Understanding the biological mechanisms associated with behavioural outcomes in very preterm children

Kanel, Dana

Awarding institution:
King's College London

Understanding the biological mechanisms associated with behavioural outcomes in very preterm children

Dana Kanel

Thesis for the Degree of Doctor of Philosophy

Child and Adolescent Psychiatry

Department of Child and Adolescent Psychiatry,

Institute of Psychiatry, Psychology & Neuroscience

King's College London

September 2021

Abstract

During the third trimester, rapid and complex neurodevelopmental processes leave the developing brain vulnerable to insult and at risk of structural alterations and developmental delays in the event that birth is premature. As such, there is increasing interest in the quality of life of those surviving preterm birth — who are at risk of developing neurological disorders and neuropsychological impairments in childhood and later life. In particular, difficulties in behaviour and cognition are among the developmental sequelae associated with preterm birth — specifically very preterm birth (VPT; prior to 33 weeks' gestation). Yet, despite existing research dedicated to understanding behavioural development in VPT children, the underlying neural substrates associated with this population's increased vulnerability to developing such difficulties remain unclear. To date, only a few studies have rigorously investigated the association between behavioural problems following VPT birth and structural and functional brain alterations that could contribute to the development of such problems.

The overall aim of this thesis was to increase our understanding of the neurodevelopmental mechanisms associated with behavioural outcomes following VPT birth. Specifically, structural and functional brain connectivities, both in the whole-brain and within specific tracts, were investigated. This thesis also aims to determine whether data acquired in the neonatal period can be used to identify those VPT children at a greater risk of experiencing behavioural difficulties. This was achieved through multimodal neuroimaging in a cohort of 511 VPT children, recruited at birth into the ePrime study, who underwent magnetic resonance imaging (MRI) at term-equivalent age. At 4–7 years, 251 participants were followed up for neurodevelopmental assessments. At 7–10 years, 64 of these children were followed up with multimodal MRI and neurodevelopmental assessments. Additionally, 46 full-term control children were recruited from the community.

Chapter 1 provides a general overview of preterm birth and brain development, as well as an introduction to neuroimaging methods used in their investigation in neonates and children. Chapter 2 includes a comprehensive review of cognitive and socio-emotional difficulties in VPT children and

their neural correlates. Chapter 3 presents an overview of the current thesis, including aims and hypotheses. Chapter 4 includes the overall methodology for the included studies.

Chapters 5 and 6 include studies of neonatal MRI data and socio-emotional outcomes, as measured by parental questionnaires, in the VPT group only. In Chapter 5, associations between neonatal structural connectivity in specific white matter (WM) tracts (uncinate fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and inferior longitudinal fasciculus), measured with diffusion characteristics (fractional anisotropy and radial diffusivity), and childhood socio-emotional outcomes are discussed. Chapter 6 examines associations between neonatal resting-state functional connectivity (rs-FC) of the amygdalae and childhood socio-emotional outcomes. Amygdalae rs-FC was estimated using seed-based connectivity analysis, with the bilateral amygdalae as seed region of interest. Results from both studies indicated an association between neonatal fronto-temporal connectivity (structural *and* functional) in the right hemisphere and childhood socio-emotional outcomes.

Chapter 7 presents a study of VPT children compared to age-matched term-born controls. Differences in WM between VPT and full-term children were explored using diffusion MRI data analysed with both voxel- and fixel-based analysis, the latter a method that measures both the microstructure (fibre density) and macrostructure (fibre cross-section) of WM tracts. Associations between childhood WM structure and behavioural outcomes in both VPT and control groups were also studied. Voxel- and fixel-based results showed alterations in the structure of several WM tracts in VPT children when compared to controls. Moreover, associations between specific WM tract structure in the corpus callosum and corticospinal tract, as measured by fixel-based analysis, and verbal comprehension were found in all children.

Taken together, the findings of this thesis deepen our understanding of the impact of VPT birth on behavioural outcomes during childhood. By combining neuroimaging techniques with behavioural tests and questionnaires to isolate specific brain mechanisms associated with behaviours of interest, further research in this field can allow for the identification of children at a greater risk of developing difficulties in later life, and thus the implementation of strategies that can prevent their emergence.

Acknowledgements

Thank you to my supervisors, Prof Chiara Nosarti and Prof Serena Counsell. I am grateful for the time you dedicated to me; Thursday mornings were a motivational push even through the harshest of lockdowns. Thank you for preparing me for academia by shaping my scientific thinking and research skills, I have learnt so much from you both.

Thank you to my colleagues at the *Centre for the Developing Brain* and *Child & Adolescent Psychiatry*. Laila, Lucy, and Tanya, your support (both work-related and emotional) helped me through so much.

I would like to thank every child, parent, and carer that took part in this study, who not only made work on Saturdays so enjoyable, but were also a constant reminder of what brought me here and why I am passionate about this work.

Finally, thank you to my family & friends, Sophie for the Ts, Rory for dotting the Is and crossing the Ts (and so much more). To my parents, this would not have been possible without your support, thank you for all you've done for me and for teaching me how to get through, cow by cow.

Table of Contents

List of Figures

List of Tables

List of Equations

List of Abbreviations

AD	Axial diffusivity
ADC	Apparent diffusion coefficient
BOLD	Blood oxygenation level dependent
CBQ-VSF	Children's Behaviour Questionnaire – Very Short Form
CSF	Cerebrospinal fluid
CST	Corticospinal tract
dMRI	Diffusion magnetic resonance imaging
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EmQue	Empathy Questionnaire
ePrime	Evaluation of Preterm Imaging Study
EPT	Extremely preterm
FA	Fractional anisotropy
FBA	Fixel-based analysis
FC	Fibre cross-section
FD	Fibre density
FDC	Fibre density and cross-section
fMRI	Functional magnetic resonance imaging
FOD	Fibre orientation distributions
FWE	Family-wise error
GA	Gestational age
GLM	General linear model

GM	Grey matter
IFOF	Inferior fronto-occipital fasciculus
ILF	Inferior longitudinal fasciculus
IMD	Index of Multiple Deprivation
IQ	Intelligence quotient
MD	Mean diffusivity
MOG	Middle occipital gyrus
MPT	Moderately preterm
MRI	Magnetic resonance imaging
OFC	Orbitofrontal cortex
NODDI	Neurite orientation dispersion density imaging
PHG	Parahippocampal gyrus
PMA	Postmenstrual age
PRI	Perceptual reasoning index
PSI	Processing speed index
RD	Radial diffusivity
rs-FC	Resting-state functional connectivity
rs-fMRI	Resting-state functional magnetic resonance imaging
SDQ	Strengths and Difficulties Questionnaire
SES	Socioeconomic status
SLF	Superior longitudinal fasciculus
SRS-II	Social Responsiveness Scale-II
TEA	Term-equivalent age
TSA	Tract-specific analysis
UF	Uncinate fasciculus
VCI	Verbal comprehension index
VLBW	Very low birth weight
VPT	Very preterm
WISC-IV	Wechsler intelligence scale for children IV
WM	White matter
WMI	Working memory index

Publications & conference abstracts

Publications

Kanel, D., Counsell, S.J., Nosarti, C., 2021. Advances in functional and diffusion neuroimaging research into the long-term consequences of very preterm birth. *J Perinatol* 41, 689-706.

Vanes, L.D., Hadaya, L., **Kanel, D.,** Falconer, S., Ball, G., Batalle, D., Counsell, S.J., Edwards, A.D. and Nosarti, C., 2021. Associations between neonatal brain structure, the home environment, and childhood outcomes following very preterm birth. *Biological Psychiatry Global Open Science* 1, 146-155.

Kanel, D., Vanes, L., Pecheva, D., Hadaya, L., Falconer, S., Counsell, S.J., Edwards, A.D. and Nosarti, C., 2021. Neonatal white matter microstructure and emotional development during the pre-school years in children who were born very preterm. *eNeuro*, ENEURO.0546-0520.2021.

Conference abstracts

Kanel, D., Pecheva, D., Falconer, S., Edwards. A.D., Counsell, S.J., Nosarti, C. (2019, June). *Neonatal white matter microstructure and emotional development during the pre-school years in children who were born very preterm.* Poster presentation at Human Brain Mapping, Rome.

Kanel, D., Davidson, A., Hadaya, L., Pecheva, D., Edwards. A.D., Counsell, S.J., Nosarti, C. (2020, July). *Neonatal white matter microstructure and emotional outcomes in school-age children who were born very preterm.* Poster presentation at International Congress of Infant Studies, online.

Kanel, D., Hadaya, L., Davidson, A., Pecheva, D., Christiaens, D., Pietsch, M., Tournier, J.D., Edwards, A.D., Counsell, S.J., Nosarti, C. (2020, Sept). *The use of fixel-based analyses to investigate white matter micro- and macro-structure in school-aged preterm children*. Poster presentation at Flux, online.

Kanel, D., Vanes, L., Pecheva, D., Hadaya, L., Falconer, S., Edwards. A.D., Counsell, S.J., Nosarti, C. (2021, March). *Neonatal white matter microstructure and emotional development during the pre-school years in children who were born very preterm.* Oral presentation at Fetal Neonatal Neurology Congress, online.

Kanel, D., Vanes, L., Pecheva, D., Hadaya, L., Falconer, S., Edwards. A.D., Counsell, S.J., Nosarti, C. (2021, April). *Neonatal white matter microstructure and emotional development during the pre-school years in children who were born very preterm.* Poster presentation at Society for Research in Child Development, online.

Declaration of authorship

The work presented in this thesis was conducted by the author at the *Centre for the Developing Brain* and *Child & Adolescent Psychiatry*, King's College London between June 2018 and September 2021. This is a thesis incorporating peer-reviewed, published papers.

Chapter 5

Diliana Pecheva performed tract-specific analysis on the neonatal diffusion data.

Chapter 6

Gareth Ball and Lucy Vanes preprocessed rs-fMRI data.

Funding and COVID-19 impact statement

The work presented as part of this PhD was funded by a generous fixed-term grant from Action Medical Research and Dangoor Education, which allowed me to complete my PhD in 39 months. Due to the COVID-19 lockdowns in England throughout 2020 and 2021, all in-person research was suspended between March-October 2020 and January-March 2021. After restrictions eased, I was able to continue collecting data and reach the recruitment target of 50 very preterm children aged 8–10 years, however the final control group only included 46 term-born participants (target control group n=50). This target number was determined by available funds at the time. Due to these Covid 19-related delays, I began writing the first two studies (Chapters 5 & 6 of the current thesis) using MRI (at term) and neurodevelopmental outcome data previously collected by other team members before the beginning of my PhD (when children were aged 4–7 years); Chapter 7 includes behavioural and MRI data I collected.

Chapter 1: Preterm Birth and the Developing Brain

Significant medical advances in neonatal care have led to a decrease in mortality rates among neonates born preterm (<37/40 weeks' gestation). This has meant an increase in the number of survivors of premature births in recent years, which now represents one in ten births (Chawanpaiboon et al., 2019). Despite the benefits of such medical advances, surviving preterm infants are at a greater risk of a range of both mental and physical morbidities (Manuck et al., 2016; Saigal and Doyle, 2008). Such problems likely result from insults and injuries to the brain that affect vital processes occurring during the later stages of neural development. As a result, the brains of preterm neonates are usually smaller at term-equivalent age compared to term-born controls (Bouyssi-Kobar et al., 2016; Lemola et al., 2017), and these infants are at greater risk of atypical brain development, even in the absence of major perinatal complications. Therefore, attention has increasingly focused on the quality of life of survivors, who are at risk of developing a range of problems which span from the more severe medical complications such as cerebral palsy, respiratory illnesses and learning disabilities to the less severe, yet much more common, cognitive deficits and behavioural problems (Johnson and Wolke, 2013). Long-term consequences of such cognitive and behavioural impairments include detrimental effects on academic performance and general functioning in daily life (Kroll et al., 2017). Taking into account the gradual increase of preterm individuals in our society, it is vital to better understand the developmental trajectory of their neurodevelopmental problems, as well as to identify those individuals most at risk, to aid both families and educational professionals by providing targeted interventions (Johnson et al., 2015).

1.1 Preterm birth epidemiology

1.1.1 Definitions

The gestational age of a newborn infant is categorised as preterm and term (WHO, 1977). Term birth occurs between 37 and 41 completed weeks of gestation. Preterm birth is defined as birth occurring after fewer than 37 weeks of gestation. Within this classification, births are termed moderately preterm (MPT, at 33–36 completed weeks of gestation), very preterm (VPT, at 28–32 completed weeks of gestation) and extremely preterm (EPT, at <28 completed weeks of gestation).

1.1.2 Preterm birth distribution

Earlier studies reporting on data from the first decade of this millennium indicate a worldwide preterm prevalence rate of 11.1% (Blencowe et al., 2012). In the US, 13% of all births were preterm (Hamilton et al., 2007), whilst developing countries show increased rates, with one study in Malawi identifying a preterm birth rate of 20% (Van Den Broek et al., 2005). A more recent systematic review exploring the global incidence of preterm birth estimated that 14.8 m infants (10.6% of live births) are born preterm every year, of which 15% are born at or before 32 weeks of gestation (VPT) (Chawanpaiboon et al., 2019). Of the nearly 15 million preterm-born infants, 81% occur in Asia and sub-Saharan Africa (Chawanpaiboon et al., 2019). In the UK preterm births occur in around 7–8% of all live births (Delnord et al., 2015; NICE, 2015). Of those, 5% are EPT births, whilst 11% are VPT births (ONS, 2020). Therefore, altogether, approximately 1.2% of all live births occur prior to 33 weeks of gestation.

Although methodological variation in epidemiological analyses should be considered when interpreting trend analyses of preterm birth rates, these are widely accepted to be increasing globally (Hamilton et al., 2007; Joseph et al., 1998; Langhoff-Roos et al., 2006; Thompson et al., 2006). Increases in moderately preterm births might be driving these increasing rates, as very preterm births have been shown to be stable over time (Hamilton et al., 2007; Morken et al., 2005). The diverse aetiology of prematurity and its widespread implications mean it is a problem of growing significance that warrants further understanding.

1.1.3 Risk factors for preterm birth

The most common risk factors for preterm birth are family history, low socioeconomic status (SES), maternal characteristics, including age and ethnicity, infections, and multiple pregnancies (Goldenberg et al., 2008; Johansson and Cnattigius, 2010; Muglia and Katz, 2010).

Individuals with a history of preterm birth have an increased risk of delivering prematurely, indicating individual differences in preterm birth risk that are stable over time. Such differences could be attributed to genetic factors (Plunkett and Muglia, 2008) and unchanging environmental exposures. Research utilising twin cohorts suggests a maternal genetic contribution towards gestational age with heritability ranging from 15–40% (Clausson et al., 2000; Kistka et al., 2008; Treloar et al., 2000; York et al., 2014).

1.1.3.1 Socio-economic and environmental factors

Between-country differences in socioeconomic norms could, at least in part, explain differences in preterm birth rates between countries. A comparison of two countries with varying socioeconomic profiles, such as USA and Malawi, showed a negative correlation between the countries' socioeconomic position and risk for preterm birth (Hamilton et al., 2007; Van Den Broek et al., 2005). SES is also related to prematurity within countries, with research highlighting associations between preterm birth risk and parent-related proxies of low SES, including home neighbourhood and education levels (Smith et al., 2007; Thompson et al., 2006). In the UK a higher prevalence of preterm births (<37 weeks' gestation) is seen among the poorest and less educated (Matijasevich et al., 2012; Puthussery et al., 2019). Social inequality seems to have widened over the last several decades, with one study indicating increased preterm birth rates in more deprived, and decreased preterm birth rates in less deprived, areas within northern England (Glinianaia et al., 2013). Data from European studies have suggested modifiable factors responsible for such disparities, including maternal smoking during pregnancy and environmental exposures to pollutants of air and food (Delnord et al., 2015; Jardine et al., 2021).

Although not a direct measure of SES, air pollutants are increased in low SES communities (Hajat et al., 2015), and have also been shown to increase the risk of preterm birth and lower birth weight (Hansen et al., 2006; Maroziene and Grazuleviciene, 2002). Further, the relationship between air pollutants and prematurity is heightened in families from a low socioeconomic background (Lamichhane et al., 2020; Westergaard et al., 2017). One recent London-based study showed that ozone exposure, as well as traffic-related air and noise pollution, was associated with preterm birth rates (Toledano et al., 2018). Specific air pollutants have also been associated with birth complications, with the particulate matter PM10 exhibiting a relationship with lower birth weight in Northwest England (Hannam et al., 2014) and Scotland (Dibben and Clemens, 2015).

Maternal ethnicity has consistently been identified as a strong determinant of early births (Kistka et al., 2007). Preterm birth rates are twice as high and the likelihood of recurrent preterm birth is four times as high in Black women compared to White women in the US. These effects persist after adjustment for confounding risk factors, including SES (Adams et al., 1993; Collins et al., 2007; Manuck, 2017). If such differences are not explained by SES or level of perinatal care, they could instead be on account of a higher level of social stress experienced by Non-White mothers resulting from racial discrimination. This is supported by research indicating that Black mothers who reported increased levels of racial discrimination had increased risk of premature delivery of infants with low birthweight (BW) compared to Black mothers reporting less racial discrimination (Collins et al., 2004). In the UK, a recent study reported that, together with socioeconomic inequalities, ethnic inequalities were associated with preterm births (Jardine et al., 2021). Crucially, individuals of non-White ethnicities tend to exhibit increased odds for preterm birth, with greater ethnic differences apparent at earlier gestational ages (Li et al., 2019). Similarly to US-based findings, British individuals of Black ethnicity are at an increased risk for preterm birth compared to White individuals (Jardine et al., 2021; Li et al., 2019; Puthussery et al., 2019). Other UK-based findings, however, provide conflicting evidence, such as increased risk of preterm birth in Bangladeshi mothers in one study (Li et al., 2019), and a lower risk in these individuals in another, when compared with White mothers. These findings highlight the need for further research in this area.

Maternal age has also been associated with the risk of premature birth. Both a younger maternal age (during adolescence and young adulthood) and an older maternal age (over 40 years) were seen to increase the risk of preterm birth (Fuchs et al., 2018; Hoffman et al., 2007; Olausson et al., 1999; Shrim et al., 2011). In younger mothers, such effects might be attributable to lower SES (Chen et al., 2007; Olausson et al., 2000). On the other hand, increased socioeconomic position of older mothers might even mask their biological disadvantage and improve neonatal outcomes (Lawlor et al., 2011; Stein and Susser, 2000). Overall, both socioeconomical and environmental factors are associated with the likelihood of preterm birth, thus further research is required to identify and address perinatal health disparities.

1.1.3.2 Clinical factors

Pregnancy complications often result in premature births, occurring either naturally or medically induced. For example, the presence of infection is known to significantly affect the length of gestation. Previous research suggests that chorioamnionitis - the acute inflammation of the fetal membranes - contributes to approximately 25% of preterm births, with bacterial colonisation rates as high as 79% for births occurring at 23 weeks of gestation, declining to 43% at 27 weeks of gestation (Onderdonk et al., 2008). Further, preterm preeclampsia, a disorder characterised by the onset of hypertension and proteinuria in pregnant women after 20 weeks of gestation, often results in pregnancy complications and the need for a medically induced preterm delivery (Johansson and Cnattigius, 2010). Neuroendocrine stress responses could also affect gestation, with cortisol levels – known to be affected by maternal stress levels – showing a direct association with preterm delivery (Sandman et al., 2006).

In addition, preterm birth rates in twin pregnancies have consistently displayed a prevalence rate of between 40 and 60% (Blondel et al., 2006; Gardner et al., 1995). Further, nearly all higher multiple gestations (> 2 births) will result in preterm delivery (Goldenberg et al., 2008).

The risk factors for preterm birth are numerous and span social, psychological, and medical aspects. As such, prematurity affects a significant number of people every year, most often those

coming from more deprived areas and with lower SES, with long-term implications that span across the whole of the preterm individual's life.

1.1.4 Methodological considerations

A common method of determining gestational age at birth is by calculating the expected date of delivery as 280 days (40 weeks) from the last menstrual period. An alternative, more precise method of dating pregnancy is to measure foetal size using an ultrasonography (Kramer et al., 1988), and a comparison between the two methods indicate that last menstrual period results are generally overestimated by around 2–3 days (Savitz et al., 2002). Additionally, over time, there has been an increase in the number of data points collected for preterm birth rate calculation, and this has likely affected estimated trends of prevalence rates. More recent reports include larger datasets (e.g., Chawanpaiboon et al., 2019) than previously published estimates (e.g., Blencowe et al., 2012). Therefore, preterm birth rates calculated using different methodologies and at different timepoints might not be directly comparable.

1.2 Preterm birth and brain development

1.2.1 Brain development during the third trimester

The perinatal period is one of rapid change under tightly controlled conditions. It features complex maturational processes, the correct timing of which is crucial for healthy development. Specifically, cerebral cortical development during the third trimester exhibits striking morphological changes, at both micro- and macroscopic levels. At a cellular level, intense synaptogenesis (the formation of new synapses) and myelination (the surrounding of axons by myelin sheaths) occur. Macroscopically, thalamocortical afferents will establish connections to the cortical plate. These afferents target specific corresponding areas, such as visual or auditory regions, allowing the cortical system to functionally process sensory input (Kostović and Judas, 2010). Ascending thalamocortical fibres that terminate in the cortex are categorised as projection fibres, together with efferent fibres

originating in the cortex and terminating in the thalamus. In this way, projection fibres connect the cortex with subcortical structures such as deep cerebral nuclei, brainstem, and spinal cord.

In the final few weeks of the gestational period, long white matter (WM) cortico-cortical connections will mature, with interhemispheric (commissural) connections starting to develop shortly before intra-hemispheric (association) connections (35 weeks and 38 weeks of gestation, respectively) (Kostović and Jovanov-Milosević, 2006). Commissural connections connecting the two hemispheres support inter-hemispheric communication. The largest commissural pathway within the cerebral cortex is the corpus callosum, which is involved in the integration of motor, perceptual, and cognitive functions. Association fibres originate and terminate within the same hemisphere, positioned in an anterior-posterior orientation. Long association tracts connect regions between lobes, and some of the major association tracts include the arcuate fasciculus (connecting the temporal and inferior parietal cortices to the frontal lobe), uncinate fasciculus (connecting the limbic system within the temporal lobe to inferior portions of the frontal lobe), cingulum (originating from the temporal pole, forming a 'belt' around the corpus callosum, and terminating in the orbitofrontal cortex), and inferior longitudinal fasciculus (connecting the occipital and temporal lobes). All are involved in higher cognitive development, including language, memory, and socio-emotional outcomes.

The subplate zone is a transient layer 4–5 times the size of the cortical plate at the beginning of the third trimester (Kostović and Jovanov-Milosević, 2006), and from 35 weeks of gestation, a gradual decrease in the subplate zone is seen. Cortical afferents will develop connections through the subplate zone, with thalamocortical afferents 'waiting' in the subplate zone before forming connections with cortical layers (Figure 1.1).

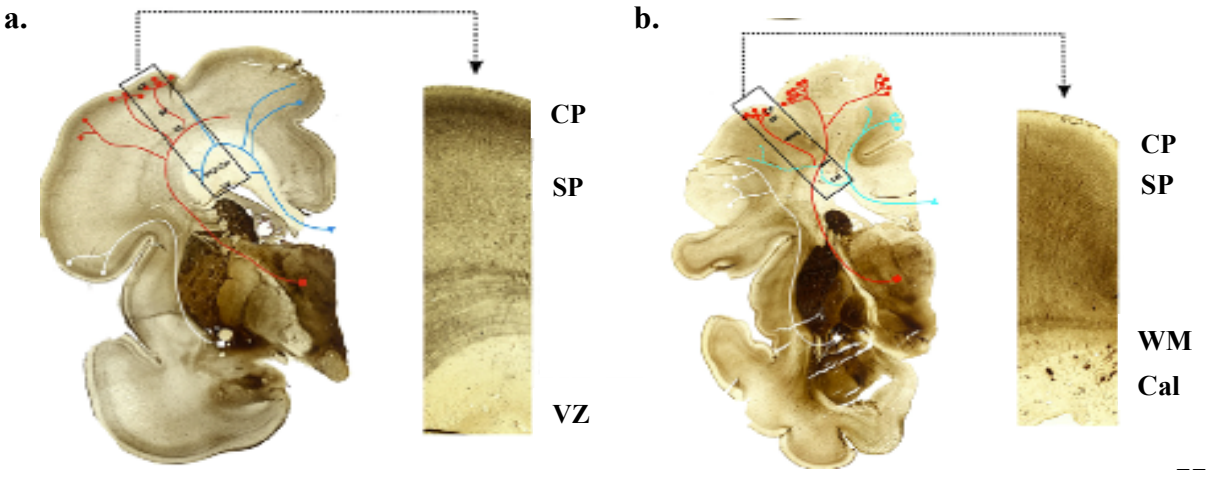


Figure 1.1. Transient fetal organisation of the developing cerebral wall during the a. early preterm phase, b. late preterm phase.
Growth of the cortical afferents: thalamocortical afferents are in red and callosal fibres in blue. Insets illustrate laminar organisation of transient zones of the cerebral wall (from pia to ventricle). CP, cortical plate; SP, subplate zone; VZ, ventricular zone; Cal, callosal fibres; WM, white matter. Adapted from (Kostović and Jovanov-Milosević, 2006).

Additionally, and on a microscopic level, the subplate is a major site of synaptogenesis, important for regulating the maturation of synaptic transmission (Kanold and Shatz, 2006). It is also crucial for fibre structure organisation and cortical circuitry formation in the developing neocortical network (Kostović et al., 2014). Subplate cells participate in axonal connections in both local circuits, exhibited as dense axonal arborisation within the subplate, as well as long-distance circuits with projections to the cortical plate (Luhmann et al., 2009). Subplate neurons contain heterogenous neuronal populations characterised by significant diversity in their morphology, neurotransmitter type, and connectivity. These include neurons that receive glutamatergic synaptic inputs arising from neocortical regions, as well as GABAergic synaptic inputs originating from local GABA interneurons (Bystron et al., 2008). Whilst the subplate will eventually disappear, the majority of its neurons will survive as interstitial neurons of the subcortical (gyral) WM (Judaš et al., 2010). Therefore, subplate cells play an important role in the generation of synchronised network activity during this fetal stage of increased plasticity, that will have long-lasting effects on the neocortical network.

During a time when the human brain is undergoing its most rapid phase of growth, it also exhibits heightened sensitivity to its environment and an increased vulnerability to insult (Volpe, 2009a). Notably, preterm birth occurs during this dynamic and vulnerable stage of brain development, potentially altering maturational trajectories and leaving the brain highly susceptible to developmental delays and structural alterations.

1.2.2 Possible factors affecting brain development during the third trimester in VPT neonates

There are two major causes for such delayed and altered development. Firstly, perinatal brain injury, a common occurrence in preterm infants that could occur either before or after delivery, is

likely to affect ongoing fetal and/or postnatal developmental events and their physiological timing. Secondly, developmental delay might be caused by abnormal exposure to certain environments and compounds, such as external stimuli and the use of drugs and procedures for life-saving clinical measures (Penn et al., 2016). These two mechanisms work together to further worsen neurological outcomes, which in turn have life-long implications on the cognitive and behavioural development of preterm individuals.

1.2.2.1 Perinatal brain injury

Haemorrhage

Infants born very prematurely are at a high risk of haemorrhages, which tend to originate in the capillary network of the germinal matrix, a brain region located on the head of the caudate nucleus that is at its thickest at 24 weeks of gestation and almost disappears by 37 weeks (Ballabh, 2010; Ballabh, 2014). This periventricular brain region is especially susceptible to burst blood vessels due to thin and fragile vessel walls and fluctuations in cerebral blood flow (Berger and Söder, 2015). Such haemorrhages might be confined to the germinal matrix, which are known as germinal matrix haemorrhage (GMH), and have an incidence rate of 25–30% of preterm births (Inder, 2006).

A more severe haemorrhage, known as intraventricular haemorrhage (IVH), occurs when the ependyma (lining of the ventricle) is damaged, and blood enters the ventricle. Severe IVH occurs in only around 4–5% of preterm infants with very low birth weight (VLBW, <1500g), with this number increasing to 20–30% in preterm infants born before 26 weeks of gestation or weighing below 750g (Volpe, 2009a).

An additional brain region susceptible to haemorrhage during the preterm period is the cerebellum, and cerebellar haemorrhage is also thought to originate from the germinal matrix (Volpe, 2009b). Incidence of this lesion is dependent on degree of prematurity, with infants born <750 g showing an incidence rate of 17%, whilst only 2% of those born 750–1499g exhibit cerebellar haemorrhage (Limperopoulos et al., 2005a).

White matter injury

Periventricular white matter injury (PWMI) involves a spectrum of injuries ranging from focal lesions, including periventricular leukomalacia (PVL), to diffuse myelin alterations, often referred to as diffuse PWMI (Kinney and Back, 1998; Volpe, 2001). While the burden of PVL has decreased dramatically with improvements in neonatal intensive care (Hamrick et al., 2004), diffuse PWMI is now thought to be the most common type of injury in the preterm brain (Back, 2017).

PVL occurs as a result of ischaemia and inflammation, both common in preterm infants (Khwaja and Volpe, 2008), and refers to a localised lesion, usually around the upper-outer angles of the lateral ventricles. Most often, PVL is microscopic in size ('non-cystic PVL') and will eventually develop into glial scars. Macroscopic ('cystic') PVL, which could grow to several millimetres in size, is observed in less than 5% of infants with VLBW (Volpe, 2009a).

Diffuse PWMI is characterised by alterations to typical myelin development, especially in the proximity of the lateral ventricles, which in turn leads to long-term irreversible damage to the WM surrounding this area (Haynes et al., 2003). During the period when infants are at greatest risk for PWMI (24 to 32 weeks of gestation), oligodendrocyte progenitors (pre-OL) are predominant in the cerebral WM. These cells have an enhanced vulnerability to hypoxic-ischemic conditions common in infants born prematurely (Volpe, 2009a). As a result, pre-OLs experience an arrested development and are unable to differentiate into cell-myelinating oligodendrocytes required for WM growth (Back and Miller, 2014). Cells in the oligodendroglial lineage that arise both before and after pre-OLs are less susceptible to hypoxia-ischemia (Back et al., 2002). Therefore, axons preparing to myelinate are more susceptible to ischemic injury when compared with both unmyelinated and myelinated axons (Alix et al., 2012). This might help explain why infants are at a greater risk for PWMI during this period. Additionally, the activation of astrocytes and microglia may also be compromised in response to ischemic-hypoxic conditions, which in turn leads to further damage and injury (Raybaud et al., 2013; Volpe, 2009a).

The potential consequences of these processes in preterm samples include a thin corpus callosum, white matter signal abnormalities, enlarged lateral ventricles, and volumetric deficits in multiple cortical regions, especially in the parieto-occipital cortex, which lies next to WM regions most susceptible to PVL and PWMI (Inder et al., 1999; Inder et al., 2005; Inder et al., 2003).

1.2.2.2 Extrauterine environments

Notably, altered neuroanatomical development occurs not only secondary to endogenous injuries, but also in response to the neonatal environment. Newborn preterm infants are typically exposed to stressful procedures and environments in the neonatal intensive care unit (NICU), which are likely to have bright lighting and increased noise levels. The level of exposure to auditory and visual stimuli the infant experiences has been of particular concern, however studies investigating associations between sensory input and brain development have produced inconclusive results.

Previous literature has suggested a reduction of sensory exposure, such as noise levels, is required for optimal brain development (Brown, 2009; Graven, 2000). Conversely, a more recent study found that preterm infants who were cared for in private rooms exhibited delayed neurological maturation when compared to those assigned to a bedspace in an open ward (Pineda et al., 2014). The same group also reported that private rooms had more silence than the open ward, highlighting the need for further research into the potential effects of sensory exposure in the NICU (Pineda et al., 2017a).

Sensory experiences in the NICU have also been used as part of interventions aiming to improve outcomes of preterm infants. Despite inconsistent findings, there is some evidence supporting the use of sensory exposure for improved development, including tactile (e.g. skin-to-skin), auditory (e.g. maternal voice, music), and visual (e.g. cycled light) stimuli (Pineda et al., 2017b). For example, preterm infants exposed to music in the NICU are shown to exhibit significantly increased maturation in specific WM tracts, including the uncinate fasciculus (UF), as well as larger amygdala volumes, two regions known to be involved in emotional processing (Sa de Almeida et al.,

2020). Results from these studies suggest that the content of sensory input, as well as levels of exposure, could differentially alter brain development in the preterm neonate.

During their time in the NICU, preterm infants will often undergo painful, albeit vital, procedures, and infants exposed to such procedures are more likely to display worse development of neural pathways, and in turn worse behavioural outcomes (Ranger et al., 2014). Neonatal procedural pain and early stressors affect brain structure and function (Vinall and Grunau, 2014), including altered thalamic development (Duerden et al., 2018), reduced frontal lobe cortical thickness (Ranger et al., 2013) and altered cerebellar structure (Ranger et al., 2015). Functional pain-perception pathways in preterm infants could be seen as early as 25 weeks of gestation (Bartocci et al., 2006; Slater et al., 2006), and one biological mechanism believed to facilitate the receptiveness of the developing cortex to external environments are the thalamocortical axons, which become sensory-driven in function during the third trimester (Kostović and Judas, 2010).

Medications such as morphine have also been associated with altered brain development in preterm individuals. Preterm neonates exposed to morphine had smaller cortical volumes in several brain regions when compared to those who were not treated with morphine (Steinhorn et al., 2015). Sedative medications such as midazolam also showed an association with reduced hippocampal volume and microstructure, and this effect was independent of procedural pain exposure (Duerden et al., 2016). Other medications commonly exposed to preterm infants are glucocorticoids, which although are useful in the treatment of lung problems, have been shown to be associated with impaired growth of the cerebellum (Tam et al., 2011). Taking these findings together, brain structure and function will be affected by not only neonatal pain, but also the medication used to treat it. This aids in highlighting the severity of issues faced by preterm neonates and highlights the need to research such alterations and their behavioural consequences.

