = 24)	Mean difference	p-value
Static face ^a	0.243	0.315	-.072	0.25
Face in array of non-social images ^b	0.437	0.477	-0.040	0.39
Naturalistic scene ^c	0.217	0.256	-0.040	0.45

^a Proportional looking time to the eye region relative to overall looking time at a static face

^bProportional looking time at an image of a face within an array of non-social images ^cProportional looking time at social content within a naturalistic scene relative to overall looking time at the stimulus

Figure Captions

Fig. 1 Scree plot from principal component analyses for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (λ_{ax}), and radial diffusivity (λ_{rad}) of the eight white matter tracts

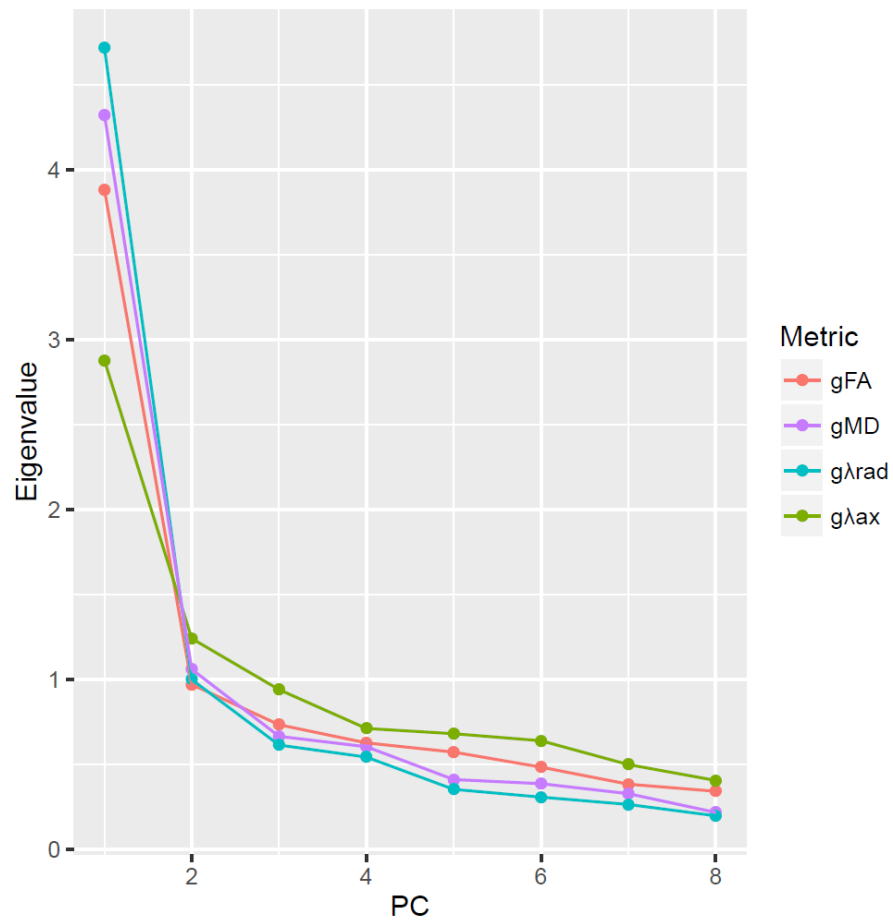


Fig. 2 Brain images show tract segmentations obtained from one representative participant. Seed points are marked with a green cross. The statistics are loadings of the average FA values of each tract on the latent measure of white matter microstructure