Nutritional intake of preterm neonates during their first few weeks in the extrauterine environment has also been associated with brain maturation. The literature has identified a positive association between neonatal energy and lipid intake and measures of brain growth, including increased brain volumes and improved WM development at TEA (Beauport et al., 2017), 5 years (Schneider et al., 2018), and adolescence (Isaacs et al., 2008). More recently, the role of specific

nutrients during this critical period were investigated in relation to WM development during childhood (Sato et al., 2021). The study indicated that whilst protein, lipid, and energy intakes were all associated with WM development, protein intake contributed most to the positive effects of nutrition, as measured by FA increases and RD decreases. No significant associations were found between carbohydrate intake and WM development (Sato et al., 2021). Additionally, breast milk has long been assumed to have beneficial effects on neurocognitive development in preterm children (Anderson et al., 1999). Exposure to breast milk has recently been shown to be positively associated with improved markers of brain development, exhibited by increased FA values within major WM tracts, with patterns of association suggesting a dose effect (Blesa et al., 2019).

1.2.2.3 Infection

Maternal infections are common during pregnancy, and infections of the fetus occur in approximately 20-30% of confirmed intrauterine infections. Additionally, chorioamnionitis complicates around a quarter to a third of all births occurring prior to 34 weeks of gestation (Bennet et al., 2018). Postnatal infection is also common in preterm neonates, with one study reporting 25% of preterm infants had confirmed sepsis and 23% had suspected infection (Rand et al., 2016). Previous literature has reported conflicting findings regarding the effect of prenatal infections, such as chorioamnionitis, on altered WM development. Some studies have indicated an association between chorioamnionitis and brain development (Anblagan et al., 2016; Pogribna et al., 2013; Reiss et al., 2022), whilst others have not (Bierstone et al., 2018; Chau et al., 2009), with one literature review indicating that around 30% of studies report an association between chorioamnionitis and perinatal brain injury (Ylijoki et al., 2012). Inconsistent findings could be attributed to methodological differences between the studies, including sample characteristics and brain injury measures. The ongoing improvements to neonatal clinical care could also contribute to inconsistent findings, with the use of certain procedures now considered to be routine care, such as antenatal corticosteroids, shown to diminish associations between chorioamnionitis and brain injury (Kent et al., 2005; Sato et al., 2011). Postnatal infections have more consistently been associated with altered WM development

during infancy (Adams et al., 2010; Chau et al., 2012; Lee et al., 2014; Nijman et al., 2013; Shah et al., 2008) and childhood (Thompson et al., 2021).

Associations between perinatal infections and altered brain development are thought to be mediated by inflammation; systemic infections cause inflammatory responses, which in turn can affect brain development (Cordeiro et al., 2015; Hagberg et al., 2015). Inflammatory responses increase the brain's susceptibility to secondary stress, including hypoxic-ischemic events (Adén et al., 2010; Eklind et al., 2001; Wang et al., 2007). Inflammation itself has been shown to directly cause brain damage; this has been demonstrated in animal models (Normann et al., 2009), as well as in human preterm infants with systemic inflammation (Van Steenwinckel et al., 2014). Such associations explain the positive effects of anti-inflammatory antenatal steroids on the relationship between chorioamnionitis and perinatal brain injury, seen in preterm neonates (Kent et al., 2005; Sato et al., 2011).

As altered neural development in preterm infants might result from both endogenous and exogenous processes, such undesirable outcomes are common in this population. Neuroimaging techniques over the past few decades has allowed the investigation of such alterations, providing increasingly detailed information on altered brain development in very preterm survivors.

1.2.3 Brain development during childhood

Parallel to the increasing of insulation in the form of myelin, events surrounding grey matter refinement occur by way of programmed cell death, synaptogenesis, sulcation and gyrification. Following the rapid development of GM and WM macrostructure, the brain expands in size and continues to grow with age, reaching approximately 90% of adult size by age five (Dekaban and Sadowsky, 1978). Whilst cerebral volume plateaus, the structural integrity and organisation of the GM and WM continues to develop and reorganise throughout the remainder of childhood, adolescence, and early adulthood. These are described in the following sections which summarise results of neuroimaging studies (Section 1.3).

1.3 Neuroimaging findings in preterm birth

1.3.1 Structural MRI

1.3.1.1 Structural MRI techniques

Structural MRI is a neuroimaging technique that can provide a detailed anatomical image of the brain. MRI signal acquired varies across different tissue types (e.g., GM, WM) due to their different compositions. An image is represented by a 3D matrix of voxels, each containing a value to represent the level of intensity. Intensity is calculated from the frequency of the raw data collected and is displayed as shades of grey. Brain volumes can be measured with structural MRI through methods that range from manual processing to fully automated. Volumes could be calculated using manual segmentation of regions of interest, ideally carried out by more than one observer.

Automatic structural magnetic resonance (MR) processing techniques can involve the registration of images using spatial normalisation, to allow the comparison of specific regions. Voxel-based morphometry (VBM) is an automated technique that utilises spatial normalisation to detect regionally specific differences in brain tissue composition on a voxel-by-voxel basis (Ashburner et al., 2003; Ashburner and Friston, 2000). Once images are spatially normalised, brains can be segmented into particular tissue types, such as GM, WM, and CSF, by identifying voxel intensities (Good et al., 2001). Deformation-based morphometry (DBM) builds on VBM by using the deformation fields that are computed as part of the spatial normalisation process, that store information on the extent of warping and intensity differences between an image and template. DBM is therefore able to characterise differences in relative positions of brain structures (Ashburner et al., 1998; Rueckert et al., 2003; Rueckert et al., 1999). Similarly, tensor-based morphometry (TBM) also uses information from deformation fields but is also able to detect local shape differences (Ashburner and Friston, 2000; Chung et al., 2001).

Additionally, cortical surface can be measured through tessellation techniques, that divide surfaces into triangles in order to capture their metric and topological properties (Dale et al., 1999; Fischl et al., 1999). This allows not only the quantification of surface area, but also the measurement

of cortical thickness, which is calculated as the closest distance between the cortical surface and the GM/WM border (Fischl and Dale, 2000).

1.3.1.2 Structural brain development

Structural MRI findings in neonatal brain development

The brain has been shown to exhibit great increases in total volume during the third trimester (28–40 weeks of gestation), in both fetuses and preterm newborns (Dimitrova et al., 2021; Gholipour et al., 2011; Huppi et al., 1998b; Kuklisova-Murgasova et al., 2011; Makropoulos et al., 2016).

Between 27 and 44 weeks of gestation, the absolute volume of cortical GM increases by 10.4% per week, the cerebellum by 9.9% and subcortical structures between 4% and 6% (Dimitrova et al., 2021). The relative volume of cortical GM (i.e., proportional to the rest of the brain) also increases over this period, representing around 25% of the total brain volume in the early preterm period, which increases to around 34% at term-equivalent age (TEA) (Makropoulos et al., 2016). More recent findings have indicated increases in the relative cortical GM volume of 36% to 44% between 37 and 44 weeks of gestation (Dimitrova et al., 2021). The same study investigated subcortical structures, with findings indicating an increase in the relative volume of lentiform nucleus, decrease in the relative volume of caudate nucleus, and no change in the relative volume of thalamus (Dimitrova et al., 2021). The cerebellum, in particular, has been shown to demonstrate an especially high growth rate, with MRI findings indicating a 3.5-fold increase from 28 to 40 weeks of gestation (Limperopoulos et al., 2005b), representing around 7% of the total brain volume by 44 weeks (Dimitrova et al., 2021).

Cortical surface area and cortical sulci maturation also show a dramatic increase after 30 weeks of gestation (Dubois et al., 2008), with peak rate of gyrification occurring at around 30 weeks of gestation, before subsequently slowing nearer to the time of birth (Wright et al., 2014). Distinguishing differences between growth trajectories of various cortical metrics, recent studies have indicated that whilst volume continues to increase after TEA, mean curvature increases until 38 weeks of gestation, before plateauing (Batalle et al., 2019; Fenchel et al., 2020).

WM volume also undergoes considerable change over the perinatal period, and MR studies have highlighted a significant increase in WM absolute volume during the third trimester (Dubois et al., 2008; Huppi et al., 1998b). Despite this increase in volume, studies using both manual and automatic segmentation techniques indicate around 60–70% relative WM volume in the early preterm period (Moeskops et al., 2013) and 46–48% at term (Anbeek et al., 2008; Makropoulos et al., 2016). More recent findings have indicated a decrease in WM relative volume from 48% at 37 weeks to 38% at 44 weeks of gestation (Dimitrova et al., 2021).

Structural MRI findings in childhood brain development

During childhood, total GM volume increases with age and peaks during pre-adolescence, followed by a decrease in GM volume (Giedd et al., 1999; Mills et al., 2016). More specifically, frontal and parietal GM volume peaks at 11 years, whilst temporal lobe GM peaks at 16 years, and occipital lobe GM increases linearly with no evidence of peak or decrease. Similarly, cortical thickness will reach its peak by around 10 years, with higher order cortical regions, such as the dorsolateral PFC and cingulate cortex, reaching peak thickness last (Shaw et al., 2008). WM volume, in contrast, increases steadily into the second and third decades of life (Mills et al., 2016). Several mechanisms could cause such increases in volume and thickness, including axon density, cross-section, axon calibre, and overall fibre architecture.

The development of specific brain regions has been studied in parallel to the emergence of behaviour in children and adolescents. In particular, brain regions known to be implemented in socio-emotional behaviour, such as limbic structures and the PFC, show significant development during late childhood and adolescence (Albaugh et al., 2017b; Casey et al., 2008). The development of such brain regions facilitates complex functions, such as emotion regulation and self-consciousness (Somerville et al., 2013). A delay in cortical maturation has been shown to be associated with socio-emotional difficulties in children and adolescents, including subclinical anxious and depressive symptoms (Ducharme et al., 2014; Newman et al., 2016). These results demonstrate the importance of studying age-dependent GM developmental trajectories in relation to mental health outcomes.

Structural MRI findings following very preterm birth

Preterm birth is associated with altered cerebral volumes, with smaller volumes reported in widespread cortical GM in preterm neonates when compared to term-born controls at TEA. Brain tissue volumes exhibit a positive relationship with GA, and infants born earlier and with lower birth weight show the largest deviations from normative brains (Dimitrova et al., 2021). Volume reductions have been reported in preterm compared to term neonates in specific regions, including parietal, occipital, and temporal cortices, cerebellum, and the brainstem (Alexander et al., 2019; Dubois et al., 2021a; Galdi et al., 2020; Inder et al., 2005; Peterson et al., 2003). One study of a large cohort of neonates born between 27 and 42 weeks, all imaged at TEA, found both positive and negative correlations between GA and specific regional brain volumes when covariates such as post-menstrual age at scan, birthweight, and sex were considered (Knickmeyer et al., 2017). A more recent study investigating cortical GM volumes in preterm neonates failed to find gestational age-dependent differences in total cortical GM volumes, although it did report larger regional GM volumes in those born earlier, specifically in primary visual, motor, and somatosensory cortices (Alexander et al., 2019). The researchers speculate a possible mechanism for this increased cortical development could involve increased sensory input with greater time ex-utero. Future research could support these novel findings in order to explain such differences.

A vulnerability to alterations as a result of preterm birth has also been observed in deep GM, including the thalami and basal ganglia (Boardman et al., 2006; Dubois et al., 2021a; Srinivasan et al., 2007). Such alterations, specifically reduced thalamic volume, are related to reduced cortical volumes encompassing widespread regions within the frontal, temporal, parietal, and occipital lobes (Ball et al., 2012). Additionally, decreased cortical surface area and cortical folding complexity are also seen in extremely preterm neonates at TEA (Ajayi-Obe et al., 2000; Kapellou et al., 2006).

Similar findings have been identified in older preterm children, with reduced cortical volumes and surface area apparent in widespread GM, including regions of sensorimotor, frontal, and temporal lobes (Gimenez et al., 2006b; Kesler et al., 2008; Peterson, 2003; Sølsnes et al., 2015). Decreased GM

volumes are reported in preterm children and adolescents in the cerebellum, basal ganglia, amygdala, fusiform gyrus, insula, thalamus, and the hippocampus (Aanes et al., 2015; Boardman et al., 2010; Counsell and Boardman, 2005; Nosarti et al., 2002; Nosarti et al., 2008; Nosarti et al., 2014; Peterson et al., 2000; Sølsnes et al., 2016), as well as altered hippocampal shape (Thompson et al., 2014). The lateral ventricles, on the other hand, are reported to be larger in preterm children (Sølsnes et al., 2016).

In addition to GM, WM structure is also altered in preterm-born individuals compared to term-born controls. Structural MRI has long been used in preterm neonates to detect the presence of cerebral WM abnormalities, such as cysts, loss of WM volume, ventriculomegaly, and corpus callosal thinning/myelination (Cooke and Abernethy, 1999; Inder et al., 2003; Stewart et al., 1999). More recent quantitative voxel-based morphometric analyses have identified that at TEA, when compared to controls, preterm neonates show smaller cerebral WM volumes (Alexander et al., 2019; Thompson et al., 2019), especially seen in the corpus callosum (Thompson et al., 2011). These alterations are apparent not only during the perinatal period, but also in preterm children and adolescents (de Kieviet et al., 2012b; Gimenez et al., 2006a; Nosarti et al., 2008; Rademaker et al., 2004), with males appearing particularly vulnerable to adverse effects of preterm birth (Kesler et al., 2008; Reiss et al., 2004).

Methodological considerations

When comparing MR images at TEA of neonatal groups of different gestational ages, one methodological issue concerns neonates' postmenstrual age at scan. Some studies have reported an association between neonates' GA and age at scan, citing reasons such as prolonged need for critical care for infants born at the low end, and later birth for infants born at the high end, of the GA range (Alexander et al., 2019; Dubois et al., 2021b). Therefore, it is custom to control for both GA and age at scan in statistical models.

1.3.2 Diffusion MRI

1.3.2.1 Diffusion Weighted Imaging

Diffusion MRI (dMRI) assesses water molecular motion in tissue and enables the microstructural properties of human brain tissue to be assessed. Water diffusion could be affected by its physiochemical properties (e.g., viscosity and temperature) as well as its structural components (e.g., intracellular organelles, membranes). dMRI works on the premise that in an unrestricted environment, water will diffuse to a similar extent in all directions (isotropic diffusion). On the other hand, in tissues that have an ordered structure, water molecular displacement will vary depending on the tissue structure and orientation (anisotropic diffusion) (Beaulieu, 2002). For example, coherent organisation of long neuronal axons within WM tracts favours diffusion along, rather than across, the length of the axons. If a WM tract is affected as a result of illness or insult, its diffusion characteristics will be altered in terms of the molecular motion and direction of diffused water particles.

In order to extract diffusion information, first an image with no diffusion attenuation (b = 0) is obtained. Diffusion-encoded gradients are applied to sensitise the MR signal to the magnitude of diffusion within the brain. The degree of diffusion weighting for each gradient, known as the b value, will vary depending on factors such as the amplitude and duration of the gradient. Signal obtained in these images is dependent on displacement of water *along the direction in which the diffusion gradient was applied* (therefore it is said to be 'rotationally-variant'). Through the application of several diffusion-weighted gradients in various directions, it is possible to produce a rotationally invariant estimates of tissue diffusivity. In diffusion weighted imaging (DWI), total net diffusion in a voxel can be represented by apparent diffusion coefficient (ADC) and calculated from Equation 1 (Le Bihan et al., 1986).

$$D = -\frac{1}{b}\ln\left(\frac{S}{S_0}\right)$$

Equation 1. Equation for calculating apparent diffusion coefficient. S and S_0 are signal measured with and without diffusion weighting and b reflects the degree of diffusion-weighting applied, determined on the timing, duration, and amplitude of the gradient.

1.3.2.2 Diffusion Tensor Imaging

The most common method of modelling water diffusivity is through the Diffusion Tensor model (diffusion tensor imaging, DTI) (Pierpaoli et al., 1996). (Basser et al., 1994). Within each voxel, the tensor (D) is represented by a 3 x 3 symmetric matrix used to describe the diffusion profile (Equation 2). The three diagonal elements give the diffusivities along the x-, y-, and z- axes, whilst the off-diagonal elements give the correlation between them. As D has six independent elements, it requires a minimum of six diffusion-weighted images and one non-diffusion weighted image in order to characterise the diffusion tensor.

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

Equation 2. 3x3 matrix used to represent diffusivity along three orthogonal axes of the tensor.

The diffusion tensor can be visualised as an ellipsoid representing probability of diffusion from the origin (Figure 1.2). In isotropic diffusion, this probability is equal in all directions and the tensor is represented as a sphere. In anisotropic diffusion, the orientation of the tensor ellipsoid will align with the underlying tissue microstructure. The ellipsoid can be calculated from D, using the orthogonal eigenvalues (λ_1, λ_2 and λ_3) – rotationally-invariant, scalar metrics representing the diffusivities along the three principal axes of the tensor. Eigenvectors are also calculated, which define the orientation of the eigenvalues (Pierpaoli and Basser, 1996; Tournier et al., 2011). The largest eigenvalue, λ_1, defines the orientation of the tensor. In anisotropic tissues, such as cerebral WM, the largest eigenvalue will be the one representing the diffusion coefficient along the dominant fibre orientation.

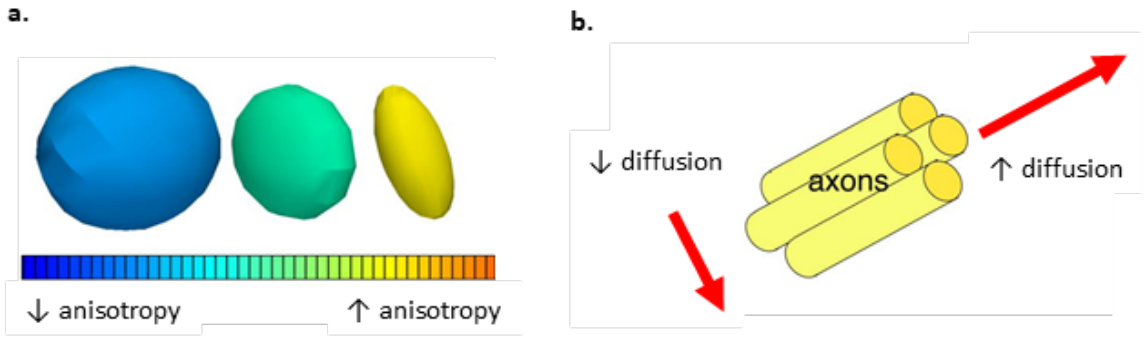


Figure 1.2. a) Three examples of diffusion tensors, illustrate differences in tensor anisotropy and orientation. b) Illustration of anisotropic diffusion, in a coherently oriented tissue. Increased diffusion measured parallel and decreased perpendicular to axons in fibre tract. Adapted from (O'Donnell and Westin, 2011).

Mean diffusivity (MD) describes the directionally averaged diffusivity of water molecules and is calculated using Equation 3. λ_1 represents axial diffusivity (AD), or the estimated magnitude of diffusion parallel to the principal axis of diffusion (along the main fibre orientation). When averaged, λ_2 and λ_3 represent radial diffusivity (RD), which is the estimated magnitude of diffusion across the direction of the fibres, perpendicular to λ_1.

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

Equation 3. Mean diffusivity (MD) is calculated by finding the mean of all three eigenvalues.

A widely used DTI metric is fractional anisotropy (FA), which measures the degree to which diffusion within the voxel is isotropic, i.e., the degree to which diffusion along one axis occurs preferentially over others (Pierpaoli and Basser, 1996). FA is calculated with Equation 4, and varies between 0 and 1, whereby 0 indicates isotropic, spherical tensor and 1 corresponds to the anisotropic limit. Higher FA represents greater proportion of water moving parallel to WM fibres than perpendicular to them (Pierpaoli and Basser, 1996), and is characteristic of well-developed WM tracts.

$$FA = \frac{\sqrt{3((\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2)}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

Equation 4. Equation used to calculate fractional anisotropy (FA) from the three eigenvalues (λ1, λ2 and λ3).

DTI models have been criticised due to the average smoothing effect that presumes some homogeneity within a voxel. Image resolution in DTI typically ranges between 1 and 3 mm and each voxel can contain many thousands of axons. Therefore, DTI is not suitable for modelling multiple fibre orientations ('crossing fibres') within a voxel, and instead provides an average of these, therefore oversimplifying the underlying neuroanatomy. As voxels containing crossing fibres are present in up to 90% of all voxels (Jeurissen et al., 2013), this forms a major limitation of DTI and means that the retrieval of specific information about tissue microstructure from such measures are controversial and limited (Le Bihan, 2013).

DTI findings in neonatal brain development

As WM tracts develop, water becomes hindered in its movement, especially in the perpendicular direction to the tract. This is influenced by myelination, but the presence of changing diffusivities prior to myelination suggests additional contributing factors, including an increase in axon diameter and increases in the early wrapping of oligodendroglia around the axons (Huppi et al., 1998a). Specifically, a decrease in AD over the neonatal period reflects a reduction in interaxonal space (Takahashi et al., 2000) as well as an increase in axonal number or size (Song et al., 2002a; Song et al., 2002b). Decreases in RD, on the other hand, indicate changes in myelin that result in a reduced permeability of the tract (Suzuki et al., 2003). The implications of these two processes leads to a decrease in MD, whilst FA increases (Kimpton et al., 2021; McKinstry et al., 2002; Neil et al., 1998; Partridge et al., 2004), with increasing age. Therefore, low MD and high FA represents more highly organised tracts during the neonatal period.

In addition to assessing the microstructure of specific white matter tracts, studies have also utilised DTI metrics in order to model the network topology of the brain, or the 'connectome' (Fornito and Bullmore, 2015). For example, findings have indicated neonates display well-connected and efficient networks, that show increased efficiency with age and become more segregated as neonates approach TEA (Ratnarajah et al., 2013; Zhao et al., 2019). Due to the rapid increase of connections during the third trimester, both between and within networks, it is thought that extra-uterine stressors and sub-optimal conditions are likely to influence the development of these connections.

DTI findings in childhood brain development

WM develops over childhood primarily through the myelination of axons, subsequentially influencing neurotransmission. Age-related increases in FA and decreases in MD have been reported in typical neurodevelopment, thought to reflect increased organisation of WM (Barnea-Goraly et al., 2005; Lebel et al., 2008; Schmithorst et al., 2002; Snook et al., 2005). DTI studies have also indicated that the rate of FA increase is relatively stable over late childhood and early adolescence (Krogsrud et al., 2016).

Spatially, WM follows a posterior-to-anterior gradient of development (Asato et al., 2010), and so last to mature are the fibre pathways connecting the frontal cortex, undergoing a protracted development over adolescence into adulthood (Lebel and Beaulieu, 2011). Coinciding with the timing of these frontal pathways' maturation is adolescence and pubertal changes, suggesting hormonal influences on WM development (Asato et al., 2010; Barnea-Goraly et al., 2005). These morphological developments lead to changes in functional brain circuitry, which in turn will impact behaviour.

Such age-dependent brain-behavioural interactions have been described in DTI studies investigating sub-clinical behavioural outcomes in children ranging from preschool age to adolescence (Albaugh et al., 2017a; Andre et al., 2020). Diffusion characteristics of specific WM tracts have been shown to change with age and have shown age-dependent interactions with behavioural problems. For instance, children with behavioural difficulties have been found not to exhibit changes in FA values between childhood and adolescence, whilst those who are more well-

adjusted show have demonstrated age-dependent FA increases. These effects have been observed in WM tracts associated with socio-emotional processing, including the UF (Andre et al., 2020), superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus (ILF) (Albaugh et al., 2017a). Therefore, alterations in the development of WM microstructure may result in delayed or altered socio-emotional development, highlighting the importance of studying age-dependent WM developmental trajectories in relation to behavioural outcomes.

DTI findings following very preterm birth

Findings from DTI studies have indicated altered microstructural development following VPT birth. When compared to term-born controls, preterm infants exhibited increased FA and MD in the cortical GM at TEA, with such microstructural alterations showing direct associations with GA and birth weight (Ball et al., 2013b; Bouyssi-Kobar et al., 2018). Preterm infants also exhibit altered microstructural characteristics of WM tracts, with findings indicating decreased FA and increased MD in widespread WM association, projection, and commissural tracts (Alexandrou et al., 2014; Anjari et al., 2007; Batalle et al., 2017; Boardman et al., 2010; Dimitrova et al., 2020; Huppi et al., 1998a; Neil et al., 1998; Pannek et al., 2013; Thompson et al., 2019). Studies investigating specific tracts found similar alterations, most commonly in the corpus callosum, thalamic connections, and corticospinal tract (CST) (Ball et al., 2013a; Groppo et al., 2012; Hasegawa et al., 2011; Thompson et al., 2012), and more recently, in the cerebellar peduncles (Machado-Rivas et al., 2021). Such alterations in WM microstructure in the form of increased diffusivities (MD, RD and AD) and decreased FA are also shown to be associated with white matter injury in preterm infants (Adams et al., 2010; Counsell et al., 2006; Liu et al., 2012; Miller et al., 2002; Thompson et al., 2012; van Pul et al., 2012a), highlighting the effects of perinatal brain injury on WM microstructure.

Group differences have also been reported in older preterm populations, with studies identifying significant alterations in WM microstructure when compared to term-born controls. Many studies have identified both decreased FA and increased MD and ADC in preterm children and adolescents (Constable et al., 2008; Dodson et al., 2017; Dubner et al., 2019; Duerden et al., 2013;

Groeschel et al., 2014; Jo et al., 2012; Kelly et al., 2016a; Li et al., 2015a; Mullen et al., 2011; Murray et al., 2016; Pieterman et al., 2018; Travis et al., 2015; Travis et al., 2019; Young et al., 2018). At the same time, some studies have found no differences in DTI metrics between VPT and term-born controls (Bruckert et al., 2019; Sølsnes et al., 2016). Finally, research has also identified increased FA and decreased diffusivity measures in preterm children (Dodson et al., 2017; Tokariev et al., 2019). Such conflicting results of DTI studies could result from differences in study samples, imaging methods and analysis techniques. As discussed above (section 1.3.2.2: Diffusion Tensor Imaging), the DTI model is criticized for its inability to account for crossing fibres within voxels. It is possible that increases in FA might reflect a reduced number of crossing fibres, and not necessarily increased maturity in these tracts (Groeschel et al., 2014), and therefore careful interpretation of FA results should be applied, and if possible, supplemented with additional diffusivity measures such as RD and AD.

Connectome studies have identified altered network architecture in preterm children, with findings indicating an effect of GA on reduced efficiency, worse organisation, decreased communication capacity, and diminished directional strength of brain connectivity (Fischi-Gomez et al., 2014; Kim et al., 2014; Thompson et al., 2016; Young et al., 2018).

1.3.2.3 Advanced dMRI analyses

Neurite orientation dispersion and density imaging

More advanced diffusion imaging techniques include neurite orientation dispersion and density imaging (NODDI), which measures WM microstructure in terms of the fraction of tissue comprising axons and dendrites (‘neurite density index’, NDI), as well as the degree of dispersion (bending and fanning) of neurite structures (‘orientation dispersion index’, ODI), within each voxel (Zhang et al., 2012). These metrics allow a more distinct characterisation of WM microstructure, with NDI providing information on axon density and myelination, whilst ODI quantifies the coherence of axons, allowing the distinction between voxels containing crossing fibres to those with a single fibre orientation.

As neonates mature, their dendritic structure develops with an increase in cellular density and complexity (Kostović and Jovanov-Milosević, 2006). Studies measuring age-related changes of NODDI within the cortex can inform us of the timings of such processes. A recent study found increases in ODI throughout the cortical GM before reaching a plateau at 38 weeks gestational age (Batalle et al., 2019). NDI, on the other hand, was reported to show a decreasing trend before 38 weeks of gestation in the middle frontal, cuneus, temporal, and occipital gyri, whilst increasing in somatosensory areas and occipital and orbitofrontal cortices through to 47 weeks of gestation (Batalle et al., 2019). The writers infer from the findings that dendritic arborisation takes place predominantly prior to 38 weeks, whilst increases in cellular and organelle density continues after this period. In neonatal WM, NODDI parameters also increase with age, with both ODI and NDI showing positive associations with PMA between 25 and 43 weeks of gestation (Kimpton et al., 2021). Further, a study utilising both DTI and NODDI metrics in order to characterise network topologic development found increases in efficiency over the neonatal period (Batalle et al., 2017).

One study investigating NODDI parameters in preterm children identified microstructural alterations when compared with term-born controls, including increased ODI in widespread WM regions encompassing major association, projection, and commissural tracts (Kelly et al., 2016b).

Fixel-based analysis

In recent years, more advanced diffusion MRI models have allowed for the distinction of multiple fibre populations in a single voxel (Tournier et al., 2011). A fixel refers to a single *fi*bre population within a vo*xel*, and fixel-based analysis (FBA) can identify specific fibre pathways, even in regions containing crossing fibres (Raffelt et al., 2017). One diffusion characteristic of interest here is the total intra-axonal volume of axons within a given fixel, which is a quantity related to a WM tract's 'ability to relay information'.

Figure 1.3 illustrates different ways in which total intra-axonal volume of a fibre bundle may vary. Firstly, fibre density (FD) illustrates altered tissue microstructure whereby decreases in volume can be seen *within-voxel*. Intra-axonal volume will be determined by both the number of axons within

the tract as well as axon diameter, which is thought to modulate transmission speed, timing and firing rate (Perge et al., 2012). Secondly, fibre cross-section (FC) depicts tissue macrostructure through quantifying the number of voxels the fibre bundle occupies. Thirdly, differences in fibre density and cross-section (FDC) will occur when WM is altered in both its microstructure within-voxel and macrostructure across the entire tract. FDC is considered as a comprehensive measure related to total intra-axonal volume within a pathway, and therefore most likely to reflect differences in 'ability to relay information' (Raffelt et al., 2017). Figure 1.3 is a schematic representation of these diffusion metrics.

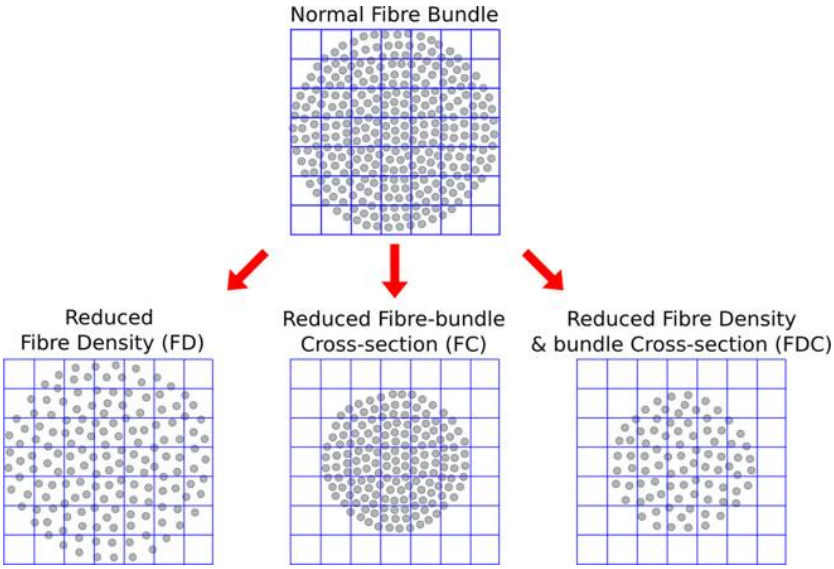


Figure 1.3. A schematic representation of a white matter cross-section (grey circles represent axons, the grid represents imaging voxels).
White matter deficit might manifest as decreases in: fibre density (FD), which captures the intra-axonal compartmental volume; fibre cross-section (FC), which estimates the spatial extent occupied by the tract perpendicular to its direction; and fibre density & cross-section (FDC), which takes into account both FD and FC to produce a comprehensive measure related to total intra-axonal volume within a pathway (Raffelt et al., 2017).

The following metrics may be calculated with FBA. Firstly, fibre density (FD) is an estimate of the density of axons within a fibre population in a voxel, measured through an estimation of the intra-axonal volume fraction of fibres aligned with corresponding direction. Increased FD could indicate increased axon diameter or increased number of axons within a given space (Genc et al., 2018), whilst a decrease could be due to a loss of axons (Gajamange et al., 2018). Secondly, fibre

cross-section (FC) refers to a morphological measure of the cross-sectional area in the direction perpendicular to the orientation of a fixel. Each subject's FC is calculated in relation to the template, and so a FC > 1 represents a larger fibre bundle in the subject than in the template. Thirdly, fibre density and cross-section (FDC) represents a combined measure of changes in both microscopic density (FD) and macroscopic morphology (FC), calculated as FD multiplied by FC (Raffelt et al., 2017).

Findings from studies of preterm neonates have identified associations between age at scan and FBA metrics over the neonatal period. A recent study identified positive correlations between neonates' age (38–47 weeks of gestation) and FD, FC, and FDC in various WM tracts. Tracts where associations were found between all three metrics and age at scan included the corpus callosum and ILF. Associations with FD only were reported in the forceps minor and major, corona radiata, inferior fronto-occipital fasciculus, and SLF. Associations with FC only were reported in the CST and cerebellum (Pecheva et al., 2019).

Pecheva and colleagues (2019) also investigated the relationship between FBA metrics and GA at birth, reporting associations between increased prematurity and decreased FD, FC and FDC. Associations with FC were indicated in more WM tracts than with FD. These results are supported by findings of significant differences in FBA metrics between VPT and full-term neonates at TEA (Pannek et al., 2018). Preterm infants exhibited reduced FD, FC, and FDC in all three metrics in the corpus callosum, whilst reduced FD only were apparent in the fornix. Reductions in FC only were more widespread, including optic radiations, cingulum, cerebral & cerebellar peduncles and SLF. Distinctions between VPT and full-term controls have been identified in older children, with similar findings of more widespread deficits in FC compared to FD in the VPT group (Kelly et al., 2020).

Methodological considerations

Structural brain alterations following VPT birth might be caused by specific medical factors, rather than an inevitable consequence of preterm birth (Boardman et al., 2007). Such factors might include the presence of respiratory illness (Boardman et al., 2007), intrauterine growth restriction

(Zimine et al., 2002), sex (Ball et al., 2017; Pecheva et al., 2019), and drug administration (Modi et al., 2001; Murphy et al., 2001). Research has also highlighted an exacerbated level of altered WM microstructure in preterm infants and children with inflammatory conditions and lung disease (Alexandrou et al., 2014; Bonifacio et al., 2010; Dubner et al., 2019; Shim et al., 2012). Therefore, research in the preterm field is required to take such clinical variables into consideration, by investigating direct associations between variables and WM structural development (e.g., Barnett et al., 2018; Pecheva et al., 2019).

To summarise, preterm birth has long-term consequences affecting both GM and WM micro- and macrostructure. It is still unclear whether these occur due to brain reorganisation, WM dysmaturity or instead the downstream effects of injury, and future longitudinal imaging research in this area will give us insights into the developmental trajectories of such structural alterations.

1.3.3 Functional MRI

1.3.3.1 Functional MRI techniques

The immense structural development occurring during the third trimester, or the period between VPT birth and TEA, has implications for the functional organisation of the brain, both during this period and later in the individual's life. Functional magnetic resonance imaging (fMRI) is a neuroimaging technique that provides information about neural activity through an indirect mechanism of measuring blood oxygenation levels (Kwong et al., 1992). Specifically, fMRI is sensitive to the relative changes in concentrations of deoxyhaemoglobin, that occur in response to neuronal activation, by exploiting their different magnetic properties (Ogawa et al., 1992). This is referred to as the blood oxygen level dependent (BOLD) contrast, an indirect marker of the temporal pattern of neural activity. This marker smooths and delays the original neural activity, and therefore has been said to suffer from limited temporal resolution (Kim et al., 1997). BOLD activity may be measured within spatially isolated regions-of-interest, or the connectivity of two regions. Functional connectivity is measured through the temporal correlation of spatially distant regions' BOLD activity,

and GM regions that show temporally correlated BOLD signal fluctuations are assumed to have related neural activity, i.e., they are functionally connected. fMRI could be used to measure BOLD activity both in the absence of any stimulation during a 'resting-state' study, as well as in response to a stimulation during 'task-based' studies (Biswal et al., 1995).

1.3.3.2 Resting-state functional MRI

fMRI studies performed without stimulation or task have discovered that the "resting brain" contains very distinct patterns of spontaneous low frequency activity. Resting state networks (RSNs) might be studied with resting-state fMRI (rs-fMRI) by identifying prominent resting-state FC (rs-FC) patterns in the whole brain. RSNs have distinct spatial patterns and time courses and are present even in sleep and under sedation (Fukunaga et al., 2006; Greicius et al., 2008). In adults, RSNs correspond to activation patterns in the active brain during tasks (Smith et al., 2009). One explanation for this points to several 'task-like behaviours' performed at rest, such as future preparation, learning consolidation and rehearsal (Buckner and Vincent, 2007). The default mode network (DMN), one of the more commonly studied RSNs, is active during rest and is thought to be actively implicated during internal or introspective thoughts (Raichle, 2015).

Resting-state fMRI findings in neonatal brain development

RSNs develop over time in neonates and children, with the strengthening of connections between spatially remote regions resulting in more cohesive and connected circuits. Even so, functional RSNs that are comparable to networks seen in adults have been identified in the neonatal brain, and fetal research has indicated an age-dependent increase in rs-FC in both interhemispheric (Thomason et al., 2013) and intrahemispheric (Thomason et al., 2015) connections. By TEA, there is evidence of functional networks confined to primary sensory and motor brain regions (Doria et al., 2010; Fransson et al., 2011; Fransson et al., 2007; Lin et al., 2008), whilst the development of full RSNs in infancy was shown to be primitive or incomplete (Eyre et al., 2021; Gao et al., 2013; Gao et al., 2009; Smyser et al., 2010). Therefore, primary networks such as the visual and auditory networks

develop before higher-order spatially-distant networks (Keunen et al., 2017), and this pattern is mimicked in developmental milestones, whereby infants grasp basic sensory functions within the first few years of life (e.g., Adams et al., 2004) whilst higher order cognitive functions develop well into early adulthood (Casey et al., 2000). For example, development of DMN by infancy is debated, with some identifying no rs-FC patterns resembling the DMN (Eyre et al., 2021; Smyser et al., 2010), whilst others have suggested otherwise (Doria et al., 2010).

Resting-state fMRI findings in childhood brain development

In general, the development of cognitive abilities arises not solely from a particular brain area, but instead from networks of activity spanning multiple brain regions (Petersen and Sporns, 2015). Over childhood and adolescence, these functional networks reconfigure, showing strengthening of connectivity within RSNs (de Bie et al., 2012; Sherman et al., 2014). Earlier studies reported that, whilst rs-FC between anatomically proximate ROIs decreased, long-range connections gradually increased (Fair et al., 2009; Supekar et al., 2009). This suggests that, with time, children display a dampening of non-specific local activity and strengthening of long-range links, indicating specialised networks that facilitate cognitive development (Uddin et al., 2011).

More recently, however, studies have indicated variation in trajectories of networks responsible for different functional tasks. For example, sensorimotor networks are already well-developed in childhood, showing little change between childhood and adulthood (Gu et al., 2015). Alternatively, the overall connectivity of networks associated with higher-order cognitive abilities, including the DMN (Fan et al., 2021), salience network (SN) (Uddin et al., 2011) and dorsal attention network (DAN) (Rohr et al., 2018), show increases in strength and efficiency with age. These increases in network rs-FC, specifically in the DMN and DAN, are shown to be associated with improved attentional skills in childhood (Rohr et al., 2018). Therefore, more recent theories suggest that whilst network structure does continue to evolve after late childhood, such developments are not primarily distance-dependent, but instead coincide with the development of specific cognitive abilities (Grayson and Fair, 2017).

Altered connectivity within functional networks has been implicated in the development of psychiatric and neurocognitive disorders (Menon, 2011). For example, the DMN and SN have been shown to play an important role in the development of autism (Menon and Uddin, 2010), and detection of aberrant connections may indicate biomarkers of vulnerability for psychopathology in the developing brain (Menon, 2013). The functional connectivity of specific brain regions has also been studied from a developmental point of view, with the bilateral amygdalae showing particular importance for the development of emotion-related functions. Although structurally mature by the age of five (Giedd et al., 1996), the amygdalae's functional expression and regulation goes through major changes over childhood and adolescence, which in turn allow it to function as a major hub for processing affective and biologically salient cues (Pessoa and Adolphs, 2010). Its functional connectivity with other cortical and subcortical structures has been reported to be weaker in children than adults, suggesting increased amygdalae integration and segregation with age (Qin et al., 2012). Functional networks involving the amygdalae have been shown to undergo hierarchical changes during this developmental stage (Casey et al., 2019), and these are thought to underlie the changes in emotional reactivity and regulation throughout this developmental period.

Resting-state fMRI findings following very preterm birth

Studies assessing rs-fMRI in preterm neonates have highlighted similar overall RSN topography to FT infants, although networks display aberrant developmental trajectories. At TEA, preterm infants exhibit networks that are less segregated and integrated (Bouyssi-Kobar et al., 2019; Scheinost et al., 2016b), and show reduced complexity of intrinsic rs-fMRI activity (Smyser et al., 2016), when compared to term-born neonates. Differences in specific, well-established networks have also been detected in this population, with precursors of the DMN being detected in term, but not preterm, neonates (Smyser et al., 2010). Such differences in network maturation supports findings of structural brain development in this cohort.

Whilst reduced rs-FC is common in preterm infants compared to controls (Eyre et al., 2021; Kwon et al., 2015; Smyser et al., 2016), increased rs-FC at TEA is reported within the lateral motor

network. One cause for this could include extrauterine exposure during a period of heightened sensorimotor plasticity, which modulates parieto-motor connectivity and leads to abnormally increased connectivity within this region (Eyre et al., 2021). Although some studies identified more prominent alterations in higher-order association networks compared to primary networks (Smyser et al., 2016), more recent work has suggested these are equally affected (Eyre et al., 2021), and this discrepancy could be due to differences in approach to RSN definition, network mapping and inclusion criteria.

As discussed earlier in this chapter, thalamocortical connections that develop throughout the third trimester (Kostović and Jovanov-Milosević, 2006) are disrupted by VPT birth, which results in not only structural (Ball et al., 2013a), but also functional alterations in VPT infants (Smyser et al., 2016). Altered thalamus rs-FC with both higher-order cortical regions (Toulmin et al., 2015) and subcortical regions, including the bilateral amygdalae (Scheinost et al., 2016a), have been reported in this population. Ball and colleagues (2016) extended these findings by identifying disrupted rs-FC between additional deep GM nodes, namely the basal ganglia, and high-order cortical regions. Similarly, smaller rs-fMRI magnitudes have also been reported between the left amygdala and both subcortical and cortical regions in VPT infants compared to FT controls (Rogers et al., 2017). These findings support the notion that subcortical GM is particularly vulnerable to developmental alterations following preterm birth, and that subcortical-cortical connections are especially affected. Further, rs-FC alterations are more pronounced in those infants with increased levels of white matter injury and dependent on severity of, and proximity to, injury (Damaraju et al., 2010; Lubsen et al., 2011; Wheelock et al., 2018; Wilke et al., 2014).

Limited research has suggested that cohorts of VPT children also display reduced rs-FC both between and within RSNs when compared to term-born controls (Damaraju et al., 2010; Lubsen et al., 2011; Wheelock et al., 2018; Wilke et al., 2014), however, this area requires further investigation. In a recent analysis of the bilateral amygdalae rs-FC, Johns and colleagues (2019) found a significant increase between the amygdalae and both the parietal lobe and the left superior temporal gyrus, in VPT adolescents compared to term-born controls.

Resting-state connectivity has been shown to be a reliable method for assessing large-scale brain networks in neonates and children. Moreover, task-based and resting-state fMRI used in conjunction could be used to test comprehensively brain function associated with outcome behaviours.

1.3.3.3 Task-based functional MRI

Task-based fMRI techniques

Task-based studies can measure neural functional activity in response to specific tasks, by comparing activity during 'on' (experimental) and 'off' (baseline) conditions, implicating certain hemodynamic responses in specific mental operations required to complete the task (Soares et al., 2016) (Figure 1.4). Such studies could measure both regional BOLD activity as well as functional connectivity.

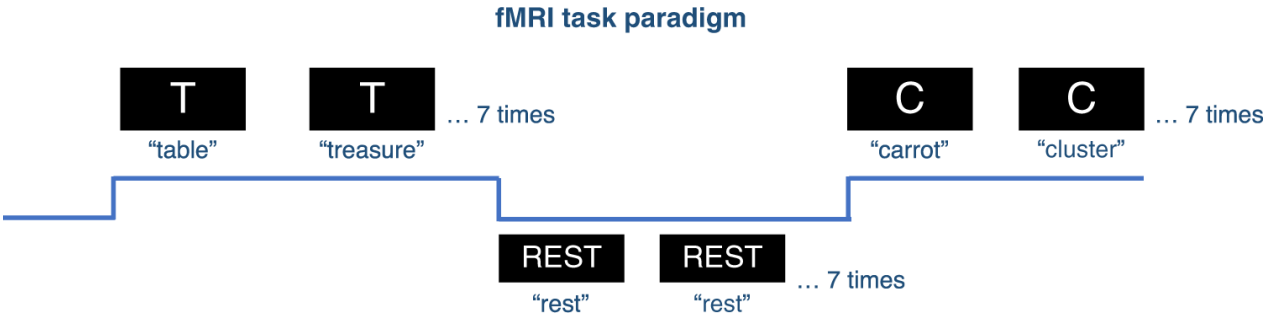


Figure 1.4. Graphic representation of a 'verbal fluency' task-based MRI paradigm. During this task, participants are asked to overtly generate a word starting with a letter visually presented to them ('experimental condition'). During the 'baseline' condition, participants are visually presented with the word 'rest' and are instructed to read 'rest' aloud. Taken from (Kanel et al., 2021a) (Appendix A).

Task-based fMRI findings in neonatal brain development

Task-based fMRI studies have utilised the stimulation of various senses and measured BOLD responses in the young infant brain, whose hemodynamic responses are shown to mature alongside structural development (Arichi et al., 2012). BOLD activation patterns have been analysed in infants, both preterm-born and full-term, in response to sensory input. Brain-behaviour associations are seen

in relation to various types of sensory development by TEA, including olfactory (Arichi et al., 2013), tactile (Allievi et al., 2016; Arichi et al., 2010), visual (Born et al., 1998; Erberich et al., 2003; Lee et al., 2012), auditory (Anderson et al., 2001), and motor (Erberich et al., 2006). Differences in developmental timings have also been shown between primary brain networks. For example, the auditory cortex responds to sensory stimulation at an earlier age then does the visual system (Anderson et al., 2001; Born et al., 2000; Ment and Constable, 2007).

Task-based fMRI findings in childhood brain development

fMRI studies have investigated the neural underpinnings of a range of cognitive abilities during childhood. An increased ability to plan, organise, and problem solve, as well as improved attention and memory, is observed by adolescence. The prefrontal cortex is thought to play an important role in these developments and is shown to be implicated in various task-based fMRI paradigms that require higher-order cognitive skills (Taylor et al., 2012). In addition to the frontal lobe, tasks that require more specific cognitive abilities have been associated with various brain regions. Presented here are examples task-based fMRI findings of such cognitive abilities, namely working memory and cognitive control.

Findings from a recent meta-analysis of child neuroimaging studies reported that, during working memory tasks, children show activations in well-established memory regions seen in adult neuroimaging studies, including posterior parietal and frontoparietal regions. Additionally, children show activations in regions not typically part of the working memory network, such as the insula (Yaple and Arsalidou, 2018). Further, involvement of the hippocampal region during working memory tasks has been reported to decrease with age (von Allmen et al., 2014). Taking these findings together, it is possible that specialised memory-related networks develop over time in individuals, but more studies with smaller age ranges are needed to address this hypothesis.

Developmental studies have increasingly focussed on the development of specific cortical and subcortical neural systems that underlie increases in cognitive control needed for the regulation of motivational behaviour (Cohen-Gilbert and Thomas, 2013). Task-based fMRI studies using emotional

cues have indicated age-related changes that may aid in explaining such behavioural developments during childhood and adolescence. For example, with age, amygdala functional connectivity decreases with another subcortical region, the ventral striatum, which in turn leads to improved cognitive control to emotional cues (Heller et al., 2016). Further, between early to late childhood, amygdala-PFC functional connectivity is shown to 'switch' from being positively coupled to exhibiting a negative connectivity (Gee et al., 2013). At the same time, amygdala reactivity decreases over time, and these two findings support the theorised regulatory role of the PFC (Silvers et al., 2017). When assessing the behavioural correlates of these neurodevelopmental changes, the authors found this 'valence switch' to be directly related to emotion regulation, possibly providing a neurobiological basis for improvements in emotional processing during this developmental period (Gee et al., 2013).

Task-based fMRI findings following very preterm birth

Task-based fMRI studies involving preterm children have highlighted altered activation in several prefrontal regions during working memory tasks (Murner-Lavanchy et al., 2014; Taylor et al., 2012), as well as weaker deactivation of the right temporal lobe (Tokariev et al., 2019). Task-based fMRI studies have also identified altered functional connectivity in VPT children when compared with full-term controls. During language-related tasks, VPT children and adolescents display increased interhemispheric connectivity, as well as a tendency to employ altered neural systems for auditory language function compared to term-born controls (Gozzo et al., 2009; Myers et al., 2010; Wilke et al., 2014), which might represent a delay in maturation of neural networks, or the engagement of alternative circuits.

1.3.3.4 Other methods of assessing brain function

fMRI techniques have been criticized due to their poor temporal resolution, consequence of the latency and longevity of the haemodynamic response. An additional measure of neuronal activity either during tasks or at rest is magnetoencephalography (MEG), which quantifies magnetic fields

produced by dendrites of neurons during synaptic transmission. MEG quantifies oscillatory features of neural networks, including timing, amplitude, phase, and frequency, with high temporal resolution both during tasks and at rest (Buzsáki and Draguhn, 2004; Gross et al., 2013). Other than providing better temporal resolution than fMRI techniques, MEG is also quiet during scanning and therefore might be more applicable in paediatric cohorts (Taylor et al., 2012), especially those who are prone to anxiety, such a VPT children (Treyvaud et al., 2013). Additionally, multimodal approaches such as the integration of fMRI and MEG techniques can utilise haemodynamic and electromagnetic measures to provide estimates of brain activation with accurate temporal and spatial localisation (Dale and Halgren, 2001).

One study using MEG at rest has indicated global reductions in resting state phase connectivity in VPT children when compared to controls (Ye et al., 2016). Specifically, altered connectivity was identified in thalamocortical networks, confirming previous fMRI findings highlighting reduced thalamocortical connectivity in the preterm population (Ball et al., 2013a). Additional altered connectivity was identified in networks encompassing regions associated with cognitive control, working memory and visuo-spatial abilities (Ye et al., 2016). Further applications of MEG techniques investigating neural correlates of behavioural outcomes in VPT children are discussed in Chapter 2.

Events occurring during the preterm period, a vulnerable critical period, may impact brain development at this time, which in turn could have long-lasting effects on the long-term development of neural structure and function. MRI has the potential to offer a significant insight into the complex pattern of the neurobiological mechanisms that underlie human brain development. Importantly, such research might not only be able to offer a new perspective for understanding how the brain adapts following VPT birth, but also the early detection of brain alterations, paving the way for preventative methods that deter such unfavourable long-term outcomes.

For a review of neuroimaging studies investigating differences in specific brain mechanisms between preterm and term-born adults, please refer to Kanel et al. (2021a) (Appendix A).

Chapter 2: Cognitive and socio-emotional outcomes and neurodevelopment in preterm children and adolescents

Individuals who have survived preterm birth face a range of neurodevelopmental and behavioural difficulties (Delobel-Ayoub et al., 2009), with research showing that VPT children are three times as likely to experience impairments across multiple domains, including motor disorders, cognitive delay, language delay, and emotional/behavioural adjustment problems (Woodward et al., 2009). These developmental delays are apparent even after accounting for sociodemographic risk (Pritchard et al., 2014; Schieve et al., 2016), and have various real-world implications, including worse academic achievement (Hutchinson et al., 2013; Johnson et al., 2009) and worse language and mathematical abilities (Aarnoudse-Moens et al., 2009b). Later in life, preterm adults display lower education levels, have lower net income, and are more likely to be receiving welfare support (Kroll et al., 2017; Mathiasen et al., 2009). This section will focus on altered cognitive development and socio-emotional behavioural problems faced by preterm children, as well as the neurodevelopmental correlates of such difficulties, including findings from both functional and structural MRI research.

2.1 Cognitive development and its neural correlates in preterm children

2.1.1 Cognitive development in preterm individuals

2.1.1.1 General Cognition

Conceptualisations of intelligence include a general intelligence factor, as well as narrower, more specific abilities (e.g., verbal comprehension and visuospatial reasoning) (Sternberg, 2000). One commonly used method of assessing relative intelligence is the Intelligence quotient (IQ), a score derived from several standardised tests. General intelligence, as assessed by IQ tests, has been shown to predict academic achievement (Freberg et al., 2008; Mayes et al., 2009).

Previous research has highlighted an impaired general intellectual development in preterm-born children, who show average IQ scores that are 0.7–0.8 SD (roughly 12 points) lower than those of controls (Bhutta et al., 2002; Kerr-Wilson et al., 2012). This gap increases with decreasing GA, with IQ estimated to decrease by 1.5 points per week for those born before 33 weeks of gestation (Johnson, 2007). These cognitive deficits remain stable throughout childhood (Anderson, 2014; Mangin et al., 2017) and adulthood (Kroll et al., 2019), and are reported to be more pronounced in males (Nagy et al., 2021; Stålnacke et al., 2019). Subtle cognitive alterations experienced by preterm children can be assessed using neuropsychological measures for specific cognitive constructs.

2.1.1.2 Attention

Core cognitive abilities are critical for the functioning of other cognitive domains, such as learning new skills and knowledge. One such ability is attention, or the capacity to selectively focus, maintain alertness, hold information, and transfer focus between activities. Attention constitutes a foundation for the development of higher-order cognition, and correlates positively with real-world outcomes such as school performance (Muris, 2006). One neuropsychological model of attention (Petersen and Posner, 2012; Posner et al., 2013) sub-divides attention into three subcomponents: alerting, or the capacity to acquire and maintain a state of alert arousal; orienting which allows one to

prioritise sensory input by focusing attention to relevant stimuli; and executive control which involves the regulation of thoughts, feelings and behaviours (see section 2.1.1.4). Self-regulation (alerting and orienting), which occurs as a response to external stimuli, is present from very early in life, whilst the more voluntary, endogenously-controlled executive network begins to mature at around preschool age (Rueda et al., 2015). Attention can be assessed through various tasks; for example, a visual search task requires the participant to find targets in a display of non-targets as quickly as possible (Manly, 2002). Both accuracy and speed provide information about attentional abilities.

VPT children tend to struggle with top-down control of attention, with up to 41% of the studied samples displaying impaired attentional development (Anderson et al., 2011b; Delane et al., 2017; Murray et al., 2014). Studies have identified impairments in all three domains of attention, which are also associated with GA (Anderson et al., 2011b; Mulder et al., 2009; van de Weijer-Bergsma et al., 2008). Although some attentional difficulties are exhibited by preterm adolescents (Wilson-Ching et al., 2013), there is also evidence to suggest that preterm children might 'catch-up' to their term-born counterparts by adolescence (Mulder et al., 2009; Nosarti et al., 2006). Nevertheless, attentional problems are considered one of the most common difficulties for preterm individuals.

2.1.1.3 Memory

Memory abilities could be subdivided into long-term and immediate memory (known as 'working memory'). Long-term memory refers to the vast store of knowledge and a record of prior events, where information is held indefinitely (Atkinson and Shiffrin, 1968; Cowan, 2008). Working memory is the ability to hold information in order to process and manipulate it (Baddeley, 1992). It is directly associated with fluid intelligence (Engle et al., 1999) and depends in part on the ability to control attention (Unsworth and Engle, 2007). One model of working memory suggests it is made up of three subcomponents: phonological loop for maintaining verbal information, visuospatial sketchpad for visual and spatial memory, and the central executive for coordinating storage and processing (Baddeley et al., 1974). Working memory is thought to have an active role in the retrieval of information from the long-term memory store, suggesting these two entities are not completely

separate (Baddeley, 1996). One common and quick method of assessing working memory is the digit span task, whereby participants are asked to repeat a set of digits, either as heard or in reverse order (Wechsler, 2014).

Deficits in both working and long-term memory functioning have been reported to be 2.1 to 3.5 times more likely in preterm children than term-born controls (Omizzolo et al., 2014). Working memory development is of particular interest in preterm research, and studies have identified deficits in this domain using both visual (Baron et al., 2010; Rose et al., 2011) and verbal (Aarnoudse-Moens et al., 2009b; Hutchinson et al., 2013; Mulder et al., 2009) modalities. This suggests that both the phonological loop and the visuospatial sketchpad may be affected in preterm children. Results from studies of preterm adolescents suggest they may experience fewer working memory deficits than younger preterm groups. Although there is some evidence of worse performance on a few working memory tasks, preterm adolescents performed comparably to controls on most tests of working memory (Rushe et al., 2001; Saavalainen et al., 2007). As discussed in the previous section, preterm children might be able to 'catch-up' to their term-born peers by late childhood and overcome some of their difficulties. This is supported by findings indicating preterm individuals perform better on working memory tasks in early adolescence than at eight years (Curtis et al., 2002).

2.1.1.4 Processing Speed

Processing speed, or the time required to interpret and respond to incoming information, is an additional core cognitive ability that is directly associated with both working memory and fluid intelligence (Cowan, 1997; Fry and Hale, 2000). It has been postulated that increased information processing efficiency leads to better working memory as faster rates of processing might reduce decay and interference in working memory (Cowan et al., 1998), and processing speed is thought to account for some of the increases seen in working memory capacity with age (Pickering, 2001). Processing speed may be assessed through reaction times to computerised tasks that require participants to respond to the appearance of a target stimulus (Fan et al., 2005)

Preterm individuals exhibit slower processing speed compared to their term-born peers from infancy to adolescence, especially during tasks with increased complexity (Rose and Feldman, 1996; Rose et al., 2002). Such deficits in processing speed, together with working memory difficulties, are thought to account for deficits in IQ scores in preterm children (Rose and Feldman, 1996). Previous research has indicated that slower overall processing speed was explained by a greater proportion of extremely slow responses (de Kieviet et al., 2012a). This observation suggests that despite being capable of making fast and adequate responses, preterm children may find difficulties in making them continuously, causing so-called 'lapses of attention' that may interfere with daily life in situations that demand continuous concentration.

2.1.1.5 Executive Functions

Executive functions (EF) are a set of cognitive skills needed for purposeful, goal-oriented behaviour, including, but not limited to, self-regulation, attention, working memory, planning, shifting, and monitoring of performance (Anderson and Reidy, 2012). These skills allow an individual to override automatic responses and engage in goal-directed cognition (Mesulam, 2002). They were shown to be vital for real-life outcomes, including academic performance and social interactions in full-term (Best et al., 2011; Bull and Scerif, 2001; Martinussen and Tannock, 2006; Moriguchi, 2014) and preterm (Aarnoudse-Moens et al., 2013; Kroll et al., 2017) populations. One model of EF proposes three dissociable and unitary processes: working memory, shifting, and inhibition (Garon et al., 2008; Miyake et al., 2000). This model is supported by factor analyses yielding a similar three-factor structure resembling the original concepts (Lehto et al., 2003). This section will focus on shifting and inhibition only, since working memory was addressed separately in section 2.1.1.3.

Shifting, also known as cognitive flexibility, refers to the ability to switch between mental tasks in a flexible manner. This can be assessed using tasks in which an initial set of rules is learned (e.g. associating a stimulus with a particular response), followed by a second phase, in which a new set of rules that conflicts with the first is introduced (Garon et al., 2008). Response inhibition, in contrast, refers to the ability to restrain a prepotent motor response that interferes with a required goal-

directed action. Tasks that index response inhibition typically require participants to focus on one feature of the stimulus and ignore other, conflicting, features (Garon et al., 2008).

Preterm children and adolescents are at a higher risk of developing deficits in EF, with this risk increasing for those with more extreme prematurity (Taylor and Clark, 2016). Findings relying on parental reports of EFs have been contradictory, with some showing significant differences (Burnett et al., 2018) and others reporting no differences between preterm and control children (O'Meagher et al., 2017). However, studies utilising behavioural tasks directly assessing EF performance indicate that preterm children perform worse than term-born controls across various tasks assessing different domains of EF (Aarnoudse-Moens et al., 2012; Aarnoudse-Moens et al., 2009a; Anderson and Doyle, 2004; Baron et al., 2012; Bayless and Stevenson, 2006; Taylor et al., 2004; Woodward et al., 2011). Such deficits remain stable after accounting for IQ differences between the two groups (Burnett et al., 2013; Luu et al., 2011a). Research investigating task shifting performance differences has identified a significant deficit of 0.5 SD (95% CI: 0.3–0.7) in preterm children compared to controls (Aarnoudse-Moens et al., 2009a). Preterm children also showed inhibitory task performance of 0.3 SD below controls (95% CI: 0.0–0.5) (Anderson, 2014; Mulder et al., 2009). However, there is evidence to suggest that group differences in response inhibition decrease between the preschool period and early adolescence, suggesting children can ‘catch-up’ to their term-born counterparts over time (Aarnoudse-Moens et al., 2012).

2.1.1.6 Language skills

Language abilities are necessary for daily interpersonal communication, and language skills have been shown to influence social functioning in adolescents (Durkin and Conti-Ramsden, 2007). Academic achievement is also closely related to language development, with language-impaired children displaying worse performance on reading accuracy and comprehension (Botting et al., 2006) and going on to achieve fewer educational qualifications by the end of secondary school compared to term-born controls (Conti-Ramsden et al., 2009). Language development can be categorised into expressive (production) and receptive (comprehension) language (Bates et al., 1995), and covers a

range of skills such as semantics and phonological awareness. Semantics, assessed as vocabulary in children, is shown to predict later intelligence development (Bornstein and Haynes, 1998). Finally, phonological awareness refers to the ability to understand speech sounds, and can be assessed through word games such as phoneme isolation, which requires participants to isolate individual sounds within words (Wagner et al., 1999). Phonological awareness is shown to be predictive of reading skills (Wocadlo and Rieger, 2007).

Previous research has suggested the presence of language impairments in VPT children, when compared to full-term controls, from infancy to adolescence (Vohr, 2014). Delayed development is seen in both receptive and expressive language domains (Barre et al., 2011; Foster-Cohen et al., 2010; Vieira and Linhares, 2011; Wolke et al., 2008), and in task-specific abilities of semantics and grammar (Reidy et al., 2013). Deficits in phonological awareness skills have also been reported in preterm children (Hasler and Akshoomoff, 2019; Mullen et al., 2011; Mürner-Lavanchy et al., 2018), although these did not consistently survive statistical corrections for multiple comparisons. Conversely, a recent study of preterm children (EPT, VPT and MPT) failed to find any deficits in language abilities, both receptive and expressive, when compared to term-born controls (Pérez-Pereira et al., 2020).

2.1.1.7 Environmental contributing factors

Clinical variables at the time of birth might contribute to cognitive deficits later in life in the VPT population. Clinical risk associated with preterm birth, which includes a wide range of perinatal complications, has been associated with brain alterations, which in turn are shown to predict adverse neurodevelopment (Barnett et al., 2018; Pecheva et al., 2019; Spittle et al., 2021). Studies have also reported direct links between perinatal complications and later attentional deficits (Montagna et al., 2020) and executive functioning (Nagy et al., 2021; Stålnacke et al., 2019). Additionally, preterm infants exposed to an increased number of NICU ‘stressors’ (procedures ranging from nappy changes to intubation) were more likely to display deficits in motor skills at TEA (Smith et al., 2011).

Socio-demographic and family characteristics are also shown to be associated with cognitive outcomes of preterm children. Lower levels of maternal education, a proxy for SES, is related to cognitive deficiency (Beaino et al., 2011; Potijk et al., 2013; Wong and Edwards, 2013) and impaired executive functioning (O'Meagher et al., 2017) in this population. Coming from a higher socio-economic background is associated with better cognitive outcomes (Duncan and Magnuson, 2012; Sarsour et al., 2011). One possible reason for this could be due to increased resources in high-SES families that better nurture children's skills and talents. Further, studies investigating the effects of familial variables on preterm children's cognitive development indicate that having a large number of siblings is detrimental to general cognition (Beaino et al., 2011), whilst decreased parental sensitivity is associated with executive functioning (Zvara et al., 2019). These variables are likely to have an effect on the level of emotional involvement and cognitive stimulation experienced by the child, which are important for the behavioural skills required for cognitive development (Bernier et al., 2012).

Ethnicity is also related to SES, showing associations with both wealth (Bhutta et al., 2020; Gibson-Davis et al., 2021) and academic attainment (Richardson et al., 2020). Varying parenting styles are observed in people from different ethnic and cultural backgrounds, with certain parenting practices, such as disciplinary methods, shown to be differentially favoured in individual communities (Hill, 2006; Silveira et al., 2021). In fact, different parenting practices have been shown to be beneficial for academic achievement in different ethnicities (Hearne and Christie-Mizell, 2018), highlighting the interplay between these factors and the importance of considering ethnicity, together with SES and family characteristics, when investigating cognitive development in children. Additionally, ethnic disparities in cognitive development could also be, at least in part, attributed to the stress and hardship so often experienced by minority ethnic groups, which may alter the biological responses to stress that in turn impact cognitive functioning (Levy et al., 2016).

Ethnicity has been studied in relation to neurodevelopmental outcomes in preterm-born toddlers (Freeman Duncan et al., 2012; Greene et al., 2012). These studies, both based in the United States, suggest that infants of Hispanic white race/ethnicity had significantly lower language and motor scores than African-American Black and non-Hispanic White infants. Furthermore, a more

recent literature review including studies conducted in Europe, Australia, and the United States, indicated that non-White ethnicity was predictive of global cognitive impairment in VPT children under five years (Linsell et al., 2015). Despite known disparities between ethnicities, in terms of SES, family characteristics, and stressors experienced, very little is known about possible causal mechanisms linking ethnicity to cognitive development in very preterm samples (Beauregard et al., 2018).

2.1.1.8 Methodological considerations

Most studies investigating preterm childhood cohorts tend to have exclusion criteria such as the presence of perinatal brain injury (e.g., PVL), or an IQ score of less than 80. This has implications on the generalisability of the findings described here, as it means that studies are more likely to underestimate the population's levels of impairment (Anderson, 2014). Further, study participation and follow-up attrition levels are not random, as those children with increased impairments, as well as those coming from more socially disadvantaged families, are less likely to take part. Therefore studies are likely to underreport the severity of cognitive deficits in this population, skewing the results (Callanan et al., 2001).

Furthermore, using normative measures, such as IQ test scores, means that results are likely to be affected by the Flynn effect, whereby normative scores increase with time, which could lead to an underestimation of the developmental delay experienced by atypically developing groups. Therefore, it might be more accurate to compare such groups to locally matched control groups, as opposed to assessing them in relation to test norms (Anderson et al., 2010).

Finally, task impurity refers to how well a task can estimate the skill it sets out to assess, without tapping into similar underlying functions that draw on different processes. Some measures of specific cognitive constructs used in preterm children might be considered as 'impure', as they depend on multiple processes. One such example is the Tower of London task (e.g., Anderson and Doyle, 2004) that theoretically assesses planning, an EF construct. In practice, however, this task requires various other EF skills, including comprehension of instructions, inhibition, working memory, visual

perception, and sustained attention. Therefore, performance on such a task might reflect deficits in any of the subcomponents, rather than a specific deficit in planning (Anderson and Reidy, 2012).

2.1.1.9 Catch up of outcomes after VPT birth

As mentioned in the previous sections, some studies have reported no cognitive difficulties in preterm adolescents, showing comparable performance to full-term controls in various cognitive domains from as early as 12 years (e.g., Aarnoudse-Moens et al., 2012; Saavalainen et al., 2007). It has been suggested this indicates that preterm children can 'catch-up' to their term-born peers. However, overall findings are far from conclusive, as several studies have highlighted persisting cognitive deficits in preterm samples in adolescence and adulthood (e.g., Brydges et al., 2018; Kroll et al., 2017; Linsell et al., 2018; Wilson-Ching et al., 2013).