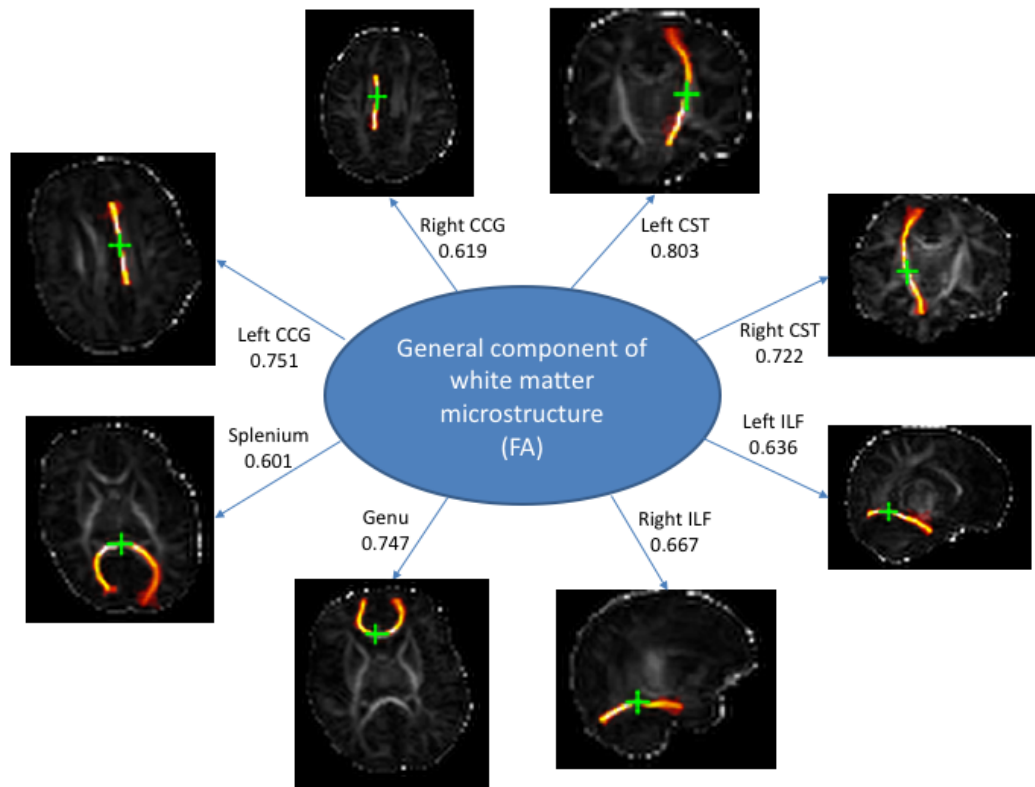


Fig. 3 Significant group differences between preterm and controls across all our general water diffusion indices