Different methodologies used in these studies could be responsible for such non-convergent results. Alternatively, it is possible that such discrepancies are a product of differences between cohort characteristics. Environmental social factors, including socioeconomic background and ethnicity, are shown to influence the ability of preterm children to catch-up to full-term children in cognitive domains (Luu et al., 2011b). As many of the cross-sectional studies in this field have not included environmental and social factors (e.g., SES and ethnicity), either reporting them or including as covariates, a comparison of results from catch-up studies might lead to biased conclusions.

Other individual differences might also help explain non-convergent results regarding preterm individuals' abilities to catch up to their term born peers in cognitive outcomes. In a recent review, long-term outcomes were shown to be predicted by children's early cognitive scores: those performing very poorly were not likely to catch up, whilst those scoring within the normal range tended to show an accelerated development relative to term-born controls (Vollmer and Stålnacke, 2019). Loss to follow-up in longitudinal studies of preterm children with cognitive impairments is a recognised issue (Callanan et al., 2001), which could bias results as those lost to follow up may have different neurodevelopmental profiles than those who are assessed. Returning participants tend to come from less deprived socio-economic groups (MacBean et al., 2019; Piedvache et al., 2021) and as

SES is a predictor of neurocognitive performance (Hackman and Farah, 2009) followed-up samples may be biased towards including high-performing preterm individuals that are more likely to catch-up to full-term controls than the complete preterm population.

Future longitudinal studies of cognitive development in preterm children and adolescents should take into consideration environmental social factors that are likely to influence preterm children's catch-up abilities. Through the use of stratified sampling, for example, catch-up abilities may be investigated in samples that are more representative of the wider population, thus limiting biased results. It is likely that a combination of social environmental factors, together with clinical variables, determine preterm children's cognitive development trajectories (Doyle et al., 2015; Martínez-Nadal and Bosch, 2021).

2.1.2 Neural correlates of cognitive development in VPT neonates and children

2.1.2.1 Structural alterations and cognitive outcomes

Cross-sectional studies involving preterm children and adolescents have repeatedly highlighted an association between impaired general cognition and reduced volumes in widespread cortical, subcortical, and cerebellar GM regions (Abernethy et al., 2004; Allin et al., 2001; Giménez et al., 2006; Isaacs et al., 2004; Nosarti et al., 2008; Peterson et al., 2000; Reiss et al., 2004; Zubiaurre-Elorza et al., 2012a). Associations between GM volume and specific cognitive outcomes have been reported in VPT children, including between hippocampal volume and memory skills (Isaacs et al., 2000), left parietal lobe volume and mathematical skills (Isaacs et al., 2001), right ventral extrastriate cortex and visuospatial processing (Isaacs et al., 2003), and widespread regions including the anterior cingulate cortex and temporal cortex, and attentional abilities (Lean et al., 2017).

Altered WM microstructure has also been investigated in relation to neurodevelopmental abilities in preterm children. Neurodevelopmental impairments in preterm toddlers have been related to altered FA in projection and association tracts, including the corpus callosum (Counsell et al., 2008). Similar associations have been identified in school-aged children and adolescents, with increased FA and decreased diffusivity values in various WM tracts being associated with better

cognitive outcomes, including IQ (Dubner et al., 2019; Kennedy et al., 2021; Skranes et al., 2007; Vollmer et al., 2017; Wang et al., 2013; Young et al., 2019; Yung et al., 2007), executive functions (Vollmer et al., 2017), language skills (Andrews et al., 2010; Bruckert et al., 2019; Feldman et al., 2012; Mullen et al., 2011; Mürner-Lavanchy et al., 2018; Travis et al., 2016), attention (Loe et al., 2013; Murray et al., 2016), working memory (Loe et al., 2018), visuospatial processing (Skranes et al., 2007; Tokariev et al., 2019), and mathematical abilities (Collins et al., 2019).

Similar results have been identified with advanced MR analytical approaches such as NODDI, with studies identifying associations between lower NDI and poorer neurodevelopmental outcomes, including lower IQ scores (Kelly et al., 2016b; Young et al., 2019) and worse semantic (Mürner-Lavanchy et al., 2018) and mathematical performance (Collins et al., 2019).

Additionally, whole-brain WM connectivity networks have been investigated in preterm children in relation to cognitive outcomes. One study indicated that, although no associations were found between global network measures and neurodevelopmental outcomes, those with impaired IQ exhibited reduced connectivity strength within specific regional sub-networks (Thompson et al., 2016). Similarly, Fischi-Gomez et al. (2014) reported an association between FA-based structural connectivity in widespread connections and simultaneous information processing abilities.

Longitudinal neuroimaging studies in preterm samples have investigated neonatal brain structure, usually assessed at around TEA, in relation to later childhood outcomes. GM structure at TEA has been related to childhood cognitive outcomes, with one study finding an association between altered neonatal corpus callosum shape (i.e., more circular) and delayed cognitive development at two years (Thompson et al., 2012). Recently, neonatal subcortical and insular volumes at TEA have been associated with childhood cognitive outcomes in the preterm population. Results have indicated specific associations between insula and putamen volume and mathematic abilities, whilst the insula only was associated with working memory (Ullman et al., 2015). A more recent study confirmed such findings by reporting a positive association between neonatal regional tissue volumes of fronto-insular, inferior parietal and middle occipital cortices and cognitive outcomes in childhood, with the most pronounced association portrayed in the insula and inferior frontal gyrus (Ullman et al., 2015). The growth of deep GM between the early preterm period and TEA has also been shown to relate to

later cognitive outcomes, with findings indicating that caudate and putamen growth is predictive of cognitive and language development in VPT children (Young et al., 2015).

Neonatal WM structure as well as presence and severity of white matter abnormalities (e.g., cystic lesions and signal abnormalities) have also been related to later cognitive outcomes. The presence of WM abnormalities in preterm neonates (as rated by an expert) has been shown to be associated with lower IQ scores, and deficits in verbal comprehension (Iwata et al., 2012), working and long-term memory (Omizzolo et al., 2014), executive functioning (Woodward et al., 2012), and phonological awareness (Reidy et al., 2013).

Altered neonatal microstructural properties of widespread WM, including reduced FA and increased diffusivities, have been associated with later worse neurodevelopmental outcomes in preterm children, including cognitive development (Ball et al., 2017; Boardman et al., 2010; Counsell et al., 2008; Duerden et al., 2015; Pogribna et al., 2014; Ullman et al., 2015; van Kooij et al., 2012) and language abilities (Aeby et al., 2013; Barnett et al., 2018; Dubner et al., 2020; Lee et al., 2021; Mullen et al., 2011; Salvan et al., 2017). Specific associations were also identified in the neonatal structural connectivity of thalamocortical connections and cognitive development later in life (Ball et al., 2015). Slower rates of change of diffusion characteristics over the first two years of life are also predictive of worse cognitive and language development in VPT children (Young et al., 2017).

Despite many studies highlighting a positive association between FA and improved neurocognitive development, some studies found no such associations (Bruckert et al., 2019; Tokariev et al., 2019; Young et al., 2018). There are a few possible explanations for these discrepancies, ranging from basic methodological issues such as variability in group sizes, to more nuanced ones such as heterogeneity in preterm cohorts both in terms of neonatal complications and behavioural outcome. Additionally, some studies have found a negative relationship between FA values and outcomes such as language (Dubner et al., 2020; Feldman et al., 2012; Travis et al., 2015). A decrease in FA could in some cases indicate crossing fibres rather than altered diffusion characteristics of a single WM fibre.

In order to distinguish between these different potential causes of altered FA, future research can therefore benefit from analysis techniques (such as fixel based analysis) that allow for a

differentiation between multiple fibres within a voxel. Recently, FBA has been utilised to analyse associations between diffusion characteristics and cognitive outcomes in preterm children. Neonatal FBA metrics in the corpus callosum and CST showed an association with cognitive development at 1 year (Pannek et al., 2020), whilst childhood diffusion characteristics in visual, sensorimotor, and thalamocortical WM tracts showed an association with math computation ability in preterm and term-born school-aged children (Collins et al., 2021).

2.1.2.2 Functional alterations and cognitive outcomes

Findings indicating brain-behaviour associations in preterm children suggest that cognitive impairments are generally reflected in functional alterations of the brain, and that these are apparent from a very early age. Studies investigating associations between functional connectivity and general cognitive outcomes have utilised longitudinal methodologies to specifically investigate rs-FC of thalamocortical networks and childhood cognitive development. For example, the thalamus-salience network connectivity at one year predicted cognitive development of receptive and expressive language, visual reception, and working memory performance at two years (Alcauter et al., 2014). Similarly, a recent study found an association between rs-FC of the thalamus and sensory-motor cortex at TEA and cognitive and language composite scores at 2 years (Toulmin et al., 2021).

Cross-sectional studies of preterm children and adolescents have identified altered regional BOLD activity and functional connectivity, and their associations with diminished language outcomes. For example, VPT children displayed weaker bilaterality between the superior temporal gyrus (STG) language regions and worse performance on verbal comprehension tests (Wilke et al., 2014). Further, findings from studies utilising a task-based fMRI paradigm indicate altered neural alterations during language processing. One study reported that, although preterm adolescents exhibited similar associations to full-term controls between accuracy on a semantics task and BOLD activation in the left middle temporal gyri, they also displayed altered associations between accuracy and functional connectivity of frontal and temporal language areas (Schafer et al., 2009). Preterm

adolescents also showed an association between altered functional connectivity of the STG during a passive language task and performance on receptive language tasks (Myers et al., 2010).

The literature mentioned in this section has highlighted that, even in the absence of cognitive performance differences between preterm and term-born children, neural signatures associated with behavioural outcomes may differ between the two groups. Such findings could indicate compensatory neural processes, whereby preterm individuals rely on different neural pathways in order to adequately perform a given task (Daamen et al., 2014).

2.2 Socio-emotional development and neurodevelopmental correlates in preterm children

2.2.1 Socio-emotional development in preterm individuals

In comparison to adult disorders, childhood and adolescent psychiatric disorders are less likely to meet clear-cut diagnostic criteria (Cummings et al., 2014). For this reason, paediatric psychopathology research tends to focus on dimensional socio-emotional constructs and traits to identify atypical psychological development. Socio-emotional development refers to a set of skills that allows individuals to efficiently deal with emotions and successfully interact and communicate within a social context (Montagna and Nosarti, 2016). Emotional competence is the ability to successfully express emotions, understand emotions of self and others, and regulate emotional expressiveness. At around preschool age, children begin to successfully regulate their emotions, as well as understand others' emotional states (Denham, 1998; Hyson, 2004). Social competence refers to the social interaction effectiveness of a child (Fabes et al., 2006), and can be split into three skills: developing positive relationships, coordinating and communicating actions and feelings, and recognising and regulating emotions in social settings. Social competence is learnt in early childhood through relationships and experiences in contexts such as the home environment (Dykas and Cassidy, 2011) and educational settings (Bierman, 2011). Finally, self-regulation can be considered as an additional socio-emotional construct, although it is very similar to, and required for the development

of, both social and emotional competence. Self-regulation can be compartmentalised into three distinct abilities: emotion regulation, behaviour regulation, and cognitive/attentional regulation (Weissberg et al., 2013). This set of skills helps us to organise the various concepts of social and emotional development. However, they are highly inter-related and will greatly affect each other's development (Campbell et al., 2016).

The importance of socio-emotional development in childhood is highlighted by its ability to predict later real-life outcomes, including levels of education, employment, criminal activity, and substance abuse (Ahmad et al., 2021; Jones et al., 2015). Further, socio-emotional characteristics in childhood, including temperamental traits such as negative affect and behavioural inhibition, low self-regulation, and poorer social processing skills also predict the development of a spectrum of psychopathological disorders such as anxiety and depression disorders later in life (Cisler et al., 2010; Dodd et al., 2020; Hirshfeld-Becker et al., 2008; Robson et al., 2020; Troller-Renfree et al., 2019). Such pathways to psychiatric problems are already present in infancy, with research indicating that children who later develop such difficulties show increased rates of socio-emotional difficulties from as early as 12–36 months of age (Briggs-Gowan and Carter, 2008).

Aspects of altered socio-emotional development typically observed in VPT children includes diminished social competence and self-esteem, emotion dysregulation, shyness, and timidity (Fitzallen et al., 2020; Montagna and Nosarti, 2016). These traits remain stable throughout VPT individuals' lives (Bohnert and Breslau, 2008 ; Hall and Wolke, 2012; Taylor et al., 2015). Such difficulties can result in a clinical diagnosis, with findings showing VPT children are more likely to meet criteria for mental health disorders (Yates et al., 2020). Alternatively, difficulties can emerge as sub-clinical problems, highlighting the importance of a dimensional approach when describing psychological impairments in this population (i.e., psychopathology is understood as a set of difficulties that lie on a continuum). Difficulties in specific constructs can be captured using a variety of assessments that summarise grouped behaviours to identify problematic areas.

2.2.1.1 Internalising and externalising problems

Two commonly used indicators of developmental psychopathology are the socio-emotional constructs of internalising and externalising problems. Internalising symptoms include anxiety, sadness, social withdrawal, and fearfulness, whilst externalising symptoms include overactivity, poor impulse control, noncompliance, and aggression (Achenbach and Edelbrock, 1981; Werry and Quay, 1971). Internalising problems are thought to stem from an over-regulation of negative emotions that become maladaptive. Externalising problems are thought to result in part from the under-regulation, or poor self-regulation, of emotions and behaviours (Cicchetti and Toth, 2014). These two difficulties are not mutually exclusive, and it is understood that a child or adolescent could very well be depressed or anxious, while also displaying hostile, antisocial behaviour (Merrell, 2001). The presence of these symptoms in childhood and adolescence is related to an increase in psychiatric diagnoses later in life (Cicchetti and Cannon, 1999).

The preterm literature has investigated internalising and externalising profiles of preterm-born children and adolescents. These have been studied using parent-reported and teacher-reported questionnaires such as the Infant Toddler Social and Emotional Assessment (ITSEA), which assesses socio-emotional development (with scores for internalising, externalising, dysregulation, and competence) in toddlers (Briggs-Gowan et al., 2004). The Child Behaviour Checklist (CBCL), a measure for school-aged children, includes subscales for internalising (anxious/depressed, withdrawn/depressed, and somatic complaints) and externalising symptoms (aggression and rule-breaking) (Achenbach and Rescorla, 2000). Compared to term-born controls, studies using the CBCL and ITSEA have identified increased internalising symptoms, yet similar externalising symptoms, in preterm children (Loe et al., 2013; Samuelsson et al., 2017) and toddlers (Spittle et al., 2009). However, the presence of externalising symptoms in preterm children is disputed, with other studies using the CBCL highlighting increased level of this dimension in MPT children (Arpi and Ferrari, 2013; Potijk et al., 2012).

2.2.1.2 Temperament

A further socio-emotional construct is temperament, which is made up of a group of related traits that are relatively stable over time and across situations (Rothbart and Bates, 1998). Temperament is defined as individual differences in emotional reactivity and self-regulation (Rothbart and Derryberry, 1981). Emotional reactivity is the tendency to experience frequent and intense positive and negative emotional arousal (Spinrad et al., 2004). Negative affectivity (NA) is a temperamental trait primarily responsible for emotional reactivity, and high levels of this factor index a proneness to experience negative emotions, such as fear, anxiety, sadness, anger, guilt, and a sense of rejection (Putnam et al., 2001). NA is common to both anxiety and depression disorders (Lonigan et al., 1994; Ormel et al., 2013), and when present in childhood, could predict the later development of both subclinical internalising problems (Gartstein et al., 2012) and clinical psychopathology (Carthy et al., 2010; Forbes et al., 2017; Laceulle et al., 2014). An additional temperamental trait is self-regulation (also known as effortful control), which refers to the process of initiating, maintaining, or modulating arousal intensity (Putnam et al., 2001; Thompson, 1994) and has been implicated in the development of anxiety disorders in children (Carthy et al., 2010; Cisler et al., 2010).

Temperament has been extensively studied in preterm children, and although some studies have reported increased levels of negative affectivity (Caravale et al., 2017; Lejeune et al., 2015), other studies observed no differences in this temperamental trait between preterm and term-born children (Voigt et al., 2013). Conflicting results have even been reported within the same study when considering different measures of negative affectivity (Voigt et al., 2013). Preterm children have also been reported to display lower levels of self-regulatory behaviour (Spittle et al., 2009; Wolf et al., 2002), and a recent study indicated that the decreased levels of effortful control in preterm children were similar to those of children who had undergone institutional deprivation (Reyes et al., 2020). Finally, a specific temperamental profile of increased NA and decreased EC has been shown to predict internalising and externalising problems in VPT children, highlighting the importance of temperamental development in this cohort (Cassiano et al., 2019; Martins et al., 2021).

2.2.1.3 Social development

As previously mentioned, poor social competence during childhood and adolescence is reported to be a prominent risk factor for the development of adult psychiatric disorders (Cannon et al., 1997; van Os et al., 2010). For example, theory of mind (ToM), an important aspect of social cognition that allows a person to correctly infer the mental states of others, has been shown to be directly associated with psychiatric disorders (Fett et al., 2011; Hezel and McNally, 2014). Emotion recognition is an additional social processing skill that requires a person to correctly recognise facial emotional content, critical for social functioning. This ability has been shown to be consistently disrupted in a range of psychiatric disorders such as depression and anxiety, whereby patients fail to correctly identify facial expressions and tend to view them as sadder than controls (Anderson et al., 2011a; Bourke et al., 2010; Simcock et al., 2020).

The ability to recognise facial emotions emerges as early as 7 months (Bayet et al., 2014), and shows considerable improvements with age throughout childhood and adolescence (Theurel et al., 2016). The developmental trajectories of the recognition of different facial expressions vary, although the literature reports conflicting findings regarding the timings of these developments. For example, whilst some studies have reported that the recognition of anger is mostly developed by middle childhood (Gosselin, 1995; Lawrence et al., 2015), others have suggested this is developed at a later age (Montirosso et al., 2010; Rodger et al., 2015; Thomas et al., 2007). These inconsistent findings could be due to methodological differences, i.e., different methods of collecting emotion recognition data (e.g. free labelling vs expression matching, or the use of context to aid interpretation) requiring different levels of abilities (Theurel et al., 2016). Other findings, such as that disgust is one of the most difficult expressions to recognise in children, are more widely accepted (Widen and Russell, 2013).

Impaired social skills and social withdrawal are exhibited by preterm children and adolescents (Johnson and Wolke, 2013). These difficulties have been reported through parent-reported social competence questionnaires that indicate significantly worse scores for preterm children than full-term

controls (Hille et al., 2001; Korzeniewski et al., 2017; Ritchie et al., 2015; Samuelsson et al., 2017). Social development might also be assessed in preterm children with standardised tasks that, for instance, tap into social attention and social cognition (Dean et al., 2021). Social attention might be assessed through eye tracking, and preterm infants have been shown to display decreased visual attentional preference towards social stimuli, a well-known indicator of later poor social communication development (Imafuku et al., 2017). Social cognition might be assessed with tasks that probe ToM skills and require the ability to identify nonverbal social cues from a range of stimuli, including facial expressions, social scenarios, and animated shapes. Preterm children performed worse on such tasks by displaying less appropriate descriptions of moving shapes (Williamson and Jakobson, 2014), less accurate responses to an emotion recognition task of angry faces (Mossad et al., 2020), and more misattribution errors of social scenarios (Mossad et al., 2021). These findings indicate that children born preterm exhibit impairments in the ability to infer the mental states of others through social cues. It is likely that such impairments in social processing skills underlie the difficulties VPT children often experience in establishing and maintaining social contacts.

2.2.1.4 Environmental contributing factors

Environmental factors both at the time of birth and throughout a child's life might play an important role in the development of socio-emotional difficulties. Perinatal factors shown to affect the later development of socio-emotional outcomes in preterm infants include physical contact with a parent during the first few months in the NICU, which is associated with improved outcomes (Browne, 2004). Further, painful procedures experienced by preterm neonates are shown to increase the likelihood of developing emotional problems in childhood (Voigt et al., 2013). One explanation for this could be an altered cortisol reaction to socio-emotional stress, which was found in preterm infants experiencing greater pain-related stress (Provenzi et al., 2016).

Parental well-being and parent-child relationships are also known to significantly predict preterm children's socio-emotional outcomes. This is especially true during the postnatal period, during which parental attachment is reported to be of lower quality in parents of preterm neonates

than full-term controls (Ruiz et al., 2018). These deficits are shown to have detrimental effects on infants' emotion regulation abilities (Provenzi et al., 2017). Additionally, NICU-related parental stress is associated with the later socio-emotional difficulties in preterm children (Woodward et al., 2014). This parental stress is shown to mediate the relationship between procedure-related neonatal pain and later socio-emotional development (Voigt et al., 2013). Maternal well-being throughout the child's life will also greatly affect children's emotional development, with research highlighting associations between both increased maternal depressive (Huhtala et al., 2014) and anxiety (Lean et al., 2020) symptoms and the well-being of preterm children. One possible mechanism for this could be parenting styles, which are altered in those experiencing mental health difficulties (Crosby Budinger et al., 2013), and are shown to have a strong effect on child emotion regulation abilities (Clark et al., 2008). Finally, a recent study found that family dysfunction, based on the McMaster Model of Family Functioning (Epstein et al., 2003), was associated with socio-emotional and psychiatric outcomes in VPT children (Lean et al., 2020). Interestingly, this same study did not find an association between social risk and outcomes in preterm children, although this relationship was evident in full-term controls.

Environmental factors outside of the home are also thought to affect psychological outcomes in preterm individuals. Preterm children are more likely to experience problems in creating and maintaining close relationships than term-born controls, and these difficulties are associated with increased emotional problems (Ritchie et al., 2018). They are also more often bullied than their term-born peers, which is also related to increased levels of emotional problems (Wolke et al., 2015). Recently, research has investigated the effects of peer victimisation (a form of bullying) on psychological outcomes in VPT children, with findings indicating a positive correlation with psychotic experiences in early adulthood (Liu et al., 2021).

2.2.1.5 Methodological considerations

When considering the socio-emotional difficulties in preterm children it is important to consider their cognitive profiles. Previous literature has identified an association between cognitive

development and psychiatric disorders in this cohort (Johnson et al., 2010), as well as a mediating effect of general cognition on the development of poorer emotional development and social functioning (Bayless et al., 2008; Månsson et al., 2014). For example, altered attention orienting skills could lead to impaired gaze-following (a skill requiring ToM) and subsequent difficulties in socio-communicative abilities (Karmiloff-Smith et al., 2012). Similarly, multisensory processing affecting speech could have consequences on social interactions (Stevenson et al., 2014; Wickremasinghe et al., 2013). However, cognitive deficits do not entirely account for difficulties in socio-emotional development entirely, as suggested by research highlighting that such difficulties remain even after controlling for altered neurodevelopment and impaired cognition (Delobel-Ayoub et al., 2009; Johnson and Marlow, 2011).

Further, data collection might be exposed to some methodological biases, especially when reporting on questionnaire answers from different respondents, including parents, teachers, or the children themselves. For example, results from within the same study indicated that whilst preterm adolescents reported they experience less emotional problems than controls, their parents reported increased levels compared to parents of controls (Dahl et al., 2006).

2.2.2 Neural correlates of socio-emotional development in preterm neonates and children

2.2.2.1 Structural alterations and socio-emotional outcomes

Results of several cross-sectional studies have highlighted associations between altered GM volumes and social and emotional development in preterm samples. Firstly, emotional competence has been shown to relate to GM measures in preterm children, with internalising problems showing associations with both total GM volume and relative percentage volume of right temporal lobe in MPT children (Rogers et al., 2014). Both internalising and externalising problems were associated with reduced cortical thickness of frontal regions in VPT children (Zubiaurre-Elorza et al., 2012b). Secondly, deficits in social competence in the form of poorer social adjustment scores have been related to smaller caudate volumes in preterm adolescents (Nosarti et al., 2005). Peer problems have

also been related to brain volumes, showing associations with smaller hippocampal volume in preterm children (Rogers et al., 2012) and larger fusiform gyrus volumes in preterm adolescents (Healy et al., 2013).

Diffusion MRI studies in clinical and healthy paediatric populations have reported associations between socio-emotional outcomes and diffusion characteristics of well-characterised WM tracts implicated in socio-emotional processing. For example, findings have indicated associations between alterations in the ILF and inferior fronto-occipital fasciculus (IFOF) and facial affect recognition (Genova et al., 2015; Unger et al., 2016). Additionally, diffusion characteristics of the UF have been implicated in emotion regulation (Eden et al., 2015) and general socio-emotional processing (Von Der Heide et al., 2013).

Cross-sectional studies in preterm children have identified associations between increased emotional difficulties and decreased FA in widespread WM, including association tracts (e.g., cingulum, IFOF, ILF, and SLF), projection fibres (e.g., the anterior thalamic radiation and CST) and commissural fibres (such as the corpus callosum, forceps major, and minor) (Kelly et al., 2016b; Loe et al., 2013). Emotional problems in VPT children have been related to both increased ODI in corpus callosum, and decreased NDI in widespread WM, including the corpus callosum, UF, IFOF and ILF (Kelly et al., 2016b). Socialising difficulties have also been related to WM microstructure in VPT children, with studies reporting associations between social processing deficits and decreased FA values in widespread WM, including the external capsule and superior fasciculus (Skranes et al., 2007). Similar findings were reported within tracts connecting the cingulate and precuneus, two major hubs of the DMN, and those connecting the cortico-basal ganglia-thalamo-cortical loop (Fischi-Gomez et al., 2014). The cortico-basal ganglia-thalamo-cortical loop plays an important role in the development of EFs (Cummings, 1993) that allow simultaneous processing of cognitive, sensorimotor, and motivational information (Groenewegen et al., 2009).

One longitudinal study has shown that structural MRI at TEA predicted socio-emotional outcomes in childhood, and specifically increased bilateral amygdalae volume were associated with emotion dysregulation in the form of elevated fear responses in 12-month-old preterm infants (Cismaru et al., 2016). More recently, the developmental trajectories of GM volumes between birth

and school-age were also shown to be related to internalising problems in a VPT sample, with associations highlighted between anxiety disorders and slower volume growth of the whole brain, as well as specific regions including the amygdala, hippocampi, and orbitofrontal cortex (Gilchrist et al., 2021).

Longitudinal studies have also reported on associations between neonatal WM development and later socio-emotional outcomes. Earlier studies utilised qualitative reporting of WM abnormalities at TEA and related these with later emotion regulation impairment (Clark et al., 2008) and poorer socio-emotional competence (Jones et al., 2013; Spittle et al., 2009). More recent DTI studies have identified associations between altered neonatal diffusion characteristics and impairments in childhood socio-emotional competence. For example, higher ADC in the right orbitofrontal cortex at TEA was associated with peer problems at five years (Rogers et al., 2012), whilst altered cingulum diffusion characteristics at TEA were associated with socio-emotional competence scores at two years, both in the forms of increased diffusivities (AD) (Lee et al., 2021) and increased FA (Rogers et al., 2016). Increased FA in the cingulum at TEA has also been associated with a composite measure of socio-emotional difficulties, including estimations of internalising symptoms and social competence, at five years (Brenner et al., 2021). Although higher FA might reflect larger numbers of WM fibres and/or greater level of myelination, it might also be indicative of smaller axonal diameter, reduced branching, and fewer crossing fibres, which are more likely to be causes of impaired development (Jeurissen et al., 2013). Further research could investigate similar relationships with other relevant WM tracts, including association fibres such as the UF and IFOF.

2.2.2.2 Functional alterations and socio-emotional outcomes

Few cross-sectional studies have investigated functional alterations in preterm children and their associations with socio-emotional development. In VPT adolescents, altered rs-FC between the bilateral amygdalae and the posterior cingulate was associated with emotional difficulties (Johns et al., 2019).

Task-based MEG has also been employed in studies with VPT individuals. During a theory of mind task, VPT children aged 7-13 showed decreased activations in regions involved in false belief processing such as the right inferior frontal gyrus and the temporal-parietal junction (TPJ) (Mossad et al., 2017). VPT children also recruited the left TPJ, whilst controls recruited the right TPJ. This might be explained with evidence suggesting children's tendency, with age, to go from bilateral TPJ activation during theory of mind tasks to selectively recruiting the right TPJ. It is possible that older VPT children would display more right lateralised activations, as seen in a cohort of VPT adults performing the same task (Mossad et al., 2016). Task-based functional connectivity, measured through MEG, has also been investigated during an implicit emotion face processing task in VPT children. Results indicated reduced functional connectivity for angry and fearful faces in networks that include the amygdalae, superior temporal sulci, and anterior cingulate gyrus (Mossad et al., 2020). In a more recent study that employed both fMRI and MEG techniques, activity was measured during a social attribution task, which utilises ToM skills (Klin, 2000; Schultz et al., 2003), in VPT children. fMRI results indicated participants activated typical ToM regions, including the frontal gyri and left superior and inferior parietal lobules (Mossad et al., 2021). MEG results indicated a brain-behaviour association between task performance and connectivity in one network that included the frontal cortex, subcortical regions, and the temporal gyrus, and a socio-cognitive network that included classic ToM regions such as the angular gyrus, frontal regions, and the temporal gyrus.

Only one preterm cohort, thus far, has been investigated for longitudinal associations between neonatal rs-FC and later socio-emotional development. One study indicated that rs-FC of the amygdalae at TEA and was associated with internalising symptoms at two years (Rogers et al., 2017). The authors found specific associations between amygdalae-insula rs-FC and depressive symptoms, and amygdalae-cingulate rs-FC and anxiety symptoms. A more recent study from the same cohort, which included both preterm and term-born infants, identified associations between rs-FC of the ventral attention network (including right ventrolateral prefrontal and right lateral parietal cortices) and the DMN (Sylvester et al., 2018a) and behavioural inhibition at two years. Finally, in the same cohort, researchers highlighted the contribution of participants' SES as well as neonatal striatum rs-

FC in the development of behavioural inhibition difficulties and externalising symptoms at two years (Ramphal et al., 2020).

2.2.3 Summary and Future Research

Neuroimaging research has allowed the identification of specific patterns of altered structural and functional neurodevelopment in preterm-born children and adolescents that might explain impairments in various behaviours that span across cognitive and socio-emotional development. Nevertheless, much work is still needed to identify specific neural alterations implicated in the development of impaired outcomes. Early identification of such difficulties could aid in targeting emerging socio-emotional difficulties and their downstream consequences, for example, through preventative techniques.

The relationship between cognitive development and WM diffusion characteristics in VPT children has been extensively documented. However, due to methodological issues inherent to DTI, including the inability to detect voxels with crossing fibres, these findings could usefully be supplemented with methodologies that allow the distinction of multiple fibre bundles within a voxel. Although findings of associations between cognitive development and WM connectivity have been supported with studies using NODDI analyses, these should also be interpreted with caution as NODDI parameters have been called into question, with some suggesting their assumptions are oversimplified (Jelescu et al., 2016). For example, the NODDI model assumes that neurite density and the mean diffusivity of tissue are directly related, an assumption which recent findings suggest is invalid (Lampinen et al., 2017). Therefore, more advanced diffusion MRI models that allow for the distinction of multiple fibre populations in a single voxel, such as FBA, should be utilised to investigate WM development in the preterm population, and its associations with cognitive outcomes.

Further, despite the existence of research dedicated to understanding socio-emotional development in very preterm born children, the underlying neural substrates associated with this population's increased vulnerability to developing socio-emotional difficulties remain unclear. Pinpointing altered neurodevelopment already present at birth that could predict such behavioural

difficulties during childhood might help implement preventative strategies and therapies. Therefore, further research would need to determine associations between childhood socio-emotional outcomes and infants' structural brain connectivity, specifically in tracts known to be involved in socio-emotional processing, as has been done in the cingulum, for example (Brenner et al., 2021). This is also true for neonatal functional connectivity, which has been investigated in only one preterm cohort, and only in association with behaviours during the toddler years. It is currently unclear whether such associations are also present with children's behaviour at school age.

For a review of neuroimaging studies investigating associations between specific brain mechanisms and behavioural outcomes in preterm adults, please refer to Kanel et al. (2021a) (Appendix A).

Chapter 3: Aims & Thesis Overview

3.1 Aims and Hypotheses

Very preterm birth is accompanied by alterations in grey and white matter development, as well as deficits in socio-emotional and cognitive outcomes. This thesis aims to investigate the relationships between brain structure and function and behavioural outcomes in very preterm children.

3.1.1 Neonatal connectivity and childhood socio-emotional development

The aims and hypotheses of the studies in Chapters 5 and 6 were based on the data collected before the beginning of my PhD by other team members (please see 'Funding and COVID-19 impact statement' for further details). Data collected at Timepoint 2 (see Section 4.2) included parental questionnaires focussing on children's socio-emotional outcomes. I performed factor analysis in order to study children's latent socio-emotional profiles and investigate their association with neonatal brain development. Methods for determining adequate sample size for factor analysis are described in Section 4.2.2.3. Available neuroimaging data at TEA included DTI metrics of specific WM tracts, as well as resting-state functional MRI data. For these studies, I chose to analyse the microstructural characteristics of WM tracts and resting state functional connectivity of regions reported in the literature to be associated with socio-emotional outcomes in paediatric samples (Eden et al., 2015; Genova et al., 2015; Von Der Heide et al., 2013).

3.1.1.1 Structural connectivity and socio-emotional outcomes

The aim of this study was to assess associations between diffusion characteristics of WM tracts implicated in socio-emotional processing assessed at TEA and socio-emotional development in very preterm children. I tested the hypothesis that fractional anisotropy and radial diffusivity in white matter tracts implicated in socio-emotional processing (i.e., UF, IFOF, ILF and SLF) at TEA would be associated with the later development of socio-emotional difficulties in very preterm children.

3.1.1.2 Functional connectivity and socio-emotional outcomes

The first aim of this study was to investigate resting-state functional connectivity of the bilateral amygdalae in neonates born VPT and to explore associations with childhood socio-emotional development. This brain region was chosen based on previous findings indicating its associations with socio-emotional development in preterm children (Johns et al., 2019; Rogers et al., 2017). I tested the hypothesis that altered neonatal resting-state functional connectivity of the bilateral amygdalae is associated with socio-emotional development in very preterm children. Exploratory analyses were further conducted to explore function–structure associations between connectivities related to socio-emotional outcomes, as seen in Chapters 5 and 6.