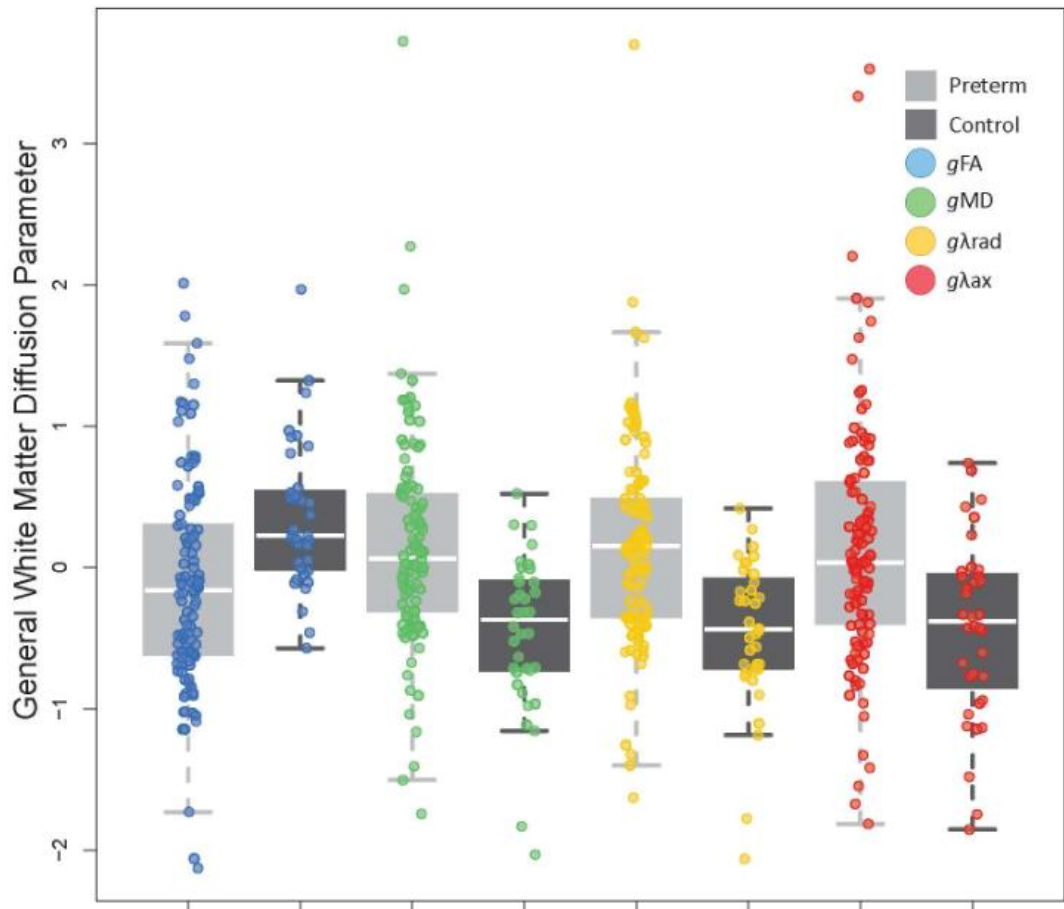


Fig. 4 Associations between PMA birth and general measures of fractional anisotropy (gFA) mean diffusivity (gMD), radial diffusivity ($g\lambda_{rad}$) and axial diffusivity ($g\lambda_{ax}$). Regression lines and 95% CIs (shaded) are shown for linear regression models between PMA at birth and white matter microstructure, corrected for age at scan and sex

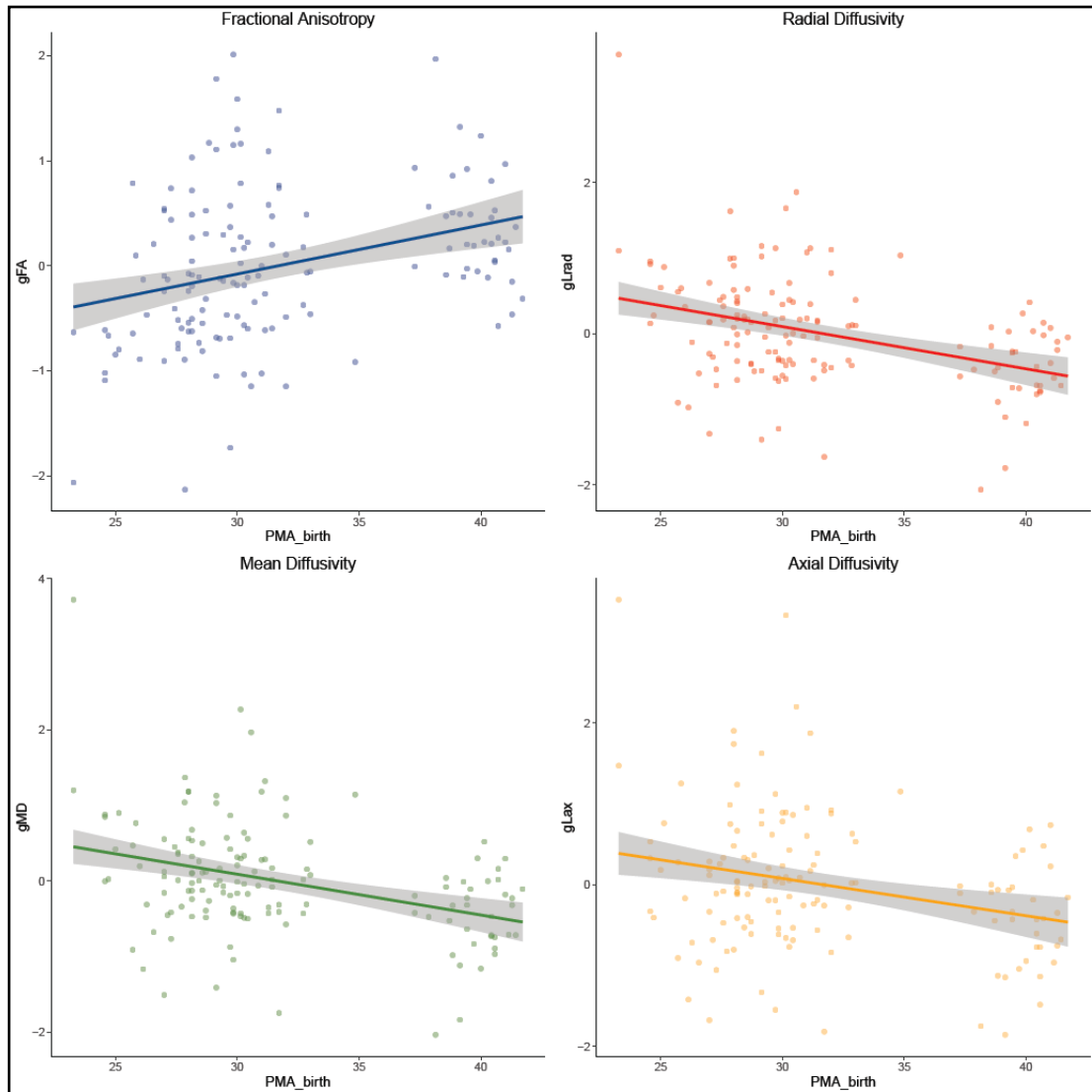
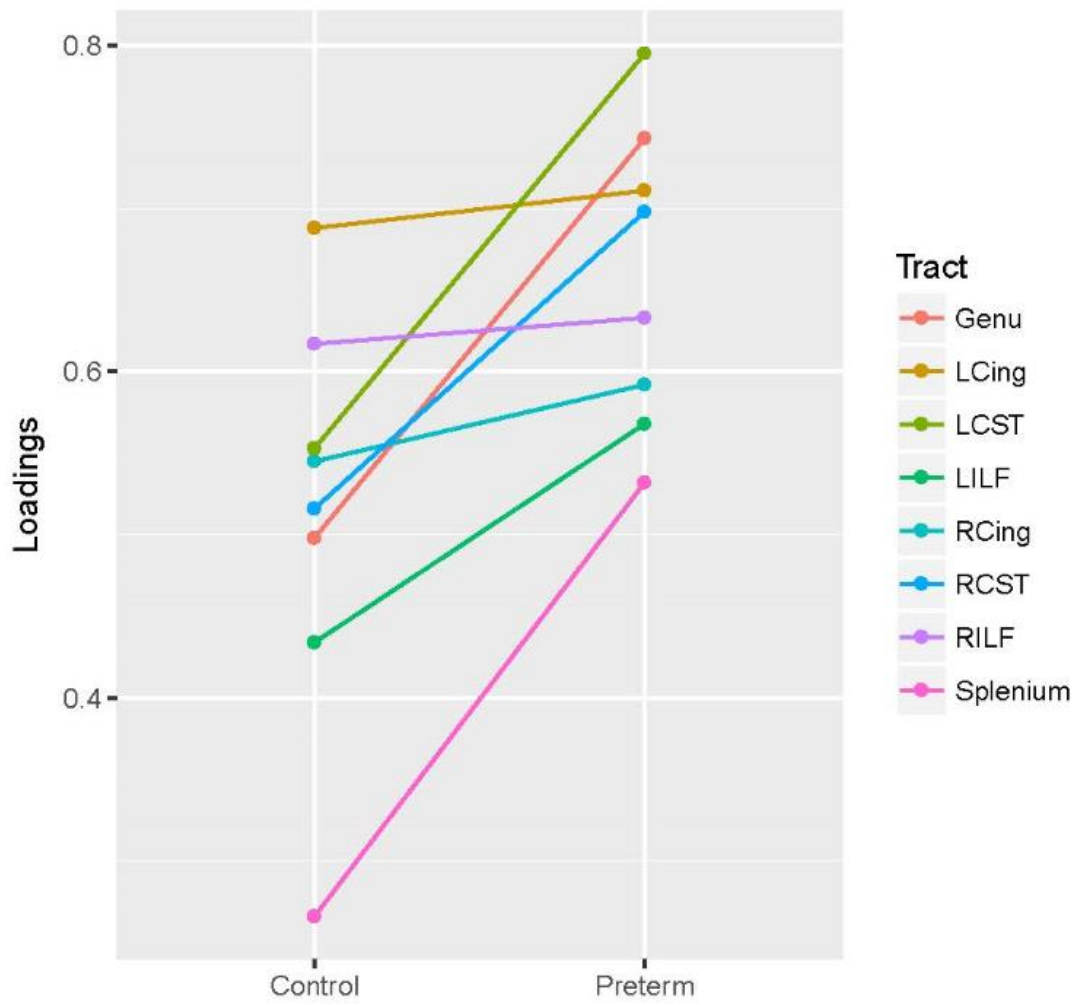


Fig. 5 Differences in tract loadings for gFA between control and preterm, in comparison to overall loadings



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