3.1.2 Childhood structural connectivity and behavioural development

The first aim of this study was to investigate diffusion characteristics of WM in VPT children in relation to term-born controls. I tested the hypothesis that VPT children would exhibit altered WM diffusion characteristics, when compared to full-term controls, as measured by both fixel-based and voxel-based analyses. The second aim of this study was to investigate associations between WM structure and behavioural outcomes in VPT and term-born controls. I tested the hypothesis that cognitive and socio-emotional outcomes would be associated with WM diffusion characteristics in very preterm children. I also tested the hypothesis that this brain-behaviour associations would be altered in VPT children in comparison to term-born controls.

3.2 Thesis outline

Chapters 1 provides an overview of preterm birth and its impact on neonatal brain development, and the use of MRI to study neonatal populations.

Chapter 2 provides an overview of cognitive and behavioural outcomes in preterm children, as well as their structural and functional neural correlates.

Chapter 4 presents methodologies implemented for the collection of data from the ePrime study, a large neonatal neuroimaging study of very preterm infants, followed-up three times during childhood (at 22 months, 4-7 and 8-10 years).

Chapter 5 explores the relationship between white matter diffusion characteristics using DTI metrics at term-equivalent age and childhood socio-emotional outcomes in a cohort of 151 very preterm children.

Chapter 6 explores the relationship between resting-state functional connectivity of the bilateral amygdalae at term-equivalent age and childhood socio-emotional outcomes in a cohort of 129 very preterm children.

Chapter 7 presents the application of fixel-based and voxel-based analyses to a child population to assess diffusion characteristics of white matter tracts and their differences between very preterm and term-born children, as well as their associations with cognitive outcomes.

Chapter 8 summarises key findings in this thesis and outlines potential future work.

Appendix A includes a literature review of neuroimaging studies identifying neurobiological correlates of cognitive and behavioural development in preterm adults.

Chapter 4: General Methods

4.1 Evaluation of Preterm Imaging study (ePrime): Baseline and follow-up assessments (Timepoints 0 & 1)

4.1.1 Participants

Participants in this study were originally recruited as part of the ePrime study (Eudra: CT 2009-011602-42), a large neonatal neuroimaging study that recruited preterm newborns between 2010 and 2013 from hospitals within the North and Southwest London Perinatal Network. Inclusion criteria were being born before 33 weeks GA (including VPT & EPT neonates), and infants' mothers aged over 16 years and not a hospital patient. Exclusion criteria included major congenital malformation, prior MRI, care in centre where preterm MRI was routine, metallic implants, parents unable to speak English or subject to child protection proceedings.

Altogether, 3619 neonates admitted to neonatal units at 14 London Hospitals were screened; 788 did not meet the inclusion criteria, leaving 1831 eligible infants. Six hundred and sixty-two infants were recruited, 151 withdrew before imaging, and recruitment closed once 511 neonates were successfully recruited onto the ePrime study. One family withdrew, leaving a total of 510 infants (Edwards et al., 2018).

4.1.2 Clinical and socio-demographic data collection

As part of neonatal data collection, perinatal clinical and socio-demographic data were collected, with permission, from the Standardized Electronic Neonatal Database. Demographic characteristics of the 510 participants can be seen in Table 4.1.

Table 4.1. Infant demographic and clinical characteristics at Timepoint 0

Characteristics	ePrime sample (n=510)
Sex: Male, n (%)	253 (49.5)
Gestational age at birth (weeks), median (IQR)	30 (27, 31)
Birth weight (g), mean (SD)	1306.1 (397.7)
Gestational age at scan (weeks), median (IQR)	43 (41, 44)
Twin or triplet birth, n (%)	153 (29.9)

IQR = Interquartile range; SD = standard deviation.

Socio-demographic data collected included maternal age when leaving full time education, collected at enrolment, through a parental questionnaire. This variable was binarized into two categories: higher educational level (leaving full-time education ages >19 years) and lower education level (leaving full-time education ages ≤19 years), as in the UK this cut-off coincides with the completion of graduate studies (Belfield et al., 2018). Further, family SES was evaluated with the Index of Multiple Deprivation (IMD) score, determined by parents' postcode at the time of infant's birth (Department for Communities and Local Government, 2011; https://tools.npeu.ox.ac.uk/imd/). The IMD measures social risk by comparing each neighbourhood to all others in the country and is based on seven domains of deprivation (with varying weighting, as follows): income (22.5%), employment (22.5%), education skills and training (13.5%), health and disability (13.5%), barriers to housing and services (9.3%), living environment (9.3%) and crime (9.3%). Family socio-demographic characteristics of the 510 participants can be seen in Table 4.2.

Table 4.2. Family socio-demographic characteristics at Timepoint 0

Characteristics		ePrime sample (n=510)
IMD quintiles, n (%)	1 (least deprived)	91 (17.8)
	2	82 (16.0)
	3	129 (25.2)
	4	135 (26.4)
	5 (most deprived)	73 (14.3)
Maternal age upon leaving formal education, n (%)	≤16 years	49 (9.6)
	17-19 years	76 (14.9)
	≥19 years	348 (68.1)
	Still in full-time education	16 (3.1)
	Not stated	21 (4.1)

IMD = Index of Multiple Deprivation.

Parental ethnicity was also collected. Where possible, we report maternal and paternal ethnicity. However, when paternal ethnicity was not available, we report maternal ethnicity only (Table 4.3). Ethnicity was grouped according to classification by the Office of National Statistics (ONS): White (English/Welsh/Scottish/Northern Irish/British, Irish, Any other White background); Mixed/Multiple ethnic groups (White and Black Caribbean, White and Black African, White and Asian, Any other Mixed/Multiple ethnic background); Asian/Asian British (Indian, Pakistani, Bangladeshi, Chinese, Any other Asian background); Black/African/Caribbean/Black British (African, Caribbean, Any other Black/African/Caribbean background); Other ethnic group (Arab, Any other ethnic group).

Table 4.3. Participants' ethnicity at baseline assessment.

Ethnicity	**Child's ethnicity based on both parents' ethnicity (n=400)**	**Child's ethnicity based on maternal ethnicity* (n=105)**
White	194 (48.50)	57 (54.25)
Mixed/Multiple ethnic groups	43 (10.75)	29 (27.62)
Asian/Asian British	98 (24.5)	18 (17.14)
Black/African/Caribbean/Black British	65 (16.25)	1 (0.95)

Ethnicity was grouped according to ONS classification; number (%)
* Paternal ethnicity not reported.
Six participants had no parental ethnicity data.

4.1.3 Neonatal Sickness Score

Clinical data regarding the participants' health during the perinatal period were also collected. These included the following: preeclampsia and pregnancy induced hypertension, antenatal hypertension, placental abruption or antenatal haemorrhage, premature rupture of membranes, urinary tract infection, gestational diabetes, oligohydramnios, polyhydramnios, drug abuse, in vitro fertilization, bacterial infection (all y/n), mode of delivery (vaginal/elective/emergency), sex, gestational age (GA; weeks and days), birth weight (grams), multiple pregnancy (singleton/multiple), antenatal steroid administration (no/partial/full course), twin-to-twin transfusion, chorioamnionitis,

intrauterine growth restriction, surfactant administration (surf), treatment for patent ductus arteriosus, surgical treatment for necrotising enterocolitis, formula feeding, feeding on maternal expressed breast milk (all y/n), days on mechanical ventilation (vent), days on continuous positive airway pressure (cPAP), and days on parenteral nutrition (TPN).

In order to summarise the twenty-eight perinatal clinical variables obtained from all ePrime participants (n=511), a Principal Component Analysis (PCA) was performed using Promax rotation. The Kaiser-Meyer-Olkin Measure of Sampling Adequacy was .73 and the Bartlett's Test of Sphericity was significant ($\chi 2 = 3597.79$ $p < 0.01$) showing that the sample was adequate for a PCA (Preacher and MacCallum, 2003). All variables were coded so that higher values reflected greater clinical risk. Communalities were checked, and as all were above .2, no items were removed (Costello and Osborne, 2005). The result of the analysis produced one factor comprising five items all pertaining to neonatal sickness: GA, TPN, cPAP, vent and surf, and explained 72% of the variance of all variables. The reliability of the scale was also good (α=.86).

4.1.4 Neonatal MRI data collection (Timepoint 0)

Out of 511 successfully recruited infants, 507 underwent successful MRI scans at TEA, or between 38–44 weeks GA. MR imaging was performed on a 3-Tesla system (Philips Medical Systems, Best, The Netherlands) using an eight-channel phased array head coil on a neonatal intensive care unit. During the scans, ear protection was used (President Putty, Coltene Whaledent, Mahwah, New Jersey, USA; MiniMuffs, Natus Medical, San Carlos, California, USA), and the following parameters were monitored: pulse oximetry, temperature, and heart rate. Some parents of infants (87%) chose sedation to be administered for the scans, for which Chloral hydrate (25–50 mg kg^{-1}) was used.

Details of MR images acquired are as follows. High-resolution anatomical images were acquired with pulse sequence parameters: T2 weighted fast-spin echo imaging: TR = 8670 ms, TE = 160 ms, flip angle 90°, slice thickness 2 mm with 1 mm overlapping slices, in-plane resolution 0.86x0.86mm; T1 high resolution volume (3D MPRAGE): TR = 17 ms, TE = 4.6 ms, flip angle 13°, slice thickness

0.8 mm, in-plane resolution 0.82x0.82mm. Diffusion MRI data were acquired in the transverse plane in 32 non-collinear directions with the following parameters: TR = 8000 ms, TE = 49 ms, voxel size: 2mm isotropic, b-value: 750 s/mm^2, sense factor of 2, 1 non-diffusion-weighted image, $b = 0$. Whole brain functional imaging was performed using a T2* gradient echo planar image acquisition (sequence parameters: TR = 1500 ms; TE = 45 ms; flip angle = 90°; field-of-view: 200 mm; matrix: 80 × 80 (voxel size: 2.5 × 2.5 × 4 mm), 256 volumes (total scan time = 6 min 24 s).

4.1.5 Brain injury classification

ePrime participants were classified into three groups (major injury / minor injury / no injury) based on qualitative rating of their neonatal MRI at TEA. Data on these groups are shown in Table 4.4. Major injury was defined as cystic periventricular leukomalacia or more severe, higher-grade haemorrhages (causing enlarged ventricles and parenchymal infarction). Minor injury was determined using a qualitative scale developed by Inder and colleagues (Inder et al., 2003). Participants belonging to the major injury group were excluded from follow-up analyses in the following chapters.

Table 4.4. Classification of brain injury in the ePrime sample

Brain injury classification, n (%)	**Neonatal sample with MRI at TEA (n=507)**
Major	40 (7.89)
Minor	265 (52.27)
None	202 (39.84)

4.1.6 Neuropsychological and behavioural functioning at 18-22 months (Timepoint 1)

Out of the 511 recruited infants, 483 toddlers aged 18–22 months completed the Bayley Scales of Infant Development-III (Bayley, 2006), and parents filled out questionnaires assessing general development, language (PARCA-R (Johnson et al., 2008)) and autism symptoms (M-CHAT (Robins et al., 2001)).

4.2 Follow-up assessment at Timepoint 2

4.2.1 Participants

From 4 years of age, a convenience sample of children was recruited from families who accepted invitations to undergo further examination and testing (Kleine et al., 2020; Montagna et al., 2020). This study was approved by Stanmore Ethics Committee (14/LO/0677) in compliance with the national legislation and the code of ethical principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all the children's carer(s). Mean age of children seen at Timepoint 2 was 5.02 years (SD = 0.79; range = 4.18–7.17).

Invitations for follow-up were sent in chronological order of birth to all children who were eligible for testing based on their age (n = 306). Of those, 55 (18%) were not assessed due to various reasons (see Figure 4.1). Clinical and socio-demographic characteristics of the 251 participants can be seen in Tables 4.5 and 4.6.

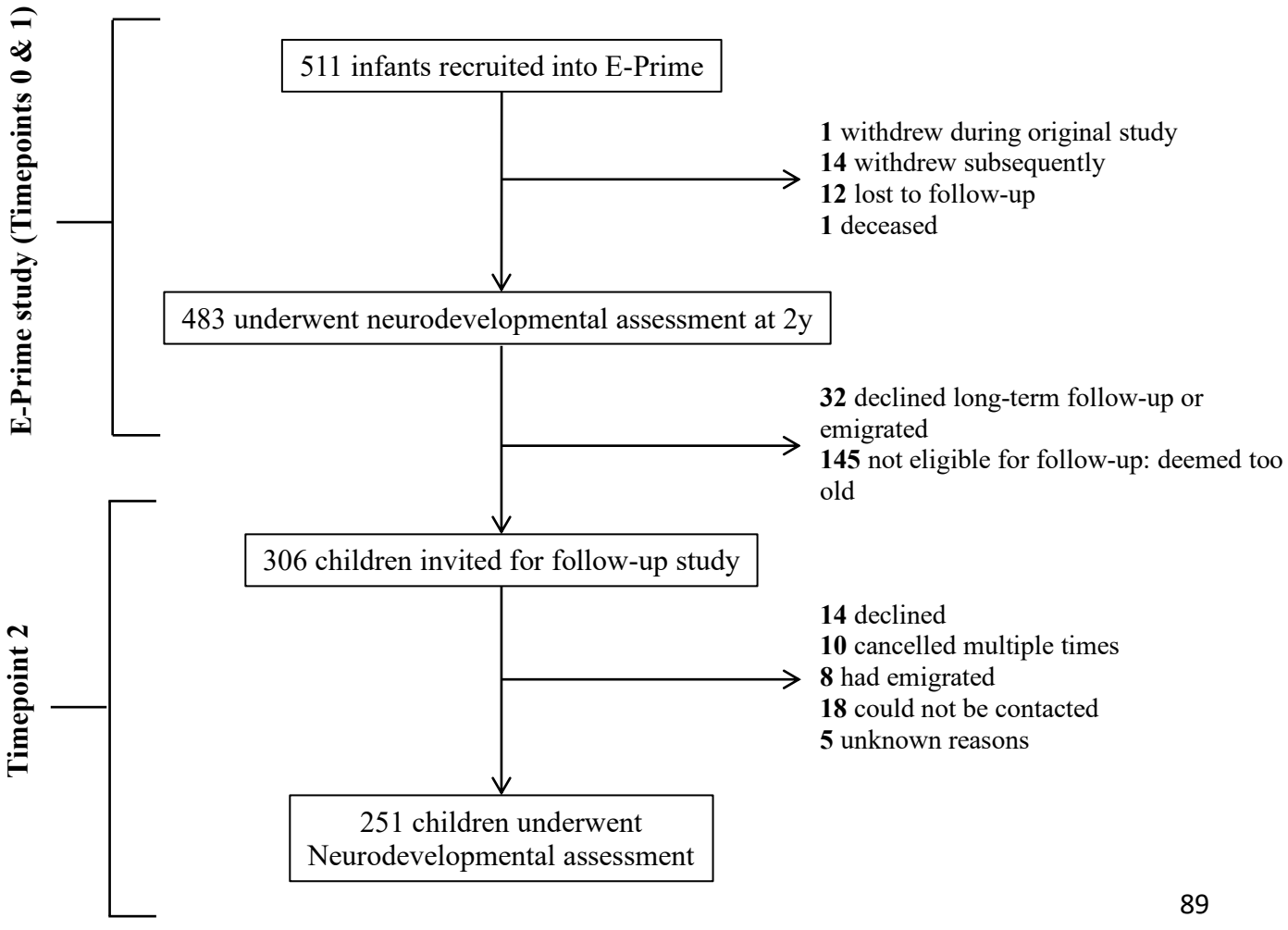


Figure 4.1. Recruitment flow chart at Timepoints 0, 1 & 2
TEA = term-equivalent age; PMA = post-menstrual age

Table 4.5. Childhood demographic and clinical characteristics at Timepoint 2

Characteristics	Follow-up sample (n=251)
Sex: Male, n (%)	132 (52.8)
Gestational age at birth (weeks), median (IQR)	30 (27, 31)
Birth weight (g), mean (SD)	1309.0 (394.1)
Gestational age at scan (weeks), median (IQR)	43 (41, 44)
Twin or triplet birth, n (%)	83 (33.2)

IQR = Interquartile range; SD = standard deviation.

Table 4.6. Family socio-demographic characteristics at Timepoint 2

Characteristics		Follow-up sample (n=251)
IMD quintiles, n (%)	1 (least deprived)	58 (23.1)
	2	39 (15.5)
	3	57 (22.7)
	4	64 (25.5)
	5 (most deprived)	32 (12.7)
Maternal age upon leaving formal education, n (%)	≤16 years	21 (8.4)
	17-19 years	41 (16.3)
	≥19 years	175 (69.7)
	Still in full-time education	5 (2.0)
	Not stated	9 (3.6)

IMD = Index of Multiple Deprivation.

Parental ethnicity (collected at Timepoint 0) is summarised for participants followed-up at Timepoint 2. Where possible, we report maternal and paternal ethnicity. However, when paternal ethnicity was not available, we report maternal ethnicity only (Table 4.7).

Table 4.7. Participants' ethnicity at Timepoint 2.

Ethnicity	Child's ethnicity based on both parents' ethnicity (n=197)	Child's ethnicity based on maternal ethnicity* (n=51)
White	106 (53.8)	34 (66.7)
Mixed/Multiple ethnic groups	22 (11.2)	1 (2.0)
Asian/Asian British	39 (19.8)	8 (15.7)

Black/African/Caribbean/Black British	30 (15.2)	8 (15.7)

Ethnicity was grouped according to ONS classification; number (%)
* Paternal ethnicity not reported.
Three participants had no parental ethnicity data.

The following sample representativeness comparisons assessed differences between children taking part in follow-up assessment at Timepoint 2 (n = 251) and those not included in follow-up analyses (n = 260). Non-parametric tests showed that the two groups did not differ in terms of their GA at birth in weeks (W = 32226, p = 0.817), birth weight (W = 32586, p = 0.979), or sex (Chi-square = 0.532, p = 0.466). Samples also did not differ significantly in terms of ethnicity, when analyses were based on either both parents' ethnicity (Chi-square = 6.081, p = 0.193) or maternal ethnicity only (Chi-square = 9.113, p = 0.059). However, there was a significant difference in IMD scores between the two groups, with the followed-up group being less socially deprived than the group who was not followed-up, i.e., high SES (W = 28918, p = 0.031) (Figure 4.2).

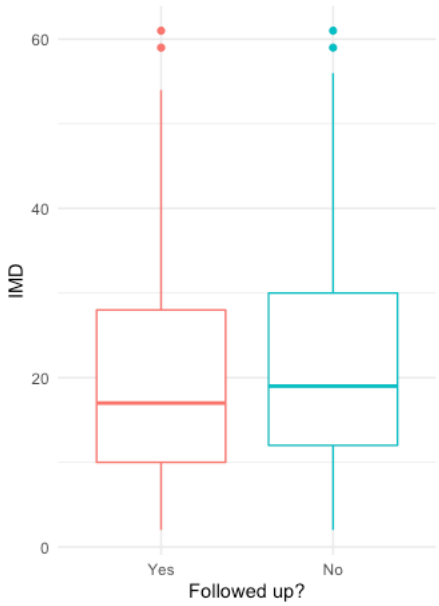


Figure 4.2. Boxplot showing IMD differences between those children who were, and were not, followed up at Timepoint 2.
IMD = Index of Multiple Deprivation

Of the infants who were assessed at 20 months (n = 483), those who were subsequently followed up at Timepoint 2 (n = 241), performed significantly better on the Bayley's cognitive tests

(collected at Timepoint 1) than those who were not subsequently followed up (n = 242) (W = 30534, $p < 0.001$) (Figure 4.3).

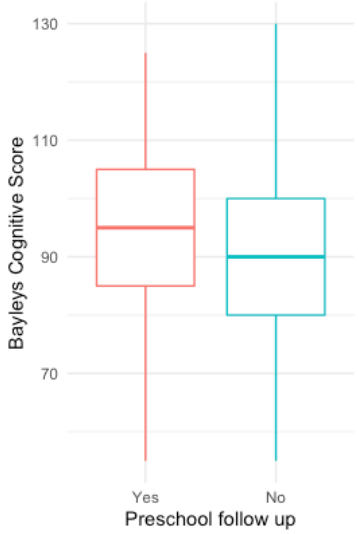


Figure 4.3. Boxplot showing cognitive score differences between children included and excluded from follow-up analyses at Timepoint 2.

4.2.2 Neuropsychological and behavioural assessment

In order to assess cognitive performance and behavioural competence, children took part in a neurodevelopmental battery including both neuropsychological tests and parental questionnaires assessing cognitive performance and behavioural competence (all measures are described in Table 4.8).

4.2.2.1 Cognitive development

The Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV, (Wechsler, 2012)) was administered to all children in order to assess general intellectual development. Executive functions were assessed through a variety of games including the Attention Network Task (Fan et al., 2002; Rueda et al., 2004) for inhibition, Digit Span (Wechsler, 2003) for working memory, Dimension Change Card Sorting (Zelazo, 2006) for shifting and Track-It (Fisher et al., 2013) for sustained attention.

Behavioural aspects of executive functions were also assessed using the parents-rated questionnaire Behaviour rating inventory of executive functions – Preschool edition (BRIEF-P) (Gioia et al., 1996; Gioia et al., 2000).

4.2.2.2 Behavioural development

Parents completed questionnaires that referred to children's socio-emotional abilities. Social impairment was assessed using the Social Responsiveness Scale-2 (SRS-2 (Constantino and Gruber, 2012)), and behavioural problems were investigated using the Strengths and Difficulties Questionnaire (SDQ) (Goodman and Goodman, 2009; Goodman, 2001). The SDQ is a questionnaire primarily used to detect children with mental health difficulties and to estimate prevalence of disorders in specific populations, in various settings including clinical, community and research. The SDQ is highly correlated with the Rutter questionnaire (Goodman, 1997) and the Child Behaviour Checklist (Achenbach, 1991; Goodman and Scott, 1999), and has high diagnostic accuracy in both the general population (Goodman et al., 2000) and preterm samples (Johnson et al., 2014). Further, parent-rated temperamental traits were collected using the Children's Behaviour Questionnaire – Very Short Form (CBQ-VSF) (Putnam and Rothbart, 2006; Rothbart et al., 2001). Subscales of the very short CBQ have been shown to correlate with the following behavioural outcomes: a) negative affect and internalising/emotional problems; b) surgency and externalising problems and c) effortful control and attention, externalising, social problems, and executive function measures. Empathy was assessed using the empathy questionnaire (EmQue) (Rieffe et al., 2010). The EmQue has been shown to correlate with the Prosocial Behaviour subscale of the SDQ, as well as an Empathy Task that examines children's responses to emotional displays by the experimenter (Rieffe et al., 2010), based on a previous task displaying pain by (Zahn-Waxler et al., 1992). Inattentive and hyperactivity symptoms were assessed using the ADHD rating scale IV preschool version (DuPaul et al., 1998; McGoey et al., 2007).

Performance-based social competence was investigated using the Penny Hiding Game for assessment of Theory of Mind (San José Cáceres et al., 2014). Further, an emotion recognition task was created especially for children, based on an emotion recognition task used in adults (Gao and Maurer, 2009, 2010). The use of different intensities in an emotion recognition task to detect subtle differences in performance has been used in previous literature (Horning et al., 2012; Kessels et al.,

2014). Morphs were created using Phantamorph software (http://www.fantamorph.com/index.html). Figure 4.4 shows an example of 6 different emotions at 2 different intensities.

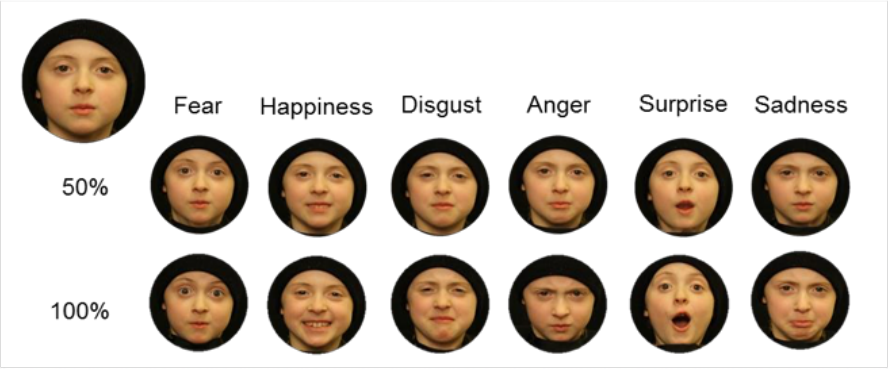


Figure 4.4. Example of stimuli used in the emotion recognition task.

Children were presented with images of children's faces (either original or those created with Phantamorph) and asked to sort each face into a 'house'. Houses consisted of a plastic box, each with a schematic face on it. Examples of these faces are shown in Figure 4.5.

Figure 4.5. Examples of stimuli used to label 'houses' in the emotion recognition task.

The task was divided into two blocks, with the first comprising 8 pictures for each of the following emotions: happiness, surprise, and fear, and the second block comprising 8 pictures for each of the following emotions: sadness, anger, and disgust. Each block also contained 4 pictures representing neutral facial expressions, for a total of 8 neutral stimuli. Before starting, the experimenter introduced the game with the following: *'Each box represents a house, inside of which people are telling stories. In one house they tell happy stories, in another they tell scary stories, as well as disgusting, sad, angry, and surprising stories* [point to appropriate house]. *In the neutral house, no one is telling any stories. Now more people arrive. Your job is to find the right house for*

them – they can only go to the house if they have the same feeling as the people inside of that house'. Pictures are then presented, one by one, and the child identifies which house each stimulus belongs to.

Lower accuracy scores on the emotion recognition task correlated with higher SRS-2 T-scores, indicating increased social difficulties (Social Information Processing ($r = -0.261$; $p < 0.001$), Social Communication ($r = -0.201$; $p = 0.003$), Social Motivation ($r = -0.201$; $p = 0.003$), Restricted Interests and Repetitive Behaviour ($r = -0.228$; $p = 0.001$), Social Communication Index ($r = -0.234$; $p = 0.001$) and Total score ($r = -0.237$; $p<0.001$). Crucially, the task was most strongly associated with social information processing, suggesting it successfully assessed the key construct it was designed to, in paediatric samples.

Table 4.8. Measures used in follow-up analyses at Timepoint 2

	Measure	**Description**
General Intellectual functioning	WPPSI-IV	A cohort of intelligence tests that calculate a general intelligence score (full-scale IQ), as well as five Primary Index subscales of narrow abilities including: verbal comprehension, visual-spatial abilities, fluid reasoning, processing speed and working memory index. Raw scores are transformed into scaled scored according to age-appropriate norms.
Executive functions	ANT	Adapted from a flanker task (Eriksen and Eriksen, 1974) which assesses ability to deal with conflict and inhibit automatic responses (or 'executive attention'). The child was asked to press the right or left button according to the direction of a central animal to catch it. The central animal was surrounded by smaller animals who faced the same or opposite direction (congruent or incongruent trials).
	Digit Span	Children asked to remember progressively increasing series of numbers and to repeat numbers once in same order and once in reversed order (adapted from WISC-IV).
	DCCS	Task evaluating ability of child to shift between two different tasks. At the beginning of each task the child is required to focus on a specific dimension and to categorise items accordingly. In the post-switch phase, the child had to inhibit attention to that dimension and to sort the items based on another feature (e.g., matching some cards on the colour of the pictures and then matching the same cards on the shape of the pictures).
	Track-it	In this task, children are asked to track a single target object moving among a set of two heterogeneous distracter objects that are following a random trajectory. After some time, the objects faded away and the child indicates the square from where the target object disappeared (tracking accuracy, measure of sustained attention).
	BRIEF-P	A standardised and ecologically valid questionnaire evaluating real-world adaptive executive functions in children. The outputs comprise five executive function domains: Inhibit, Shift, Emotional Control, Working Memory and Plan/Organise. These five domains combine to form three indexes (Inhibitory Self-Control, Flexibility and Emergent Metacognition). Raw scores are transformed into scaled scored according to age-appropriate norms.
Social competence	Penny Hiding Game	Task involving the child hiding a penny in one hand and asking another person to guess the location of it, to test the understanding of theory of mind without involving verbal abilities. The Penny Hiding game gives a graded measure of social skills in the number and type of errors. Successful performance requires both hiding an object from the other person's view and hiding information from the opponent's mind (i.e., misleading them).

	Emotion recognition task	An emotion recognition task created with static stimuli from the validated Dartmouth database of children's faces (Dalrymple et al., 2013). Four boys and four girls were chosen from the database and 6 emotions (happy, surprise, fear, anger, disgust, and sadness) plus neutral faces were used. For every emotion, two levels of intensity were created by morphing a neutral face with the emotional face of the same model, to create, for example, 50% and 100% happy faces. The total number of correct responses the child made was added up to produce an emotion recognition score.
	SRS-II	A quantitative standardised parent-rated measure of autistic traits that detects deficiencies in reciprocal social behaviour. This questionnaire assesses social impairment, and the two outputted subscales align well with DSM-V criteria of autism spectrum disorders: a) Social Communication and Interaction, and b) Restricted Interests and Repetitive Behaviour. Raw scores are transformed into T-scores and the questionnaire is normed for children.
Behavioural problems	SDQ	A validated parent-rated screening questionnaire for behavioural problems. Behaviours are summarised for subscales including negative (emotional symptoms, conduct problems, hyperactive/inattentive and peer problems) as well as positive (prosocial behaviours) outcomes.
	CBQ	A validated parent-rated questionnaire which assesses children's (ages 3-7) temperament and summarises results into three broad scales: negative affectivity, effortful control and surgency.
	EmQue	This parent-rated questionnaire summarises empathy-related behaviours into three subscales: emotion contagion, attention to others' emotions and prosocial responses to others' emotions.
	ADHD Rating Scale IV	A parent-rated, norm-referenced questionnaire that requires respondent to rate the frequency of occurrence of ADHD symptoms according to the diagnostic criteria defined by the DSM-V (Association, 2013) and provides a total score and two separate subscales (Inattention and Hyperactivity/Impulsivity).

ANT = Attention Network Task; BRIEF-P = Behaviour Rating Inventory of Executive Function – Preschool edition; CBQ = Children's Behaviour Questionnaire (very short version); DCCS = Dimension Change Card Sort; EmQue = Empathy questionnaire; SDQ = Strengths and Difficulties Questionnaire; SRS-II = Social Responsiveness Scale II; WPPSI-IV = Wechsler Preschool & Primary Scale of Intelligence – Fourth edition.

4.2.2.3 Factor analysis

In order to summarise the 12 socio-emotional outcomes variables, maximum-likelihood factor analysis with Varimax rotation was performed (more information is provided in Chapter 5 Methods). The statistical literature suggests an N:variable ratio of at least 10 (Everitt, 1975), and therefore, a sample size of 151 participants and 12 variables was an appropriate for this type of analysis.

4.3 Follow-up assessment at Timepoint 3

4.3.1 Participants

At around 8 years, ePrime participants were invited back to take part in follow-up assessments including behavioural data collection and an MRI scan at the Evalina Newborn imaging Centre at St. Thomas hospital, London. In addition to this, full-term control participants were

recruited from the community, both from local schools and from within the university. This study was approved by Stanmore Ethics Committee (18/LO/0048) in compliance with the national legislation and the code of ethical principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all the children's carer(s).

Invitations for follow-up were sent to families of ePrime children who took part in the follow-up assessment at Timepoint 2, in chronological order of birth (n = 251). At the time of writing, 101 families have been attempted to get in contact with. Of those, 81 were successfully contacted, of which 17 refused to take part due to various reasons including not wanting an MRI scan (7), the child having severe medical problems (3), not having enough time to partake (1), and not wanting to come in during COVID-19 (1). 5 families did not give a reason for not wanting to take part. This left 64 ePrime participants in the preterm experimental group. Recruitment details are summarised in Figure 4.6. Demographic characteristics of the 64 participants are displayed in Table 4.9. Mean age of children seen at Timepoint 3 was 8.50 years (SD = 0.62; range = 7.5–10.5).

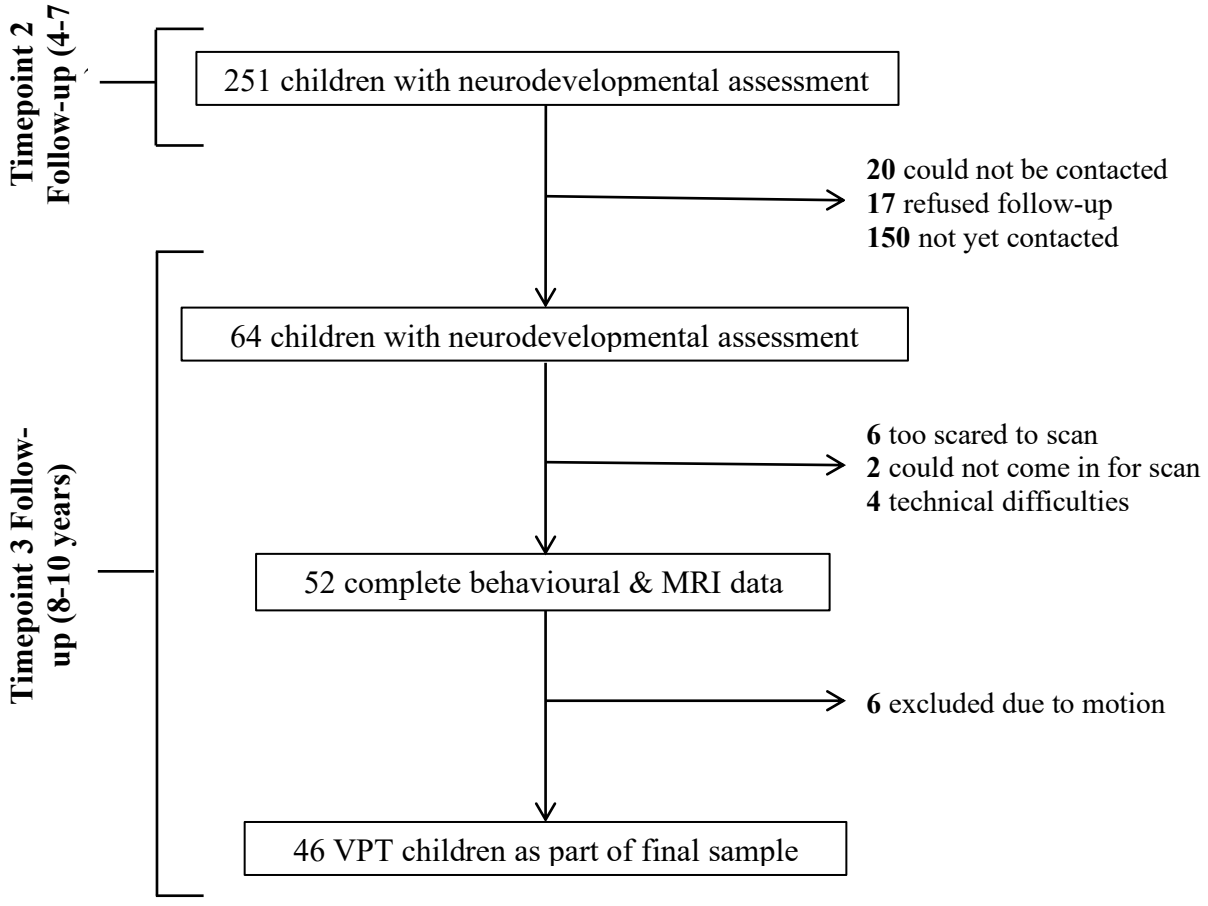


Figure 4.6. Recruitment flowchart at Timepoint 3.
VPT = very preterm

The following sample representativeness comparison assesses differences between children who took part in the follow-up at Timepoint 3 (n = 64; median age = 8.5) and those not yet followed-up after Timepoint 2 (n = 187). Please note that Timepoint 3 recruitment is still ongoing, aiming to assess all children seen at Timepoint 2. The two groups did not differ significantly in terms of their GA at birth (W = 6074.5, p = 0.858), birth weight (W = 6253.5, p = 0.5912), sex (Chi-square = 0.002, p = 0.964), or WPPSI IQ scores at Timepoint 2 (W = 6303.5, p = 0.168). Samples also did not differ significantly in terms of ethnicity, when analyses were based on either both parents' ethnicity (Chi-square = 1.064, p = 0.901) or maternal ethnicity only (Chi-square = 1.015, p = 0.908). However, there was a significant difference in IMD scores between the two groups, with the followed-up group coming from less deprived backgrounds than those who were not followed-up, i.e., high SES (W = 4950, p = 0.039) (Figure 4.7).

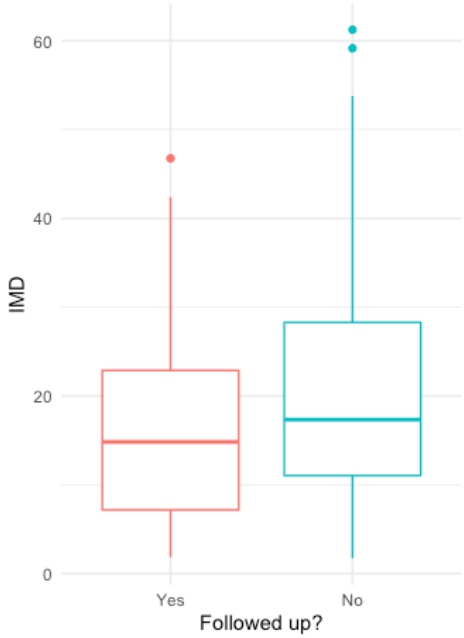


Figure 4.7. Boxplot showing IMD differences between those children who were, and were not, followed-up at Timepoint 3.

In addition to the preterm group, full-term control participants were recruited from the community, with inclusion criteria being full-term birth (38-42 weeks). Control participants were recruited through advertising the study on a university fortnightly circular for research volunteer recruitment, as well as in local school's notice boards. Altogether 46 control participants were recruited, and their demographic characteristics are displayed in Table 4.9.

Table 4.9. Childhood demographic and clinical characteristics at Timepoint 3.

Characteristics		**All children (n=110)**	**Preterm group (n = 64)**	**Control group (n = 46)**
Sex: Male, n (%)		50 (43.8)	33 (51.6)	17 (37.0)
Gestational age at birth (weeks), median (IQR)		32.50 (29.14, 39.57)	30.07 (27.96, 32.00)	40.00 (39, 40.85)
Age at assessment (years), median (IQR)		8.50 (8.25, 10.58)	8.46 (8.25, 8.83)	8.75 (8.10, 9.15)
IMD quintiles, n (%)	1 (least deprived)	35 (31.8)	20 (31.3)	15 (32.6)
	2	21 (19.1)	12 (18.8)	7 (15.2)
	3	24 (21.8)	17 (26.6)	7 (15.2)
	4	29 (26.4)	13 (20.3)	15 (32.6)
	5 (most deprived)	4 (3.6)	2 (3.1)	2 (4.3)

IMD = Index of Multiple Deprivation; IQR = Interquartile range.

Participants' ethnicity was collected again for all children at Timepoint 3. These are displayed in Table 4.10.

Table 4.10. Participant ethnicity at Timepoint 3.

Ethnicity	**All children (n=104)**	**Preterm group (n=64)**	**Control group (n = 40)**
White	70 (67.3)	36 (52.9)	34 (85.0)
Mixed/Multiple ethnic groups	10 (9.6)	6 (9.4)	4 (10.0)
Asian/Asian British	15 (14.4)	13 (20.3)	2 (5.0)
Black/African/Caribbean/Black British	9 (8.7)	9 (14.1)	0 (0.0)

Ethnicity was grouped according to ONS classification; number (%)
Six control participants had no ethnicity data.

Of the 110 children recruited into the study (64 preterm, 46 control), ten were too scared to complete the MRI scan (6 preterm), two were unable to complete due to clinical issues (including

severe autism and cerebral palsy), and three had incomplete scans due to technical difficulties, leaving a total of 95 completed MRI scans (53 preterm, 41 control participants). Children who underwent MRI did not differ significantly from those who did not in terms of their age (W = 782, p = 0.547), sex (Chi-square = 0.032, p = 0.859) or group (i.e., preterm vs controls) (Chi-square = 0.997, p = 0.318). However, the two groups did perform differently on the WISC, with the children who underwent MRI having significantly higher full-scale IQ scores compared to those who did not (W = 319, p = 0.002) (Figure 4.8).

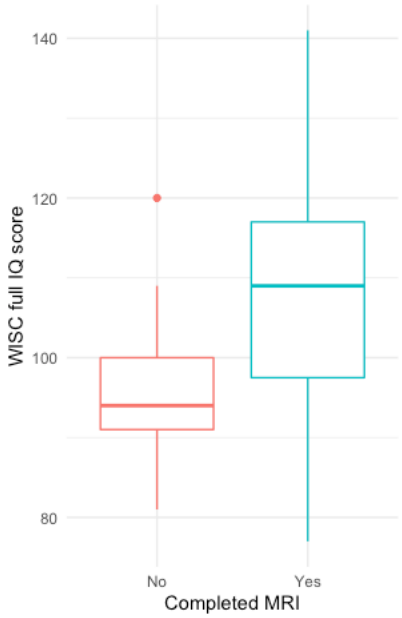


Figure 4.8. Boxplot showing differences in WISC scores between children who underwent childhood MRI and those who did not, at Timepoint 3.

4.3.2 Childhood behavioural data collection

4.3.2.1 Neurobehavioural tests

For full descriptions of all neurobehavioural tests at follow-up at Timepoint 3 please refer to Table 4.12. Participants completed the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003), most commonly on the same day as the MRI scan. When that was not possible, the WISC was administered within one week of the MRI scan. The WISC-IV provides a score for Full Scale IQ, as well as four subscales: Verbal Comprehension, Visuo-spatial skills, Working Memory and Processing Speed.

Emotion regulation abilities were assessed using a newly created task called the Unsolvable Puzzle task, based on previous literature (Smiley and Dweck, 1994). In this task, children were asked to complete a relatively simple puzzle of 16 pieces, in two and a half minutes. The first time this puzzle was given to the children, it had two pieces missing, therefore leaving the children unable to successfully complete the task. After 2 ½ minutes, the examiner stops the child and explains to them a mistake has been made, then proceeds to give the child the correct puzzle. For the second puzzle, the child is given an unlimited amount of time to finish the puzzle. Throughout the task, participants' facial expressions are recorded using a video camera.

Finally, children completed an emotion recognition task, originally created for the follow-up assessments at Timepoint 2, described above. To investigate the impact of age on emotion recognition, emotion recognition accuracy was plotted against age as a function of group (very preterm and control). Scores from data collected at Timepoint 2 and Timepoint 3 were combined for the very preterm group. A significant main effect of age was found for emotion recognition scores, but there was no significant interaction between group and age (Table 4.11). Figure 4.9 shows a positive relationship between age and ability to correctly recognise facial expressions.

Table 4.11. Statistical analyses of the effect of age and group (very preterm and control) on Emotion Recognition scores

Predictor	**Estimate**	**T value**	***p*-value**
Age	1.267	4.837	<0.001*
Group	7.215	0.589	0.556
Age * Group	-0.415	-0.294	0.769

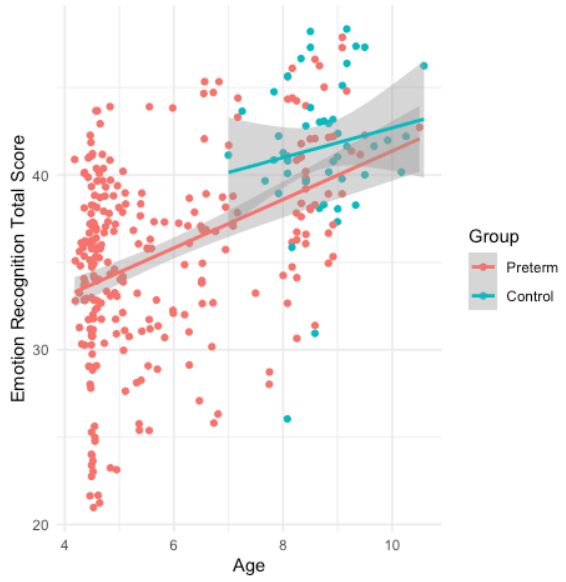


Figure 4.9. Scatterplot of Emotion Recognition Total scores against age, by group.

4.3.2.2 Parental questionnaires

For full descriptions of all parental questionnaires please refer to Table 4.12. Parents completed questionnaires probing children's executive functions as well as socio-emotional development. The following questionnaires were used: Behaviour Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000), Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997); Social Responsiveness Scale (SRS) (Constantino and Gruber, 2002); Temperament in Middle Childhood Questionnaire (TMCQ) (Simonds and Rothbart, 2004); Emotion Regulation Checklist (ERC) (Cicchetti, 1997); Spence Children's Anxiety Scale (SCAS) (Nauta et al., 2004) and State-Trait Anxiety Inventory for adults (STAI; assessing parents) (Spielberger et al., 1977).

Table 4.12. Neurobehavioural tests and parental questionnaires used in follow-up assessment at Timepoint 3

	Measure	**Description**
General intellectual functioning	WISC-IV	A cohort of intelligence tests that calculate a general intelligence score (full-scale IQ), as well as five Primary Index subscales of narrow abilities including: verbal comprehension, visual-spatial skills, processing speed and working memory index. Raw scores are transformed into scaled scores according to age-appropriate norms.
Executive functions	BRIEF	A standardised and ecologically valid questionnaire evaluating real-world adaptive executive functions in children. The outputs comprise five executive function domains: Inhibit, Shift, Emotional Control, Working Memory and Plan/Organise. These five domains combine to form

		three indexes (Inhibitory Self-Control, Flexibility and Emergent Metacognition). Raw scores are transformed into scaled scored according to age-appropriate norms.
Social competence	Emotion recognition task	An emotion recognition task created with static stimuli from the validated Dartmouth database of children's faces (Dalrymple et al., 2013). Four boys and four girls were chosen from the database and 6 emotions (happy, surprise, fear, anger, disgust, and sadness) plus neutral faces were used. For every emotion, two levels of intensity were created by morphing a neutral face with the emotional face of the same model, to create, for example, 50% and 100% happy faces. The total number of correct responses the child made was added up to produce an emotion recognition score.
	Unsolvable Puzzle task	Task created based on previous studies (Smiley and Dweck, 1994). During completion of the Unsolvable puzzle task, facial expressions are recorded and analysed using the Noldus FaceReader, which automatically quantifies facial expressions (https://www.noldus.com/human-behavior-research/products/facereader).
	SRS-II	A quantitative standardised parent-rated questionnaire of autistic traits that detects deficiencies in reciprocal social behaviour. This questionnaire measures social impairment, and the two outputted subscales align well with DSM-V criteria of autism spectrum disorders: a) Social Communication and Interaction, and b) Restricted Interests and Repetitive Behaviour. Raw scores are transformed into T-scores and the questionnaire is normed for children.
Behavioural problems	SDQ	A validated parent-rated screening questionnaire for behavioural problems. Behaviours are summarised for subscales including negative (emotional symptoms, conduct problems, hyperactive/inattentive and peer problems) as well as positive (prosocial behaviours) outcomes.
	TMCQ	A validated parent-rated questionnaire which assesses children's (ages 7-10) temperament and summarises results into three broad scales: negative affectivity, effortful control and surgency.
	SCAS-P	Normed & validated parent-rated questionnaire of anxiety disorders, with output scores for six sub-scales each tapping into a specific aspect of child anxiety, corresponding with classification of anxiety disorders by DSM-IV: separation anxiety, generalised anxiety, social phobia, panic/agoraphobia, obsessive-compulsive disorder, and fear of physical injuries.
	ERC	A validated parent-rated questionnaire assessing children's self-regulation, or ability to manage and cope with emotions, in children between ages 6 to 12. Final subscales comprised of: a) emotion regulation (expression of emotions, empathy, and emotional self-awareness) and b) emotional lability/negativity (lack of flexibility, anger dysregulation and mood lability).
Parental characteristics	STAI	Questionnaire assessing levels of anxiety in parents/carers of children, with outputs including state and trait anxiety. State anxiety measures a transitory emotional state at the exact moment of answering questions, which fluctuates over time. Trait anxiety refers to how participants feel in general and indicates a person's proneness to responding anxiously to stressful situations; it has been shown to be stable over time.

BRIEF = Behaviour Rating Inventory of Executive Function; ERC = Emotion Regulation Checklist; SCAS = Spence Children's Anxiety Scale; SDQ = Strengths and Difficulties Questionnaire; SRS-II = Social Responsiveness Scale II; STAI = State-Trait Anxiety Inventory; TMCQ = Temperament in Middle Childhood Questionnaire; WISC-IV = Wechsler Intelligence Scale for Children – fourth edition.

4.3.3 Childhood MRI data collection

MR images were acquired on a Philips 3 Tesla Achieva (Philips Medical Systems, Best, The Netherlands) system at the Evalina Newborn Imaging Centre using a 32-channel phased array head coil. Throughout the scan, pulse oximetry, heart rate and breathing were monitored. Children were given paediatric earplugs, which were placed in the external auditory meatus, as well as noise

cancelling headphones. During the scan, children watched a TV show of their choice on Netflix or Amazon Prime. Decorative boards (in 'space' theme) were put up surrounding the MRI scanner (Figure 4.10).

Figure 4.10. Image of MRI scanner and decorative boards used as part of the follow-up at Timepoint 3.

High resolution 3D T1 and T2 weighted imaging were acquired, as well as a FLAIR for clinical reporting. MPRAGE T1-weighted images were acquired using: TR = 7.894 ms, TE = 3.595 ms, TI = 900 ms; flip angle = 8°, field of view = 240 x 220 x 160 mm3 with an isotropic resolution of 1 x 1 x 1 mm3. The data were acquired with a SENSE factor of 1.5 along the first PE direction and 2 along the second PE direction. T2-weighted axial sequences were acquired using: TR = 11135 ms, TE = 90 ms, flip angle = 90°, field of view = 220 x 220 x 150.7 mm^3 with a resolution of 1.1 x 1.1 x 2.2 mm^3. The data were acquired with a SENSE factor of 1.9. T2-weighted Sagittal sequences were acquired using: TR = 11135 ms, TE = 90 ms, flip angle = 90°, field of view = 200 x 180.4 x 150.7 mm^3 with a resolution of 1.1 x 1.1 x 2.2 mm^3. The data were acquired with a SENSE factor of 1.9. An experienced neonatologist qualitatively rated the T2/FLAIR MRI structural scan of each child, and significant findings were reported to parents and GP of the child.

Participants also underwent a diffusion sequence, which included 12 non-collinear directions with b value 0 s/mm^2, 32 directions with b value 700 s/mm^2, and 64 directions with b value 2500 s/mm^2 using the following parameters: TR = 3800 ms, TE = 94 ms, flip angle = 90°, field of view = 240 x 240 x 50 mm^3, and voxel size = 2 x 2 x 2 mm^3. The data were acquired with a SENSE factor of 1.5.

Chapter 5: Neonatal white matter microstructure and emotional development in children who were born very preterm

This section is presented as a published journal article and is an exact copy of the following publication:

Kanel, D., Vanes, L., Pecheva, D., Hadaya, L., Falconer, S., Counsell, S.J., Edwards, A.D. and Nosarti, C., 2021. Neonatal white matter microstructure and emotional development during the pre-school years in children who were born very preterm. *eNeuro*, ENEURO.0546-0520.2021.

Word Count: 5,721

Manuscript title:

Neonatal white matter microstructure and emotional development during the pre-school years in children who were born very preterm

Abbreviated title:

White matter & emotional outcomes in VPT children

Author names & Affiliations:

Dana Kanel[a,b], MSc, Lucy Vanes[a], PhD, Diliana Pecheva[a], PhD, Laila Hadaya, MSc[a,b], Shona Falconer[a], PhD, Serena Counsell[a], David Edwards[a,c], FMedSci, PhD, Chiara Nosarti[a,b], PhD.

[a] Centre for the Developing Brain, School of Imaging Sciences & Biomedical Engineering & Imaging Sciences, King's College London, London, UK.

[b] Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

[c] Neonatal Unit. Evelina London Children's Hospital, London SE1 7EH, UK

Author Contributions:

SC, DE and CN Designed Research; DK, LV, DP, LH, SF and CN Performed Research; DK and CN Wrote the paper.

Corresponding author:

Chiara Nosarti, Centre for the Developing Brain, School of Bioengineering and Imaging Sciences, King's College London and Evelina Children's Hospital, London SE1 7EH, UK

e-mail: chiara.nosarti@kcl.ac.uk

Number of figures: 4

Number of tables: 5

Number of multimedia: 0

Number of words for Abstract: 228

Number of words for Significance Statement: 76

Number of words for Introduction: 654

Number of words for Discussion:1373

Acknowledgements:

The research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, by the NIHR Clinical Research Facility (CRF) at Guy's and St Thomas', and by the MRC Centre for Neurodevelopmental Disorders. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Authors report no conflict of interest

Funding Source:

This work was supported by the Medical Research Council (UK) (grant nos: MR/K006355/1, MR/L011530/1 and MR/S026460/1), Wellcome/EPSRC Centre for Medical Engineering (WT 203148/Z/16/Z), Biotechnology and Biological Sciences Research Council (grant no: BB/J014567/1), Action Medical Research and Dangoor Education (grant no: GN2606) and uses data acquired during independent research funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research Programme (RP-PG-0707-10154).

Abstract

Children born very preterm (<33 weeks of gestation) are at a higher risk of developing socio-emotional difficulties compared to those born at term. In this longitudinal study, we tested the hypothesis that diffusion characteristics of white matter tracts implicated in socio-emotional processing assessed in the neonatal period are associated with socio-emotional development in 151 very preterm children previously enrolled into the Evaluation of Preterm Imaging study (Eudra: CT2009-011602-42). All children underwent diffusion tensor imaging at term-equivalent age and fractional anisotropy (FA) was quantified in the uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and superior longitudinal fasciculus. Children's socio-emotional development was evaluated at preschool age (median=4.63 years). Exploratory factor analysis conducted on the outcome variables revealed a 3-factor structure, with latent constructs summarised as: 'emotion moderation', 'social function' and 'empathy'. Results of linear regression analyses, adjusting for full-scale IQ and clinical and socio-demographic variables, showed an association between lower FA in the right uncinate fasciculus and higher 'emotion moderation' scores (ß=-0.280; p<0.001), which was mainly driven by negative affectivity scores (ß=-0.281; p=0.001). Results further showed an association between higher full-scale IQ and better social functioning (ß=-0.334, p<0.001). Girls had higher empathy scores than boys (ß=-0.341, p=0.006). These findings suggest that early alterations of diffusion characteristics of the uncinate fasciculus could represent a biological substrate underlying the link between very preterm birth and emotional dysregulation in childhood and beyond.

Significance Statement

Children born very preterm are at a higher risk of developing socio-emotional difficulties compared to those born at term. Our study showed that early alterations of diffusion characteristics of the uncinate fasciculus in very preterm babies assessed at term-equivalent age were associated with emotional dysregulation in childhood. The identification of early biological substrates linked to emotional development could create opportunities for the prevention and targeting of emerging emotional problems in order to enhance children's mental health.

Introduction

Children who were born very preterm (<33 weeks of gestation) are at heightened risk of experiencing socio-emotional difficulties, which include diminished social competence and reduced ability to self-regulate their emotions and behaviours (Spittle et al., 2009; Jones et al., 2013; Witt et al., 2014; Montagna and Nosarti, 2016). Socio-emotional difficulties in childhood have been associated with the later emergence of psychiatric symptoms (Woodward et al., 2017; Thomson et al., 2019).

Our current understanding of the aetiology of socio-emotional difficulties associated with very preterm birth is limited. Possible underlying causes include altered neurodevelopment, implicating brain structural and functional connectivity (Counsell et al., 2014; Duerden et al., 2015; Keunen et al., 2017; Dimitrova et al., 2020). However, studies directly investigating the association between brain alterations and children's socio-emotional outcomes following very preterm birth are scarce (Fischi-Gomez et al., 2014; Mossad et al., 2017; Urbain et al., 2019). Only a few investigations to date have used a longitudinal design to identify neural features present in the neonatal period that are associated with later socio-emotional problems (Rogers et al., 2012), and studies have predominantly focused on resting state functional connectivity. These studies have suggested associations between alterations in neonatal functional amygdala connectivity and internalizing symptoms, and between alterations in ventral attention-default mode network connectivity and behavioural inhibition in preterm born toddlers (Rogers et al., 2017; Sylvester et al., 2018). Given that functional connectivity is constrained by the anatomical structure of the human cerebral cortex (Honey et al., 2009), investigating relationships between neonatal white matter diffusion characteristics and later socio-emotional outcomes may further add to our understanding of how the brain's emerging architecture contributes to shaping very preterm children's development.

Socio-emotional processing is underpinned by integrated activity across an extended socio-emotional network (Catani et al., 2013). Therefore, structural connectivity alterations within this system may represent a neural substrate of social-emotional impairments. Emotional disorders have been characterised by white matter diffusion characteristic alterations in several tracts, including the uncinate fasciculus (UF), which connects the temporo-amygdala-orbitofrontal network, the inferior fronto-occipital fasciculus (IFOF), which

connects the dorsolateral and inferolateral frontal cortex with the occipital and posterior temporal cortex, the inferior longitudinal fasciculus (ILF), which links occipital and temporal lobes and the superior longitudinal fasciculus (SLF) which connects parietal to frontal cortical regions (Jenkins et al., 2016; Wang et al., 2016).

These different tracts have been studied in relation to various behavioural outcomes, such as memory and cognition (Riley et al., 2010; Chen et al., 2020; Koshiyama et al., 2020), but also to specific aspects of socio-emotional processing: the UF with emotion regulation (Von Der Heide et al., 2013; Eden et al., 2015), the IFOF and ILF with the ability to decode human facial emotions (Philippi et al., 2009; Unger et al., 2016), and the SLF with emotional empathy (Parkinson and Wheatley, 2014).

Differences in the diffusion characteristics of these tracts between very preterm and term-born individuals have also been investigated, with previous studies showing inconsistent results, such as reduced fractional anisotropy (FA) values in the UF (Mullen et al., 2011; Travis et al., 2015; Vollmer et al., 2017; Young et al., 2018), both increased (Dodson et al., 2017) and decreased FA values in the IFOF (Salvan et al., 2014; Vollmer et al., 2017; Young et al., 2018), decreased FA values in the ILF (Travis et al., 2015; Vollmer et al., 2017; Young et al., 2018) and SLF (Young et al., 2018), and no group differences in the SLF (Vollmer et al., 2017). Further, very preterm infants and children also display increased diffusivities when compared to term-born controls, including mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) (e.g., (Young et al., 2018; Lautarescu et al., 2020; Brenner et al., 2021).

The current longitudinal investigation aimed to test the hypothesis that diffusion characteristics of white matter tracts implicated in socio-emotional processing assessed at term equivalent age are associated with socio-emotional development during the preschool years in children who were born very preterm.

Materials and Methods

1.1 Participants

511 participants were enrolled into the Evaluation of Preterm Imaging study (ePrime, Eudra: CT 2009-011602-42) (Edwards et al., 2018). They were recruited at birth in 2010-2013 from hospitals within

the North and Southwest London Perinatal Network. Inclusion criteria were birth before 33 weeks gestational age (GA) and maternal age over 16 years. Exclusion criteria included the presence of major congenital malformation, prior magnetic resonance imaging (MRI), metallic implants, parents unable to speak English, or being subject to child protection proceedings. Infants underwent MRI at term-equivalent age, defined as 38-44 weeks GA (mean = 42.24 (SD = 1.41)). At 4-7 years of age children were invited to the Centre for the Developing Brain, St Thomas' Hospital, London, for a neurodevelopmental assessment. Invitations for follow-up were sent in chronological order of birth to all children who were past their fourth birthday. The study closed on September 1st 2019. Written informed consent was obtained from participants' carer(s) following procedures approved by the Stanmore Research Ethics Committee (14/LO/0677). The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Figure 1 provides detailed recruitment information. To summarise, fifty-five children invited for follow-up study were not assessed at 4-7 years for the reasons listed in Figure 1. A further one hundred children were excluded from the final analyses, due to incomplete assessment data (n=46), motion artefacts on MRI (n=38) or significant focal perinatal brain injury (n=16), defined as periventricular leukomalacia, hemorrhagic parenchymal infarction and other ischemic or hemorrhagic lesions (Barnett et al., 2018), but not including punctate lesions or diffuse excessive high signal in white matter on T2 weighted images. The final sample consisted of 151 very preterm born participants who had T1 and T2 weighted MRI and diffusion MRI (dMRI) at 38-44 weeks term-equivalent and subsequently participated in the follow-up assessment at 4-7 years.

Figure 1.

2.2 Procedure

2.2.1 Perinatal clinical and socio-demographic data

Perinatal clinical and socio-demographic data were collected, with permission, from the Standardized Electronic Neonatal Database. Index of Multiple Deprivation (IMD) score was computed from

the postcode of the parent at the time of infant birth (Department for Communities and Local Government, 2011; https://tools.npeu.ox.ac.uk/imd/) and provided a proxy for family socio-economic status. The IMD measures social risk by comparing each neighbourhood to all others in the country and is based on seven domains of deprivation (with varying weighting, as follows): income (22.5%), employment (22.5%), education skills and training (13.5%), health and disability (13.5%), barriers to housing and services (9.3%), living environment (9.3%) and crime (9.3%). Maternal education was defined as age upon leaving full-time education, split into two groups a) at or before 19 years, b) after 19 years (Kleine et al., 2020).

2.2.2 MRI acquisition and analysis

A paediatrician experienced in MRI procedures supervised all MR imaging. Pulse oximetry, temperature, and electrocardiography data were monitored throughout the session. Silicone-based putty (President Putty, Coltene Whaledent, Mahwah, NJ, USA), as well as neonatal earmuffs (MiniMuffs, Natus Medical Inc., San Carlos, CA, USA), were used for ear protection. Oral chloral hydrate (25–50 mg kg^{-1}) was administered to infants whose parents chose sedation for the procedure.

MR imaging was performed on a 3-Tesla system (Philips Medical Systems, Best, The Netherlands) sited on the neonatal intensive care unit using an eight-channel phased array head coil. High-resolution anatomical images were acquired with pulse sequence parameters: T2 weighted fast-spin echo imaging: TR = 8670 ms, TE = 160 ms, flip angle 90°, slice thickness 2 mm with 1 mm overlapping slices, in-plane resolution 0.86x0.86mm. dMRI data were acquired in the transverse plane in 32 non-collinear directions with the following parameters: TR = 8000 ms, TE = 49 ms, voxel size: 2mm isotropic, b-value: 750 s/mm^2, sense factor of 2, 1 non-diffusion-weighted image, $b = 0$.

Diffusion-weighted images were visually inspected in 3 orthogonal planes for the presence of motion artefact and corrupt diffusion weighted volumes were excluded before tensor fitting. All participants included in analyses had 5 or fewer excluded volumes. Non-brain tissue was removed using BET (version 2.1; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET) (Smith, 2002; Jenkinson et al., 2012), images were corrected for eddy current artefacts using *eddy_correct* (Andersson and Sotiropoulos, 2016), and tensor model was fitted using *dtifit* from FSL (FMRIB, Oxford, http://fsl.fmrib.ox.ac.uk).

Tract-specific analysis (TSA) (Yushkevich et al., 2008) was used to derive dMRI measures for selected WM tracts, as described in detail in Pecheva et al., (2017). TSA is a WM analysis method that creates skeleton models of individual WM tracts onto which diffusion data can be projected for statistical analysis. All subjects were registered to a study-specific template using a tensor-based algorithm (Zhang et al., 2006). Following registration, tracts of interest were delineated from the template using deterministic tractography based on the FACT approach (Mori et al., 1999). Whole-brain tractography was seeded from a white matter mask, defined by thresholding the template FA map at 0.1, and regions of interest were drawn manually according to the protocol described by (Wakana et al., 2007), by a single rater (DP) [Table 1]. The following tracking parameters were used: maximum angle threshold of 45 degrees, step size of 0.5 mm and minimum FA threshold of 0.1. From the tractography, a surface skeleton representation with clearly-defined tract boundaries was derived for each white matter pathway. TSA samples data to be projected onto each point of the skeleton by searching for the maximum FA value along the unit normal from that point to the tract boundary. This is done for each subject. The data projection step serves two main purposes. Firstly, it is a dimensionality reduction step which increases sensitivity, similar to smoothing (Yushkevich et al., 2008). Furthermore, as tract FA values tend to be higher in the centre of a tract, projecting the maximum FA value accounts for residual misalignments and improves inter-subject correspondence by forcing a comparison between tract centres across subjects (Smith et al., 2006).

Table 1. ROI placements used to delineate tracts.

Tract	Inclusion ROI 1	Inclusion ROI 2	Exclusion ROI
UF	Entire temporal lobe identified in coronal plane at level where frontal and temporal lobe are no longer connected.	All projections into frontal lobe.	Fibres which project into anterior limb of external capsule and posteriorly.
IFOF	Occipital lobe selected in coronal plane identified halfway between posterior edge of cingulum and posterior of the brain.	Entire hemisphere in coronal plane at level of the genu of CC identified in mid-sagittal slice.	Fibres crossing medially through anterior commissure.
ILF	Entire hemisphere selected in coronal plane at posterior edge of cingulum	Entire temporal lobe identified in the coronal plane at level where frontal	Fibres that track medially into fornix and CC.

	identified at mid-sagittal slice	and temporal lobe are no longer connected.	
SLF	Identified in coronal plane at lowest axial level in which fornix can be identified as a single structure.	Projections passing through coronal plane at level of splenium of CC identified in mid-sagittal slice.	Fibre that project into external capsule.

From the tractography results, a medial surface was determined for the UF, IFOF, ILF and SLF. The medial surface simultaneously defined the tract skeleton and boundary (Yushkevich and Zhang, 2013). Diffusion data from every subject was then projected onto the skeleton. TSA sampled data to be projected onto each point of the skeleton by searching along the unit normal from that point to the tract boundary (Pecheva et al., 2017). FA values were calculated for each tract. Examples of surface representation of tracts are shown in Figure 2.

Figure 2.

2.2.3 Neurodevelopmental outcomes

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) (Wechsler, 2012) was used to estimate children's full-scale IQ. Parents completed the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), a behavioural screening measure for general childhood psychopathology, comprising 25 items categorised into five subscales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour.; the Children's Behaviour Questionnaire – Very Short Form (CBQ) (Putnam and Rothbart, 2006) which assesses the child's temperament using 36 items summarised into 3 broad scales (negative affectivity, effortful control and surgency); the Empathy Questionnaire (EmQue) (Rieffe et al., 2010), a 20 item questionnaire which measures empathy-related behaviours in young children, summarised into three scales: emotion contagion, attention to others' emotions and prosocial responses to others' emotions; and the Social Responsiveness Scale (SRS-2) (Constantino and Gruber, 2012), an assessment of social impairments associated with autism-spectrum behaviours, which

provides subscale scores for social awareness, social cognition, social communication, social motivation, restricted interests and repetitive behaviours.

To measure facial emotion recognition abilities, a new task was created based on (Gao and Maurer, 2009), which used static stimuli from the validated Dartmouth database of children's faces (Dalrymple et al., 2013). Four boys and four girls were chosen from the database and 6 emotions (happy, surprise, fear, anger, disgust and sadness) plus neutral faces were used. The task consisted of two testing blocks, whereby the first of these included pictures showing happy, surprised and fearful expressions, and the second contained pictures showing sad, disgusted and angry expressions, with both blocks including neutral faces. Stimuli were presented singly, and participants were asked to identify which emotion each image was representing. Accuracy was measured based on the correct identification of emotions. Male and female models were allocated evenly between the emotion and neutral expressions. For every emotion, two levels of intensity were created by morphing a neutral face with the emotional face of the same model, to create, for example, 50% and 100% happy faces. The use of different intensities has been shown to promote the detection of subtle differences in abilities to recognise emotions (Horning et al., 2012; Kessels et al., 2014). Fantamorph software was used to create these morphed images (http://www.fantamorph.com/index.html), by manually positioning points on the anatomical landmarks in the photograph of each face. Distortions caused by the morphing process in the eye and mouth regions were edited using Photoshop. In total, there were 56 stimuli ([2 intensity levels x 6 emotions x 4 models] + [2 neutral expressions x 4 models]). The task created here has no working memory load, and therefore only participant's accuracy is measured. The total number of correct responses the child made was added up to produce an emotion recognition score.

Lower accuracy scores on the emotion recognition task correlated with higher SRS-2 T-scores, indicating increased social difficulties (Social Information Processing ($r=-0.261$; $p<0.001$), Social Communication ($r=-0.201$; $p=0.003$), Social Motivation ($r=-0.201$; $p=0.003$), Restricted Interests and Repetitive Behaviour ($r=-0.228$; $p=0.001$), Social Communication Index ($r=-0.234$; $p=0.001$) and Total score ($r=-0.237$; $p<0.001$). Crucially, the task was most strongly associated with social information processing, suggesting it successfully measured the key construct it was designed to, in paediatric samples.

261 **2.3 Statistical Analyses**

262 Twenty-eight perinatal clinical variables obtained from all ePrime participants (n=511) were
263 summarised using Principal Component Analysis (PCA) applying Promax rotation, using SPSS 26.
264 Maternal variables were: preeclampsia and pregnancy induced hypertension, antenatal hypertension,
265 placental abruption or antenatal haemorrhage, premature rupture of membranes, urinary tract infection,
266 gestational diabetes, oligohydramnios, polyhydramnios, drug abuse, in vitro fertilization, bacterial infection
267 (all y/n), and mode of delivery (vaginal/elective/emergency). Infant variables were: sex, gestational age
268 (GA; weeks and days), birth weight (grams), multiple pregnancy (singleton/multiple), antenatal steroid
269 administration (no/partial/full course), twin-to-twin transfusion, chorioamnionitis, intrauterine growth
270 restriction, surfactant administration, treatment for patent ductus arteriosus, surgical treatment for
271 necrotising enterocolitis, formula feeding, feeding on maternal expressed breast milk (all y/n), days on
272 mechanical ventilation, days on continuous positive airway pressure (cPAP), and days on parenteral
273 nutrition (TPN). All variables were coded so that higher values reflected greater clinical risk. Communalities
274 were checked, and as all were above .2, no items were removed (Costello and Osborne, 2005).

275 R using R studio was used to perform all following analyses, using a non-random experimental
276 design. Maximum-likelihood factor analysis with Varimax rotation was performed using the *stats v3.6.2*
277 package. Factor analysis included the following outcome variables: four SDQ subscales (emotional
278 symptoms, conduct problems, peer relationship problems and prosocial behaviour), three CBQ subscales
279 (negative affectivity, surgency and effortful control), three EmQue subscales (emotion contagion, attention
280 to others' feelings and prosocial actions); the SRS-2 social communication index (SCI) and accuracy on the
281 emotion recognition task. All neurodevelopmental subscale scores were standardised. Factors were extracted
282 based on the criterion of having eigenvalues >1 and examination of scree plots. Factor scores were then used
283 in subsequent analyses.

284 In order to find the best predictors of children's socio-emotional outcomes, best-fit linear models
285 were selected using an automated model selection process, using the *glmulti* package (Calcagno and de
286 Mazancourt, 2010). Prior to model selection, multicollinearity between the chosen tracts was assessed by
287 calculating a variance inflation factor (VIF) for each tract, which consists of comparing the overall model

variance to the variance of a model that includes only that single independent tract. Two variables with VIF ≥ 10 were excluded from subsequent analyses (Hair, 2009), i.e. FA values of the left and right IFOF. For each socio-emotional outcome (Emotion moderation, Social function & Empathy), model comparison was performed using Akaike Information Criterion (AIC) (Akaike, 1974) and 8450 models were compared. Variables included in each model were: FA values of the left UF, ILF and SLF; right UF, ILF and SLF; postmenstrual age at scan (PMA), corrected age at follow-up assessment, IQ, IMD, maternal education, sex and neonatal sickness index. Linear regression was then performed to study the association between predictor variables included in the best-fit model and socio-emotional factor scores.

Results

Participants' characteristics are summarised in Table 2. Results of PCA performed to summarise perinatal clinical variables showed one factor that explained 72% of their variance. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.73, Bartlett's test of sphericity was significant ($\chi2=3597.79$, $p<0.01$), and all factor loadings were above 0.2. Factor weights were between .767 and .898 for GA, days on TPN, days on cPAP, days on mechanical ventilation and surfactant administration. This factor was labelled as 'neonatal sickness index'. Internal reliability assessed using Cronbach's alpha was good ($\alpha=.86$).

Children who were included in the final analyses had lower neonatal sickness index scores (t=2.721, $p=0.007$) and higher IQ scores (t=-3.449, $p=0.001$) compared to those who were not included. Results were similar after exclusion of non-participating children with significant focal perinatal brain injury on neonatal MRI (neonatal sickness index score: t=2.903, $p=0.004$; IQ: t=-2.752, $p=0.006$).

Table 2. Participants' characteristics (n=151)

GA at birth (weeks), median (IQR)	30.29 (28.79-31.79)

Birth weight (grams), median (IQR)	1275 (980-1570)		
PMA at MRI (weeks), mean (± SD)	42.22 (0.79)		
CA at assessment, median (IQR)	4.63 (4.1 -5.16)		
Female, number (percentage)	71 (47%)		
IQ score, mean (± SD)	108.03 (17.00)		
IMD score quintiles	1 (Least Deprived)	36	23.8%
	2	26	17.2%
	3	37	24.5%
	4	35	23.2%
	5 (Most Deprived)	17	11.3%
Maternal education ≥19 years, number (percentage)	117 (77.5%)		

a) Socio-emotional outcomes

Descriptive statistics for children's socio-emotional outcome measures are shown in Table 3.

Table 3. Descriptive statistics for outcome measures

SDQ emotional symptoms, median (IQR)	1 (0-3)
SDQ conduct problems, median (IQR)	1 (0-3)
SDQ peer relationship problems, median (IQR)	1 (0-2)
SDQ prosocial behaviour, median (IQR)	8 (6-9)
CBQ negative affectivity, mean (± SD)	4.284 (0.659)
CBQ surgency, mean (± SD)	5.133 (0.641)
CBQ effortful control, mean (± SD)	4.494 (0.485)
EmQue emotion contagion, median (IQR)	0.17 (0-0.5)
EmQue attention to others' feelings, mean (± SD)	1.299 (0.381)
EmQue prosocial, mean (± SD)	1.076 (0.399)
SRS Social Communication Index, mean (± SD)	47.037 (8.169)

Exploratory factor analysis conducted on the 12 socio-emotional outcomes showed a 3-factor structure. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.76, Bartlett's test of sphericity was significant ($\chi2$=469.977, p<0.001), and all factor loadings were above 0.4. The three latent constructs accounted for 42% of the variance in socio-emotional outcomes and are graphically displayed in Figure 3. These are summarised as: Factor 1 or 'emotion moderation', characterised by positive loadings (between .48 and .93) for CBQ negative affectivity and CBQ effortful control scores. Factor 2 or 'social function', which loads onto higher SDQ emotional symptoms, SDQ conduct problems, SDQ peer relationship problems scores and SRS-2 SCI; as well as lower scores on SDQ prosocial behaviour, EmQue prosocial actions and CBQ surgency (between -.67 and .74); indicating more emotional and behaviour problems, heightened antisocial behaviour and more socialising difficulties. Factor 3 or 'empathy' is defined by positive loadings for EmQue emotion contagion and EmQue attention to others' scores (both .56), indicating a higher degree of empathic displays. Emotion recognition scores did not substantially load onto any of the factors.

Figure 3.

b) Diffusion properties of white matter tracts

Mean FA values of the UF, IFOF, ILF and SLF, are shown in Table 4.

Table 4. Diffusion properties of WM tracts

Tract	Left FA, mean (± SD)	Right FA, mean (± SD)
UF	0.165 (0.015)	0.169 (0.015)
IFOF	0.209 (0.019)	0.207 (0.017)
ILF	0.207 (0.021)	0.198 (0.019)
SLF	0.162 (0.014)	0.188 (0.016)

c) Best-fit predictors of socio-emotional outcomes

Best-fit predictors of 'emotion moderation' were right UF FA values and full-scale IQ (AIC value = 387.387). Lower FA values in the right UF were associated with higher 'emotion moderation' scores (ß=-0.280, p<0.001) (Figure 4). In order to aid interpretation, post-hoc analyses decomposed the 'emotion

moderation' factor into the two variables that loaded onto it (CBQ negative affectivity and CBQ effortful control scores). Results showed that the association between right UF FA values and 'emotion moderation' was mainly driven by their relationship to negative affectivity scores (ß=-0.281; p=0.001). UF FA values were not significantly associated with effortful control scores (ß=-0.126; p=0.150).

Best-fit predictors of 'social function' were sex, corrected age at assessment and full-scale IQ (AIC value = 407.210). Higher full-scale IQ was associated with better social functioning (i.e., lower 'social function' factor scores; ß=-0.334, p<0.001). Best-fit predictor of 'empathy' was sex and IMD (AIC value = 346.983). Girls had higher 'empathy' scores than boys (ß=-0.319, p=0.006). FA values of the WM tracts implicated in emotion processing were not associated with 'social function' and 'empathy'.

Results of regression analyses for the three outcome models (Emotion moderation, Social function & Empathy) including best-fit predictors remained significant after applying Bonferroni correction, correcting for the six WM tracts (adjusted p value for significance =0.008) (Table 5).

Table 5. Regression analyses for socio-emotional factors

Outcome	Data Structure	Predicting Variable	Beta	p value
Emotion Moderation	Normal distribution	Right UF FA	-0.280	<0.001*
		Full-scale IQ	-0.129	0.104
Social Function	Normal distribution	Sex	0.279	0.048
		Corrected age at assessment	-0.103	0.138
		Full-scale IQ	-0.334	<0.001*
Empathy	Normal distribution	Sex	-0.341	0.006*
		IMD	-0.110	0.083

Figure 4.

Discussion

This study found that white matter diffusion characteristics in the uncinate fasciculus assessed at term equivalent age in very preterm infants were associated with childhood 'emotion moderation' scores, which summarise a latent factor reflecting both increased negative affectivity and enhanced effortful control. Negative affectivity refers to a reactive temperamental trait that is characterised by an overall negative outlook of oneself and the surrounding world (e.g., frustration, anger, sadness). Effortful control is conceptualised as an umbrella term referring to a child's capacity to focus and shift attention, intentionally inhibit a response, and respond to low-intensity stimulation and reward (Rothbart et al., 2003). The two traits, negative affectivity and effortful control, could be compared to constructs used to describe adult personality, Neuroticism and Constraint/Conscientiousness, respectively (Digman, 1990). Summary scores for negative affectivity and effortful control tend to be negatively correlated in community samples (Putnam et al., 2006), hence the factor described here as 'emotion moderation', which combines high negative affectivity and enhanced effortful control, may look unintuitive at first. This factor could be interpreted as reflecting an adaptive strategy, whereby children use regulatory skills in order to moderate the impact of reactive systems, i.e., negative emotionality (Rothbart and Bates, 1998; Nigg, 2006). In line with this hypothesis, Eisenberg and colleagues (Eisenberg et al., 2001) showed that negative emotionality and low regulation were maladaptive, while Belsky et al. (Belsky et al., 2001) found that high levels of orienting/effortful control moderated the impact of children's negative affectivity on behavioural outcomes.

Lower FA values in the right UF assessed at term were associated with higher 'emotion moderation' scores in childhood. When this factor was decomposed into the two variables that loaded onto it (negative affectivity and effortful control) we found that this association was driven by the relationship between right UF FA values and negative affectivity. Anatomically, the UF is sited withing the limbic system, and connects the 'temporo-amygdala-orbitofrontal network' (Catani et al., 2013), which has been suggested to play a pivotal role in 'affective tagging' (Von Der Heide et al., 2013), i.e., the assignment of emotional tone, such as positive and negative feelings, to the representations stored in the anterior temporal lobe (Olson et al., 2013). Diffusion characteristics of the UF have been previously implicated in a variety of psychiatric

disorders (Von Der Heide et al., 2013) including anxiety disorder (Phan et al., 2009) and major depression (Cullen et al., 2010) and have also been associated with early adversity and future psychological vulnerability to stress (Hanson et al., 2015). A study in major depression investigating diffusion characteristics and resting state functional connectivity of the UF showed structural alterations together with functional orbitofrontal cortex-amygdala inhibition, suggesting this dysconnectivity pattern was mediated by "top-down" influences from the frontal cortex to the amygdala (Zheng et al., 2018). We speculate that early diffusion characteristics of the UF may be associated with difficulties in top-down regulation, leading to children's inability to down-regulate amygdalar activity, resulting in the tendency to attribute negative feelings to certain contexts and situations, and in the overexpression of negative affect.

Furthermore, although our results did not show a direct association between UF FA values and effortful control, and the UF has not been selectively implicated in effortful/cognitive control in the published literature (Noble et al., 2013), it may nevertheless be relevant to effortful control in the context of emotions, with a previous study showing an association between UF integrity and emotional control in children with traumatic brain injury (Johnson et al., 2011).

Results showed a laterality effect, with only the right UF FA values being associated with 'emotion moderation' scores. These findings are in line with previous research, which demonstrated lateralisation of emotional processes. According to the valence hypothesis (Hellige, 2001), the processing of negative emotions preferentially engages the right side of the brain, whereas positive emotions are preferentially processed by the left side. This hypothesis is supported by functional MRI results showing participants are better at discriminating sad faces when visual stimuli are displayed in the left visual field (i.e., right hemisphere) and better at discriminating happy faces when displayed in the right visual field (i.e., left hemisphere) (Adolphs et al., 2001; Rodway et al., 2003). The valence hypothesis is also supported by research showing that direct stimulation of the right amygdala induced unpleasant emotions, whereas stimulation of the left amygdala induced both pleasant and unpleasant emotions (Lanteaume et al., 2006). Further, differences between the two hemispheres in terms of volume and number of streamlines for UF subcomponents have been previously observed (Park et al., 2004; Hau et al., 2017), suggesting left-lateralised dorso-lateral and right-lateralised ventro-medial UF subcomponents.

Diffusion characteristics of any of the neonatal white matter tracts studied here were not associated with 'social function' and 'empathy' factor scores. 'Social function' was characterised by higher factor loadings for subscales evaluating social problems, and lower factor loadings for prosocial behaviour, therefore higher 'social function' scores reflected increased overall social difficulties. Better 'social function' was associated with higher full-scale IQ, supporting previous literature highlighting the importance of cognitive development for successful social adaptation (Watson et al., 1999; Adolphs, 2001). These results could be important for translational research, as they suggest that an enhancement of children's cognitive abilities could increase their understanding of social interactions (Soto-Icaza et al., 2015), leading to a more successful psychosocial adjustment. Furthermore, both social and emotional skills are thought to be intertwined with cognitive processes, with theoretical models postulating that emotions arise from evaluations of the goal relevance of a stimulus, and that other people are the most goal-relevant stimuli in one's life (Olsson and Ochsner, 2008). Such framework could explain the inclusion of 'SDQ emotional problems' in our 'social function' factor.

Girls had higher 'empathy' scores than boys, indicating a better ability to empathise with the experiences of others. Sex differences in empathy have been widely documented in previous research (Auyeung et al., 2009), and are thought to be reinforced by gender-based expectations of parents, teachers and caregivers (Stern and Karraker, 1989).

Limitations of the present study include a lack of full-term control participants, which limits the generalisability of our findings only to those children born very preterm. In addition, the very preterm pre-schoolers who were followed-up in our study came from a relatively high socio-economic background (23.8% belonged to the least deprived IMD quintile) and had a higher mean full-scale IQ and lower 'neonatal sickness index' scores compared to non-returners. Therefore, the current sample includes those children with a more favourable outcome and may not be representative of the overall ePrime sample and the wider very preterm population. Taking this into consideration, our results may be generalisable only to relatively high functioning very preterm children.

An added limitation of the current study is that dMRI was acquired using a b value of 750s/mm^2 with 32 non-collinear directions. Further, the diffusion metric FA is not suitable for modelling crossing fibres and is more susceptible to partial volume effects, limiting our ability to delineate the SLF in its entirety.

Another limitation is the omission of the cingulum in our analyses, as this tract has been associated with emotion processing and psychiatric symptomatology (Bubb et al., 2018). Cingulum tractography was not performed because TSA determines the tract skeleton by thinning the tract down to a medial surface, and therefore tube-like structures (such as the cingulum) are ill-suited for this methodology.

Results linking neonatal white matter alterations with the tendency to overexpress negative emotions about oneself and the surrounding world in childhood, contributes to the growing body of research attempting to use an infant's connectivity profile to predict its function in the future. This has been recently demonstrated by a study that used children's connectivity fingerprints before they could read to predict their functional responses in a brain region hypothesised to be implicated in word recognition (i.e., the visual word form area) after they had learnt to read 3 years later (Saygin et al., 2016). The ability to predict typical and atypical patterns of emotional development would create opportunities for the early targeting of emerging emotional problems and their downstream consequences, including emotional disorders. This could be achieved through preventative therapies, such as emotion regulation training, that would help children to deal with potential stressors and enhance their mental health (WHO, 2004; Brown et al., 2012).

References

Adolphs R (2001), The neurobiology of social cognition. *Curr Opin Neurobiol* 11:231-239.

Adolphs R, Jansari A, Tranel D (2001), Hemispheric perception of emotional valence from facial expressions. *Neuropsychology* 15:516-524.

Akaike H (1974), A new look at the statistical model identification. *IEEE Trans Automat Contr* 19:716-723.

Andersson JLR, Sotiropoulos SN (2016), An integrated approach to correction for off-resonance effects and subject movement in diffusion mr imaging. *Neuroimage* 125:1063-1078.

Auyeung B, Wheelwright S, Allison C, Atkinson M, Samarawickrema N, Baron-Cohen S (2009), The children's empathy quotient and systemizing quotient: Sex differences in typical development and in autism spectrum conditions. *J Autism Dev Disord* 39:1509.

Barnett ML, Tusor N, Ball G, Chew A, Falconer S, Aljabar P, Kimpton JA, Kennea N, Rutherford M, David Edwards A, Counsell SJ (2018), Exploring the multiple-hit hypothesis of preterm white matter damage using diffusion mri. *Neuroimage Clin* 17:596-606.

Belsky J, Friedman SL, Hsieh KH (2001), Testing a core emotion-regulation prediction: Does early attentional persistence moderate the effect of infant negative emotionality on later development? *Child Dev* 72:123-133.

Brenner RG, Smyser CD, Lean RE, Kenley JK, Smyser TA, Cyr PEP, Shimony JS, Barch DM, Rogers CE (2021), Microstructure of the dorsal anterior cingulum bundle in very preterm neonates predicts the preterm behavioral phenotype at 5 years of age. *Biol Psychiatry* 89:433-442.

Brown CM, Copeland KA, Sucharew H, Kahn RS (2012), Social-emotional problems in preschool-aged children: Opportunities for prevention and early intervention. *Arch Pediatr* 166:926-932.

Bubb EJ, Metzler-Baddeley C, Aggleton JP (2018), The cingulum bundle: Anatomy, function, and dysfunction. *Neurosci Biobehav Rev* 92:104-127.

Calcagno V, de Mazancourt C (2010), Glmulti: An r package for easy automated model selection with (generalized) linear models. *J Stat Softw* 34:1-29.

Catani M, Dell'acqua F, Thiebaut de Schotten M (2013), A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev* 37:1724-1737.

Chen H-F, Huang L-L, Li H-Y, Qian Y, Yang D, Qing Z, Luo C-M, Li M-C, Zhang B, Xu Y (2020), Microstructural disruption of the right inferior fronto-occipital and inferior longitudinal fasciculus contributes to wmh-related cognitive impairment. *CNS Neurosci Ther* 26:576-588.

Constantino JN, Gruber CP (2012) Social responsiveness scale second edition (srs-2): Manual. Western Psychological Services (WPS).

Costello AB, Osborne J (2005), Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical Assessment, Research & Evaluation* 10:1-9.

Counsell SJ, Ball G, Edwards AD (2014), New imaging approaches to evaluate newborn brain injury and their role in predicting developmental disorders. *Curr Opin Neurol* 27:168-175.

Cullen KR, Klimes-Dougan B, Muetzel R, Mueller BA, Camchong J, Houri A, Kurma S, Lim KO (2010), Altered white matter microstructure in adolescents with major depression: A preliminary study. *J Am Acad Child Adolesc Psychiatry* 49:173-183.e171.

Dalrymple KA, Gomez J, Duchaine B (2013), The dartmouth database of children's faces: Acquisition and validation of a new face stimulus set. *PloS one* 8:e79131.

Digman JM (1990), Personality structure: Emergence of the five-factor model. *Annu Rev Psychol* 41:417-440.

Dimitrova R, et al. (2020), Heterogeneity in brain microstructural development following preterm birth. *Cereb Cortex* 30:4800-4810.

Dodson CK, Travis KE, Ben-Shachar M, Feldman HM (2017), White matter microstructure of 6-year old children born preterm and full term. *Neuroimage Clin* 16:268-275.

Duerden EG, Foong J, Chau V, Branson H, Poskitt KJ, Grunau RE, Synnes A, Zwicker JG, Miller SP (2015), Tract-based spatial statistics in preterm-born neonates predicts cognitive and motor outcomes at 18 months. *AJNR Am J Neuroradiol* 36:1565-1571.

Eden AS, Schreiber J, Anwander A, Keuper K, Laeger I, Zwanzger P, Zwitserlood P, Kugel H, Dobel C (2015), Emotion regulation and trait anxiety are predicted by the microstructure of fibers between amygdala and prefrontal cortex. *J Neurosci* 35:6020-6027.

524 Edwards AD, Redshaw ME, Kennea N, Rivero-Arias O, Gonzales-Cinca N, Nongena P, Ederies M, Falconer S, Chew A,
525 Omar O (2018), Effect of mri on preterm infants and their families: A randomised trial with nested diagnostic and economic
526 evaluation. *Arch Dis Child Fetal Neonatal Ed* 103:F15-F21.
527 Eisenberg N, Cumberland A, Spinrad TL, Fabes RA, Shepard SA, Reiser M, Murphy BC, Losoya SH, Guthrie IK (2001), The
528 relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Dev* 72:1112-1134.
529 Fischi-Gomez E, Vasung L, Meskaldji DE, Lazeyras F, Borradori-Tolsa C, Hagmann P, Barisnikov K, Thiran JP, Huppi PS
530 (2014), Structural brain connectivity in school-age preterm infants provides evidence for impaired networks relevant for higher
531 order cognitive skills and social cognition. *Cereb Cortex* 25:2793-2805.
532 Gao X, Maurer D (2009), Influence of intensity on children's sensitivity to happy, sad, and fearful facial expressions. *J Exp*
533 *Child Psychol* 102:503-521.
534 Goodman R (1997), The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry* 38:581-586.
535 Hair JF (2009) Multivariate data analysis. Upper Saddle River: Prentice Hall.
536 Hanson JL, Knodt AR, Brigidi BD, Hariri AR (2015), Lower structural integrity of the uncinate fasciculus is associated with a
537 history of child maltreatment and future psychological vulnerability to stress. *Dev Psychopathol* 27:1611-1619.
538 Hau J, Sarubbo S, Houde JC, Corsini F, Girard G, Deledalle C, Crivello F, Zago L, Mellet E, Jobard G, Joliot M, Mazoyer B,
539 Tzourio-Mazoyer N, Descoteaux M, Petit L (2017), Revisiting the human uncinate fasciculus, its subcomponents and asymmetries
540 with stem-based tractography and microdissection validation. *Brain Struct Funct* 222:1645-1662.
541 Hellige JB (2001) Hemispheric asymmetry: What's right and what's left. Harvard University Press.
542 Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P (2009), Predicting human resting-state
543 functional connectivity from structural connectivity. *Proc Natl Acad Sci U S A* 106:2035-2040.
544 Horning SM, Cornwell RE, Davis HP (2012), The recognition of facial expressions: An investigation of the influence of age
545 and cognition. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 19:657-676.
546 Jenkins LM, Barba A, Campbell M, Lamar M, Shankman SA, Leow AD, Ajilore O, Langenecker SA (2016), Shared white
547 matter alterations across emotional disorders: A voxel-based meta-analysis of fractional anisotropy. *Neuroimage Clin* 12:1022-
548 1034.
549 Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM (2012), Fsl. *Neuroimage* 62:782-790.
550 Johnson CP, Juranek J, Kramer LA, Prasad MR, Swank PR, Ewing-Cobbs L (2011), Predicting behavioral deficits in pediatric
551 traumatic brain injury through uncinate fasciculus integrity. *J Int Neuropsychol Soc* 17:663-673.
552 Jones KM, Champion PR, Woodward LJ (2013), Social competence of preschool children born very preterm. *Early Hum Dev*
553 89:795-802.
554 Kessels RP, Montagne B, Hendriks AW, Perrett DI, de Haan EH (2014), Assessment of perception of morphed facial
555 expressions using the emotion recognition task: Normative data from healthy participants aged 8-75. *J Neuropsychol* 8:75-93.
556 Keunen K, Benders MJ, Leemans A, Fieret-Van Stam PC, Scholtens LH, Viergever MA, Kahn RS, Groenendaal F, de Vries
557 LS, van den Heuvel MP (2017), White matter maturation in the neonatal brain is predictive of school age cognitive capacities in
558 children born very preterm. *Dev Med Child Neurol* 59:939-946.
559 Kleine I, Falconer S, Roth S, Counsell SJ, Redshaw M, Kennea N, Edwards AD, Nosarti C (2020), Early postnatal maternal
560 trait anxiety is associated with the behavioural outcomes of children born preterm <33 weeks. *J Psychiatr Res* 131:160-168.
561 Koshiyama D, Fukunaga M, Okada N, Morita K, Nemoto K, Yamashita F, Yamamori H, Yasuda Y, Matsumoto J, Fujimoto
562 M, Kudo N, Azechi H, Watanabe Y, Kasai K, Hashimoto R (2020), Association between the superior longitudinal fasciculus and
563 perceptual organization and working memory: A diffusion tensor imaging study. *Neurosci Lett* 738:135349.
564 Lanteaume L, Khalfa S, Régis J, Marquis P, Chauvel P, Bartolomei F (2006), Emotion induction after direct intracerebral
565 stimulations of human amygdala. *Cereb Cortex* 17:1307-1313.
566 Lautarescu A, Pecheva D, Nosarti C, Nihouarn J, Zhang H, Victor S, Craig M, Edwards AD, Counsell SJ (2020), Maternal
567 prenatal stress is associated with altered uncinate fasciculus microstructure in premature neonates. *Biol Psychiatry* 87:559-569.
568 Montagna A, Nosarti C (2016), Socio-emotional development following very preterm birth: Pathways to psychopathology.
569 *Front Psychol* 7:80.
570 Mori S, Crain BJ, Chacko VP, van Zijl PC (1999), Three-dimensional tracking of axonal projections in the brain by magnetic
571 resonance imaging. *Ann Neurol* 45:265-269.
572 Mossad SI, Smith ML, Pang EW, Taylor MJ (2017), Neural correlates of "theory of mind" in very preterm born children. *Hum*
573 *Brain Mapp* 38:5577-5589.
574 Mullen KM, Vohr BR, Katz KH, Schneider KC, Lacadie C, Hampson M, Makuch RW, Reiss AL, Constable RT, Ment LR
575 (2011), Preterm birth results in alterations in neural connectivity at age 16 years. *Neuroimage* 54:2563-2570.
576 Nigg JT (2006), Temperament and developmental psychopathology. *J Child Psychol Psychiatry* 47:395-422.
577 Noble KG, Korgaonkar MS, Grieve SM, Brickman AM (2013), Higher education is an age-independent predictor of white
578 matter integrity and cognitive control in late adolescence. *Dev Sci* 16:653-664.
579 Olson IR, McCoy D, Klobusicky E, Ross LA (2013), Social cognition and the anterior temporal lobes: A review and
580 theoretical framework. *Soc Cogn Affect Neurosci* 8:123-133.
581 Olsson A, Ochsner KN (2008), The role of social cognition in emotion. *Trends Cogn Sci* 12:65-71.
582 Park HJ, Westin CF, Kubicki M, Maier SE, Niznikiewicz M, Baer A, Frumin M, Kikinis R, Jolesz FA, McCarley RW,
583 Shenton ME (2004), White matter hemisphere asymmetries in healthy subjects and in schizophrenia: A diffusion tensor mri study.
584 *Neuroimage* 23:213-223.
585 Parkinson C, Wheatley T (2014), Relating anatomical and social connectivity: White matter microstructure predicts emotional
586 empathy. *Cereb Cortex* 24:614-625.

Pecheva D, Yushkevich P, Batalle D, Hughes E, Aljabar P, Wurie J, Hajnal JV, Edwards AD, Alexander DC, Counsell SJ, Zhang H (2017), A tract-specific approach to assessing white matter in preterm infants. *Neuroimage* 157:675-694.

Phan KL, Orlichenko A, Boyd E, Angstadt M, Coccaro EF, Liberzon I, Arfanakis K (2009), Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. *Biol Psychiatry* 66:691-694.

Philippi CL, Mehta S, Grabowski T, Adolphs R, Rudrauf D (2009), Damage to association fiber tracts impairs recognition of the facial expression of emotion. *J Neurosci* 29:15089-15099.

Putnam SP, Gartstein MA, Rothbart MK (2006), Measurement of fine-grained aspects of toddler temperament: The early childhood behavior questionnaire. *Infant Behav Dev* 29:386-401.

Putnam SP, Rothbart MK (2006), Development of short and very short forms of the children's behavior questionnaire. *J Pers Assess* 87:102-112.

Rieffe C, Ketelaar L, Wiefferink CH (2010), Assessing empathy in young children: Construction and validation of an empathy questionnaire (emque). *Pers Individ Dif* 49:362-367.

Riley JD, Franklin DL, Choi V, Kim RC, Binder DK, Cramer SC, Lin JJ (2010), Altered white matter integrity in temporal lobe epilepsy: Association with cognitive and clinical profiles. *Epilepsia* 51:536-545.

Rodway P, Wright L, Hardie S (2003), The valence-specific laterality effect in free viewing conditions: The influence of sex, handedness, and response bias. *Brain Cogn* 53:452-463.

Rogers CE, Anderson PJ, Thompson DK, Kidokoro H, Wallendorf M, Treyvaud K, Roberts G, Doyle LW, Neil JJ, Inder TE (2012), Regional cerebral development at term relates to school-age social-emotional development in very preterm children. *J Am Acad Child Adolesc Psychiatry* 51:181-191.

Rogers CE, Sylvester CM, Mintz C, Kenley JK, Shimony JS, Barch DM, Smyser CD (2017), Neonatal amygdala functional connectivity at rest in healthy and preterm infants and early internalizing symptoms. *J Am Acad Child Adolesc Psychiatry* 56:157-166.

Rothbart MK, Bates JE (1998) Temperament. In: Handbook of child psychology: Social, emotional, and personality development, vol 3, 5th ed, vol., pp. 105-176. Hoboken, NJ, US: John Wiley & Sons, Inc.

Rothbart MK, Ellis LK, Rueda MR, Posner MI (2003), Developing mechanisms of temperamental effortful control. *J Pers* 71:1113-1143.

Salvan P, Froudist Walsh S, Allin MP, Walshe M, Murray RM, Bhattacharyya S, McGuire PK, Williams SC, Nosarti C (2014), Road work on memory lane--functional and structural alterations to the learning and memory circuit in adults born very preterm. *Neuroimage* 102 Pt 1:152-161.

Saygin ZM, Osher DE, Norton ES, Youssoufian DA, Beach SD, Feather J, Gaab N, Gabrieli JD, Kanwisher N (2016), Connectivity precedes function in the development of the visual word form area. *Nat Neurosci* 19:1250-1255.

Smith SM (2002), Fast robust automated brain extraction. *Hum Brain Mapp* 17:143-155.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006), Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31:1487-1505.

Soto-Icaza P, Aboitiz F, Billeke P (2015), Development of social skills in children: Neural and behavioral evidence for the elaboration of cognitive models. *Front Neurosci* 9:333.

Spittle AJ, Treyvaud K, Doyle LW, Roberts G, Lee KJ, Inder TE, Cheong JLY, Hunt RW, Newnham CA, Anderson PJ (2009), Early emergence of behavior and social-emotional problems in very preterm infants. *J Am Acad Child Adolesc Psychiatry* 48:909-918.

Stern M, Karraker KH (1989), Sex stereotyping of infants: A review of gender labeling studies. *Sex Roles* 20:501-522.

Sylvester CM, Smyser CD, Smyser T, Kenley J, Ackerman JJ, Jr., Shimony JS, Petersen SE, Rogers CE (2018), Cortical functional connectivity evident after birth and behavioral inhibition at age 2. *Am J Psychiatry* 175:180-187.

Thomson KC, Richardson CG, Gadermann AM, Emerson SD, Shoveller J, Guhn M (2019), Association of childhood social-emotional functioning profiles at school entry with early-onset mental health conditions. *JAMA Netw Open* 2:e186694-e186694.

Travis KE, Adams JN, Ben-Shachar M, Feldman HM (2015), Decreased and increased anisotropy along major cerebral white matter tracts in preterm children and adolescents. *PloS one* 10:e0142860.

Unger A, Alm KH, Collins JA, O'Leary JM, Olson IR (2016), Variation in white matter connectivity predicts the ability to remember faces and discriminate their emotions. *J Int Neuropsychol Soc* 22:180-190.

Urbain C, Sato J, Hammill C, Duerden EG, Taylor MJ (2019), Converging function, structure, and behavioural features of emotion regulation in very preterm children. *Hum Brain Mapp* 40:3385-3397.

Vollmer B, Lundequist A, Martensson G, Nagy Z, Lagercrantz H, Smedler AC, Forssberg H (2017), Correlation between white matter microstructure and executive functions suggests early developmental influence on long fibre tracts in preterm born adolescents. *PloS one* 12:e0178893.

Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR (2013), Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain* 136:1692-1707.

Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S (2007), Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage* 36:630-644.

Wang W, Qian S, Liu K, Li B, Li M, Xin K, Sun G (2016), Reduced white matter integrity and its correlation with clinical symptom in first-episode, treatment-naive generalized anxiety disorder. *Behav Brain Res* 314:159-164.

Watson AC, Nixon CL, Wilson A, Capage L (1999), Social interaction skills and theory of mind in young children. *Dev Psychol* 35:386-391.

Wechsler D (2012) Wechsler preschool and primary scale of intelligence—fourth edition. TX: The Psychological Corporation San Antonio.

WHO, Prevention of mental disorders: Effective interventions and policy options: Summary report, World Health Organization, 2004.

Witt A, Theurel A, Tolsa CB, Lejeune F, Fernandes L, de Jonge L, Monnier M, Bickle Graz M, Barisnikov K, Gentaz E, Huppi PS (2014), Emotional and effortful control abilities in 42-month-old very preterm and full-term children. *Early Hum Dev* 90:565-569.

Woodward LJ, Lu Z, Morris AR, Healey DM (2017), Preschool self regulation predicts later mental health and educational achievement in very preterm and typically developing children. *The Clinical neuropsychologist* 31:404-422.

Young JM, Vandewouw MM, Morgan BR, Smith ML, Sled JG, Taylor MJ (2018), Altered white matter development in children born very preterm. *Brain Struct Funct* 223:2129-2141.

Yushkevich PA, Zhang H, Simon TJ, Gee JC (2008), Structure-specific statistical mapping of white matter tracts. *Neuroimage* 41:448-461.

Yushkevich PA, Zhang HG (2013), Deformable modeling using a 3d boundary representation with quadratic constraints on the branching structure of the blum skeleton. *Inf Process Med Imaging* 23:280-291.

Zhang H, Yushkevich PA, Alexander DC, Gee JC (2006), Deformable registration of diffusion tensor mr images with explicit orientation optimization. *Med Image Anal* 10:764-785.

Zheng K-Z, Wang H-N, Liu J, Xi Y-B, Li L, Zhang X, Li J-M, Yin H, Tan Q-R, Lu H-B, Li B-J (2018), Incapacity to control emotion in major depression may arise from disrupted white matter integrity and ofc-amygdala inhibition. *CNS Neurosci Ther* 24:1053-1062.

Figure 1. Recruitment flow chart; TEA = term-equivalent age; PMA=post-menstrual age.

Figure 2. Example of right sagittal and bilateral axial surface representation of tracts: a) Uncinate Fasciculus, b) Inferior Fronto-Occipital Fasciculus, c) Inferior Longitudinal Fasciculus, d) Superior Longitudinal Fasciculus.

Figure 3. a) Scree plot representing eigenvalues, used to determine number of factors to retain. b) Heatmap indicating factor loadings on Emotion Moderation, Social Function and Empathy.

Figure 4. a) Scatterplot showing negative relationship between right UF FA values and Emotion moderation scores (1 outlier removed, total n = 150). b) Scatterplot showing negative relationship between IQ scores and Social function scores (1 outlier removed, total n = 150). c) Boxplot showing sex differences in Empathy scores. Outliers were defined as values more than 1.5 times the value of the interquartile range beyond the quartiles.

Table 1.

Definitions of ROIs drawn manually to delineate white matter tracts. UF = Uncinate Fasciculus; IFOF = Inferior Fronto-Occipital Fasciculus; ILF = Inferior Longitudinal Fasciculus, SLF = Superior Longitudinal Fasciculus; CC = Corpus Callosum.

Table 2.

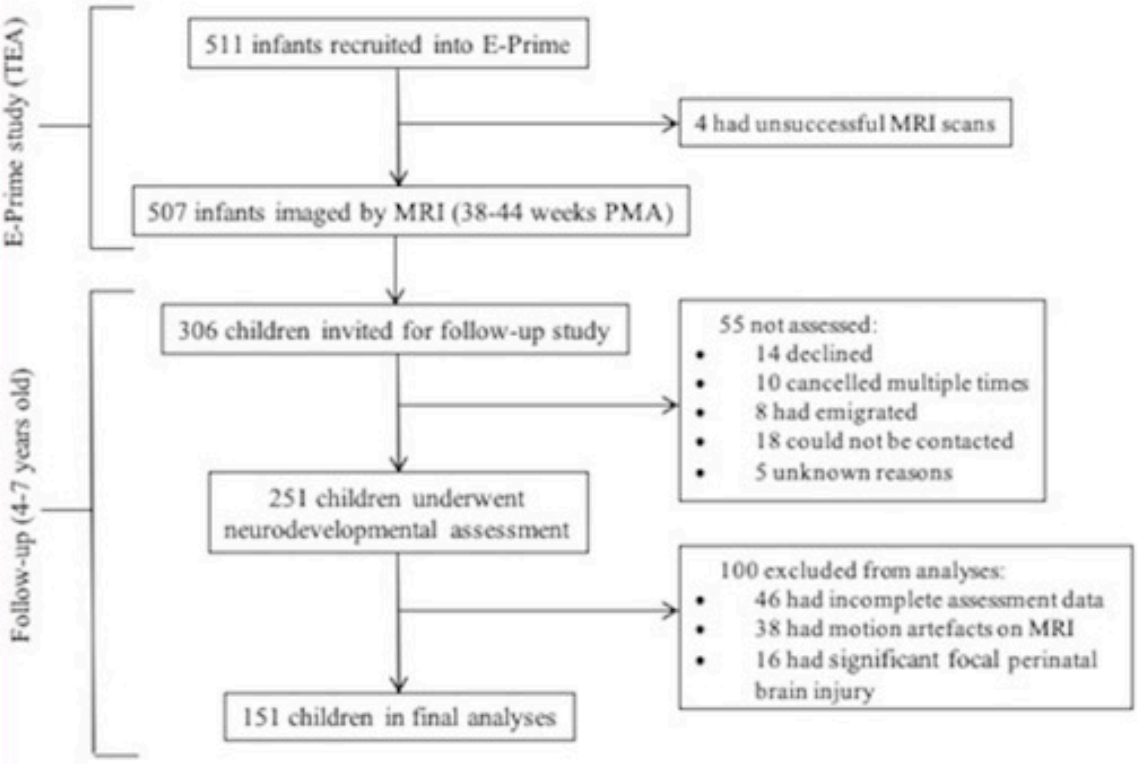
Participants' clinical and socio-demographic characteristics. CA = corrected age at assessment; GA = gestational age; IMD = Index of Multiple Deprivation; IQR = interquartile range; MRI = magnetic resonance imaging; PMA = post-menstrual age at neonatal MRI; SD = standard deviation

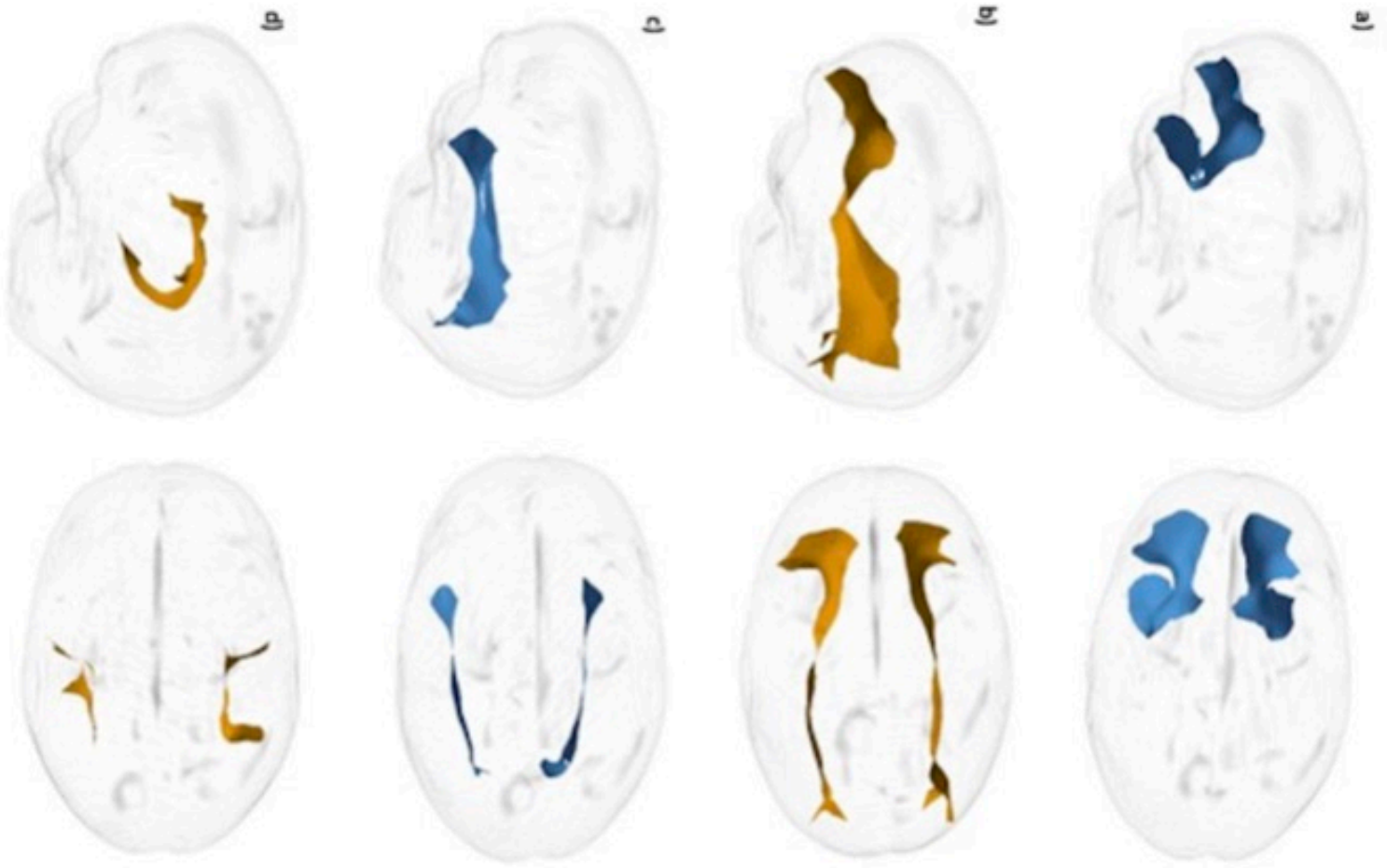
Table 3.

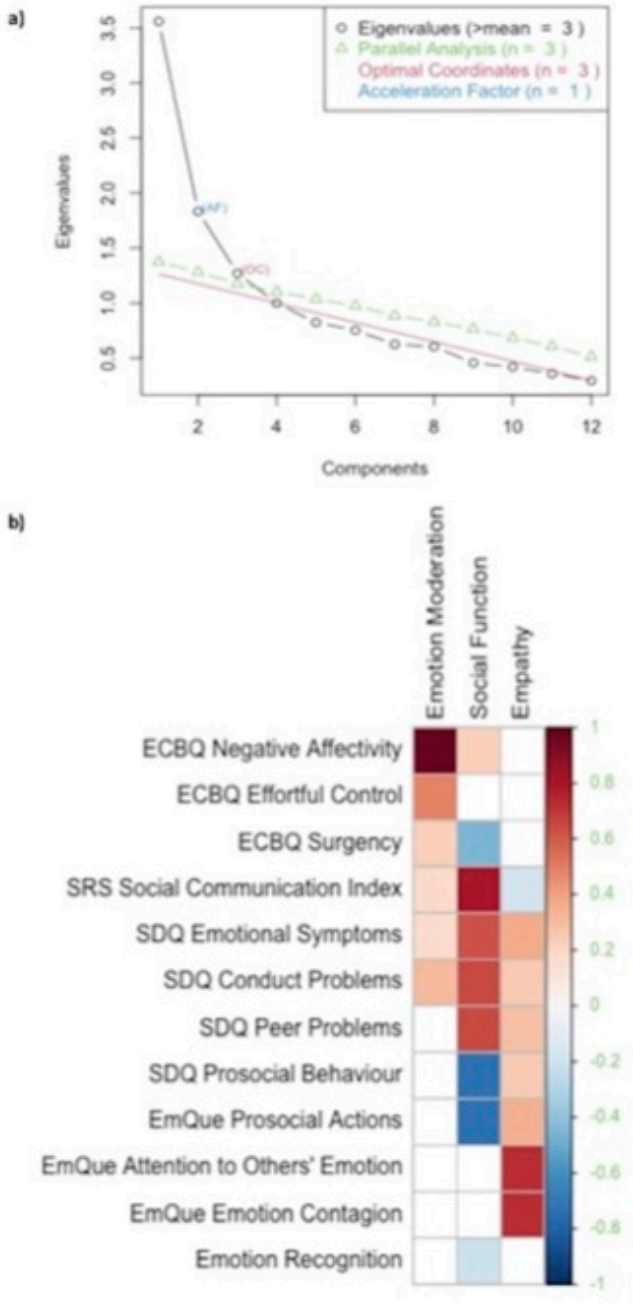
Descriptive statistics for children's outcome measures. Raw values are shown. CBQ = Children's Behaviour Questionnaire; EmQue = Empathy Questionnaire; IQR = interquartile range; SD = standard deviation; SDQ = Strengths and Difficulties Questionnaire; SRS = Social Responsiveness Scale.

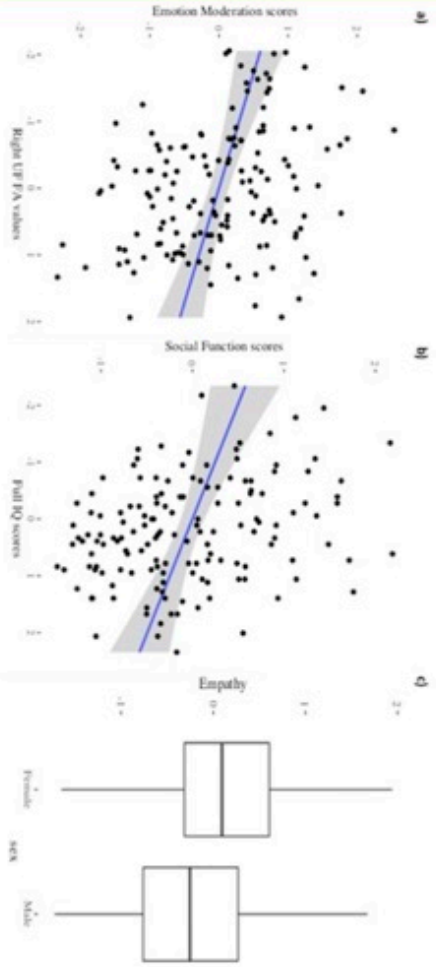
Table 4.

703 Descriptive statistics for diffusion properties of WM tracts implicated in emotion processing. UF = Uncinate
704 Fasciculus; IFOF = Inferior Fronto-Occipital Fasciculus; ILF = Inferior Longitudinal Fasciculus, SLF = Superior
705 Longitudinal Fasciculus.
706
707 **Table 5.**
708 Results from regression analyses for socio-emotional factors including best-fit predictors.
709 *Analyses significant after applying Bonferroni correction (adjusted p value for significance = 0.008).
710
711









5.1: Additional analyses

5.1.1 Exploring effects of brain injury on DTI metrics and outcomes

5.1.1.1 Statistical analyses

For brain injury group classification and data on group sample sizes, please see Section 4.1.5. Neonatal diffusion characteristics and childhood socio-emotional outcomes were compared between brain injury groups. ANOVAs were performed on all WM tract DTI metrics investigated (FA and RD for UF, ILF, and SLF), as well as socio-emotional outcomes including: CBQ subscales (Negative Affectivity, Effortful Control, Surgency), SDQ subscales (Emotional Symptoms, Conduct Problems, Peer Problems, Prosocial Behaviour), SRS Social Communication Index, EmQue subscales (Emotion Contagion, Attention to Others' Feelings, Prosocial Actions), and Emotion Recognition score. Where a significant group interaction was found after correcting for multiple comparisons, post-hoc Tukey tests were performed to determine specific significant between-group differences.

5.1.1.2 DTI metrics

Table 5.1 shows mean DTI metric values (FA and RD) for selected WM tracts (UF, ILF, SLF), for each of the three brain injury groups (major injury, minor injury, and no injury).

Table 5.1. DTI metrics in selected WM tracts for brain injury groups.

		Mean (SD)		
White Matter Tract	**DTI Metric**	**Major injury (n = 35)**	**Minor injury (n = 210)**	**No injury (n = 162)**
Right UF	FA	0.17 (0.01)	0.17 (0.02)	0.17 (0.02)
	RD	1.18 (0.07)	1.20 (0.07)	1.19 (0.07)
Left UF	FA	0.17 (0.02)	0.16 (0.02)	0.17 (0.02)
	RD	1.19 (0.07)	1.21 (0.07)	1.19 (0.07)
Right ILF	FA	0.19 (0.03)	0.19 (0.02)	0.20 (0.02)
	RD	1.27 (0.13)	1.23 (0.09)	1.20 (0.08)
Left ILF	FA	0.20 (0.03)	0.20 (0.02)	0.21 (0.02)
	RD	1.19 (0.11)	1.17 (0.08)	1.15 (0.08)
Right SLF	FA	0.18 (0.02)	0.19 (0.02)	0.19 (0.02)
	RD	1.15 (0.09)	1.18 (0.07)	1.15 (0.07)
Left SLF	FA	0.16 (0.02)	0.16 (0.02)	0.17 (0.02)

	RD	1.15 (0.09)	1.18 (0.07)	1.16 (0.07)

ILF = Inferior Longitudinal Fasciculus; SLF = Superior Longitudinal Fasciculus; UF = Uncinate Fasciculus

Table 5.2 shows results of ANOVAs among injury groups (major vs minor vs no injury) on DTI metrics. Results were considered significant after correcting for multiple comparisons (adjusted *p*-value = 6 tracts x 2 DTI metrics = 0.05 / 12 = 0.0042).

Table 5.2. ANOVA and post-hoc analyses results of DTI metrics between brain injury groups

		3-group ANOVA results		
White Matter Tract	**DTI Metric**	**F†**	**Effect-size (η_p^2)**	***p*-value**
Right UF	FA	4.564	0.022	0.011
	RD	1.981	0.010	0.139
Left UF	FA	4.523	0.022	0.011
	RD	3.074	0.015	0.047
Right ILF	FA	9.582	**0.045**	**<0.001***
	RD	12.217	**0.057**	**<0.001***
Left ILF	FA	6.659	**0.032**	**0.001***
	RD	7.573	**0.036**	**<0.001***
Right SLF	FA	6.589	**0.032**	**0.002***
	RD	5.005	0.024	0.001
Left SLF	FA	6.841	**0.033**	**0.001***
	RD	4.311	0.021	0.014

ILF = Inferior Longitudinal Fasciculus; SLF = Superior Longitudinal Fasciculus; UF = Uncinate Fasciculus.

† Degrees of freedom = 2, 404

η_p^2 = Partial Eta Squared; η_p^2 = 0.01 indicates a small effect size; η_p^2 = 0.06 indicates a medium effect size; η_p^2 = 0.14 or higher indicates a large effect size.

* Results in **bold** significant after multiple corrections (adjusted *p*-value = 0.0042).

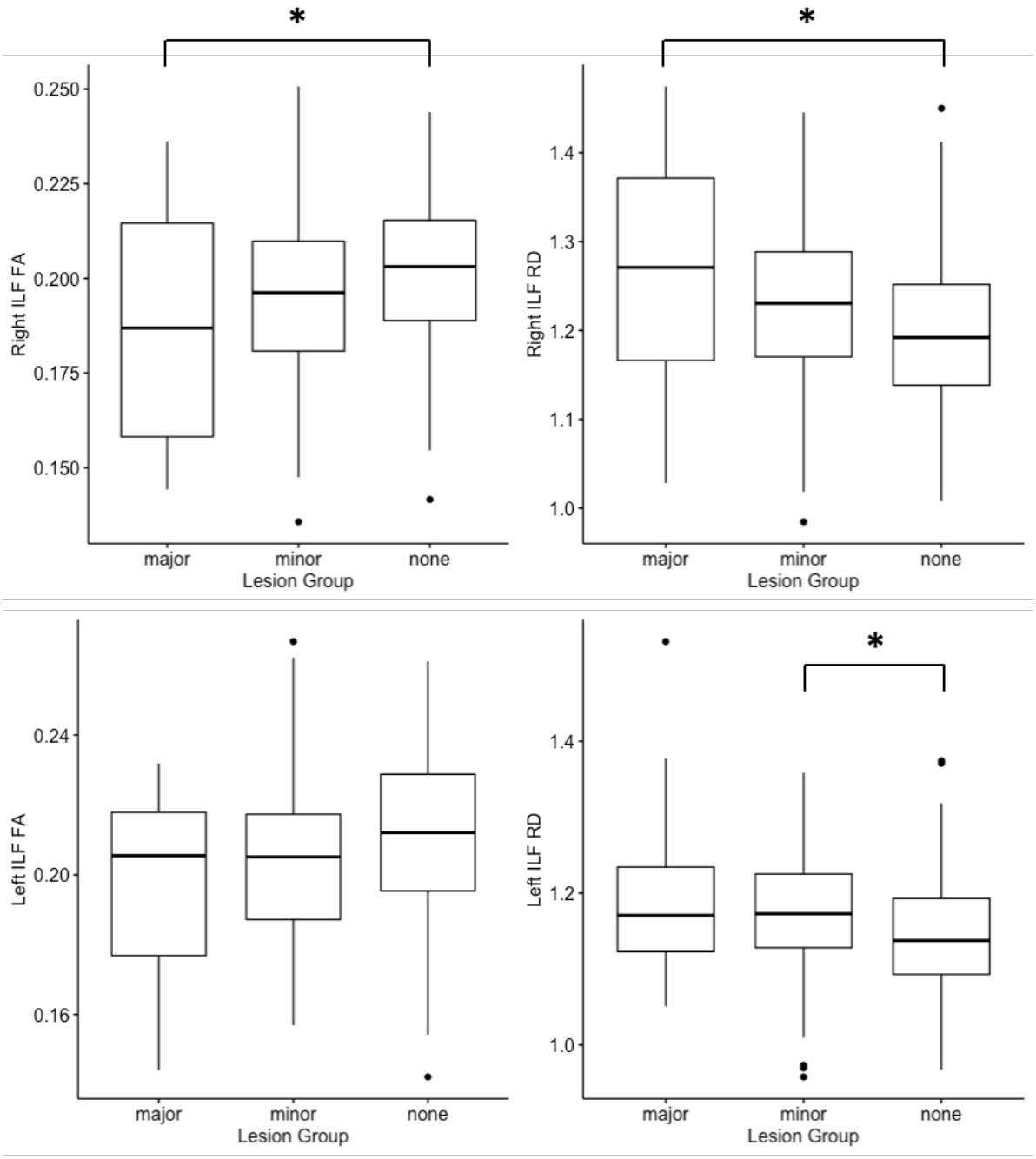


Figure 5.1. Boxplots depicting post-hoc brain injury group mean differences on DTI metrics. *Post-hoc analyses showing significant group mean differences.

DTI metrics of the right ILF (FA and RD) were significantly different between participants with major lesions and those with no reported brain lesions at TEA. Children with major brain injury had significantly lower FA and higher RD values than children with no brain injury in the right ILF. RD values in the bilateral ILF were significantly different between participants with minor lesions and

those with no reported brain lesions at TEA. These findings represent the importance of assessing various degrees of brain injury in investigations of brain development in preterm children.

5.1.1.3 Socio-emotional outcomes

Children who had major brain injury on neonatal MRI were excluded from the factor analyses, however the three groups (major injury, minor injury, and no injury) were compared in terms of individual socio-emotional outcome variables. Of the 251 participants followed-up at 4-7 years, 17 (7%) had a major brain lesion, 142 (57%) had a minor brain lesion, and 92 (37%) had no brain lesions. Mean group socio-emotional outcome scores are displayed in Table 5.3, as well as ANOVA results.

Table 5.3. Results from analyses of socio-emotional outcomes between the three brain injury groups

Variable	**Mean (SD)**			**3-group ANOVA:**	
	Major injury (n = 17)	**Minor injury (n = 142)**	**No injury (n = 92)**	**F***	***p*-value**
CBQ Negative Affectivity	4.19 (0.72)	4.25 (0.67)	4.30 (0.61)	0.768	0.465
CBQ Effortful Control	4.49 (0.48)	4.43 (0.50)	4.53 (0.48)	0.804	0.449
CBQ Surgency	4.84 (0.53)	5.09 (0.63)	5.09 (0.72)	0.343	0.710
SDQ Emotional Symptoms	2.29 (2.05)	1.72 (1.79)	1.51 (1.59)	1.010	0.336
SDQ Conduct Problems	2.32 (2.32)	1.88 (1.73)	1.51 (1.43)	1.774	0.172
SDQ Peer Problems	2.84 (2.02)	1.51 (1.52)	1.12 (1.61)	4.679	0.010
SDQ Prosocial Behaviour	6.79 (2.15)	7.50 (1.84)	7.83 (1.97)	1.399	0.249
SRS Social Communication Index	53.40 (10.60)	47.30 (7.94)	47.30 (8.87)	1.404	0.248
EmQue Emotion Contagion	0.55 (0.40)	0.33 (0.32)	0.39 (0.45)	2.593	0.077
EmQue Attention to Others' Feelings	1.27 (0.33)	1.29 (0.38)	1.27 (0.40)	0.082	0.921
EmQue Prosocial Actions	0.89 (0.44)	1.07 (0.37)	1.07 (0.43)	0.317	0.728
Emotion Recognition Score	32.90 (6.18)	33.70 (6.67)	33.60 (6.43)	0.120	0.887

No between group differences were significant after Bonferroni Correction (p-threshold = 0.05 / 12 = 0.004).
* Degrees of freedom = 2, 222

There were no significant differences in the socio-emotional outcome scores between children with major injury, minor injury, and those with no injury at TEA.

5.1.2 Exploring associations between radial diffusivity and outcomes variables

5.1.2.1 Reasons for the inclusion of RD analyses

Elevated RD values reflect increased perpendicular diffusivity within an imaging voxel, and analyses of changes in RD provide more specific information on perpendicular diffusivity in WM than analyses of FA. Early animal studies suggested RD alterations reflect changes in myelination of axons (Song et al., 2003; Song et al., 2002b; Song et al., 2005). A more recent animal study found that, whilst FA was sensitive to axonal integrity, RD was significantly associated to myelin compactness (Tu et al., 2016). However, during the period prior to TEA, in WM regions that are not yet myelinated, increases in RD might indicate a delayed wrapping of oligodendrocytes around the axon that occurs pre-myelination (Counsell et al., 2006).

5.1.2.2 Methods

For methods on DTI data collection and processing, please see Chapter 5, Section 'MRI acquisition and analysis'. Methods and analysis of socio-emotional outcomes are described in Chapter 5 Section 'Neurodevelopmental outcomes'. Statistical analyses mirrored methods used in Chapter 5, Section 'Statistical analyses'. Briefly, an automated model selection process selected best-fit linear models for each socio-emotional outcome factor, through model comparison using AIC. Variables in each model included RD values of WM tracts investigated (left and right UF, ILF, and SLF), PMA, corrected age at follow-up at Timepoint 2, IQ, IMD, maternal education, sex, and neonatal sickness index. Linear regression was then performed to study the association between predictor variables included in best-fit model and socio-emotional factor scores. Results of regression analyses were considered significant after applying Bonferroni correction, correcting for the six WM tracts x 2 DTI metrics (adjusted p-value for significance = 0.004)

5.1.2.3 General Linear Models including RD

Best-fit predictors of socio-emotional outcomes

Results of best fit model selection and subsequent regression analyses for the three outcome models (*Emotion Moderation*, *Social Function* & *Empathy*) are shown in Table 5.4.

Table 5.4. Regression analyses for best-fit predictors of socio-emotional factors

Outcome	Predicting Variable	Beta	*p*-value
Emotion Moderation	**Right UF RD**	**5.850**	**<0.002***
	Left SLF RD	-6.441	0.032
	Right SLF RD	4.586	0.096
	Full-scale IQ	-0.151	0.056
Social Function	Sex	0.279	0.048
	Corrected age at assessment	-0.103	0.138
	Full-scale IQ	**-0.334**	**<0.001***
Empathy	Right UF RD	3.545	0.006
	Right ILF RD	-1.678	0.084
	Sex	**-0.379**	**0.002***
	IMD	-0.112	0.074

* *p*-value significant after correcting for multiple comparisons (adjusted $p = 0.004$)

Best-fit predictors of *Emotion Moderation* were right UF RD values, left SLF RD values, right SLF RD values, and full-scale IQ (AIC value = 406.865). Higher RD values in the right UF were significantly associated with higher *Emotion Moderation* scores (ß=5.850, *p*=0.002) (Figure 5.1). Post-hoc results showed that the association between right UF RD values and *Emotion Moderation* was mainly driven by their relationship with Negative Affectivity scores (ß=4.483; *p*=0.001). UF RD values were not significantly associated with Effortful Control scores (ß=2.474; *p*=0.077).

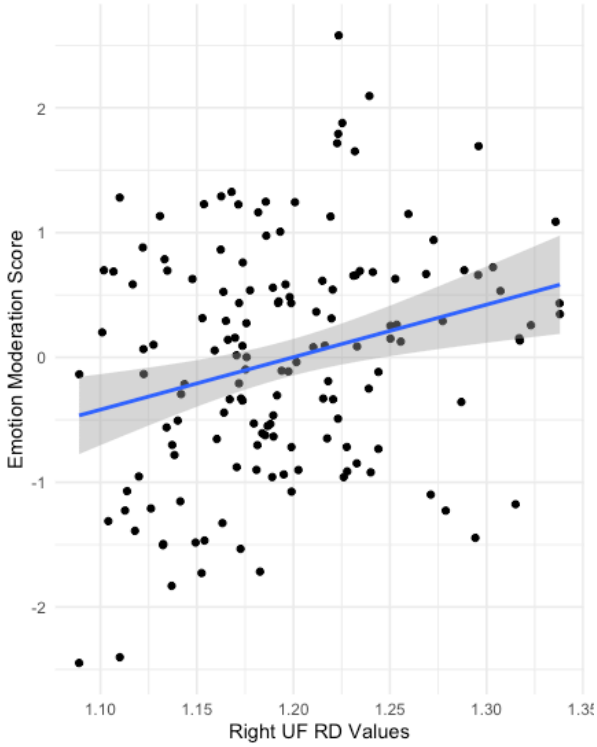


Figure 5.2. Scatterplot showing positive relationship between right UF RD values and emotion moderation scores (two outliers removed, total $n = 149$).

Best-fit predictors of *Social Function* scores were sex, corrected age at assessment and full-scale IQ (AIC value = 387.387). Higher full-scale IQ was associated with better social functioning (i.e., lower *Social Function* scores; ß=-0.334, $p<0.001$). Best-fit predictors of *Empathy* scores were sex, IMD, right UF RD, and right ILF RD (AIC value = 343.391). Girls had higher 'empathy' scores than boys (ß=-0.379, $p=0.002$). RD values for the WM tracts implicated in emotion processing were not significantly associated with *Social Function* or *Empathy* scores.

5.1.2.4 Re-analysing FA results with stricter *p* threshold as a result of additional models

Results from original analyses with FA remained significant after correcting for 6 extra models (new adjusted p-value = 0.004): lower FA values in the right UF were associated with higher 'emotion moderation' scores (ß=-0.280, $p<0.001$).

Chapter 6: Neonatal amygdala resting-state functional connectivity and socio-emotional development in very preterm children

6.1 Introduction

Children born very preterm are more likely to experience socio-emotional problems compared to their term-born peers, including atypical social development, emotion dysregulation and internalising problems (Healy et al., 2013; Johnson et al., 2010; Jones et al., 2013; Treyvaud et al., 2013). Behavioural difficulties may be investigated in the context of altered neurodevelopment following very preterm birth, as the immature nervous system is vulnerable to injury and abnormal development (Volpe, 2009a). Very preterm infants and children display significant functional connectivity alterations in terms of strength and network complexity when compared to term-born controls (Bouyssi-Kobar et al., 2019; Eyre et al., 2021; Scheinost et al., 2016b; Smyser et al., 2016; Wheelock et al., 2021). Indeed, such functional connectivity alterations in preterm neonates have been associated with the subsequent development of childhood cognitive and behavioural outcomes (Ball et al., 2017; Ramphal et al., 2020; Sylvester et al., 2018a).

Of particular interest with respect to socio-emotional development are the amygdalae, bilateral limbic regions that are central to the brain's emotional processing networks (LeDoux, 2003; LeDoux, 2000; Pessoa and Adolphs, 2010; Price, 2003). Very preterm children and adolescents compared to term-born controls exhibit altered structural and functional amygdalae development, showing smaller

amygdalae volumes (Cismaru et al., 2016) and reduced connectivity (Johns et al., 2019; Mossad et al., 2020; Scheinost et al., 2016a). Using a longitudinal design, a recent study showed that resting state functional connectivity (rs-FC) between the left amygdala and several regions (including the medial PFC, posterior cingulate and anterior insula) measured at term-equivalent age in very preterm infants predicted internalising symptoms at 2 years of age (Rogers et al., 2017).

To the best of our knowledge, no study has yet focussed on rs-FC in preterm neonates in association to childhood socio-emotional development. This study investigates neonatal amygdalae rs-FC and its association with childhood socio-emotional development.

Additionally, I explored function-structure associations between amygdalae rs-FC and the relevant diffusion characteristics of the UF that were previously shown to relate to socio-emotional outcome (outcome of Kanel et al. (2021b), Chapter 5 of the current thesis).

6.2 Materials and methods

6.2.1 Participants

511 infants were originally recruited in 2010-2013 as part of the Evaluation of Preterm Imaging study (ePrime, EudraCT 2009-011602-42)(Edwards et al., 2018), from hospitals within the North and Southwest London Perinatal Network. Inclusion criteria were birth <33 weeks' gestational age (GA) and maternal age over 16 years. Exclusion criteria were the presence of major congenital malformation, prior MRI, metallic implants, parents unable to speak English, or being subject to child protection proceedings. Infants underwent MRI at TEA, defined as 38-44 weeks GA.

Complete resting-state fMRI data were available for 298 neonatal scans after removal of incomplete or corrupt data. Infants with PMA at scan ≥ 45 weeks were excluded, as well as those with major destructive brain lesions, defined as periventricular leukomalacia, haemorrhagic parenchymal infarction and other ischemic or haemorrhagic lesions (Barnett et al., 2018), but not including punctate lesions.

251 children were invited for a neurodevelopmental follow-up assessment at the Centre for the Developing Brain, St Thomas' Hospital, London, between the ages of 4 and 7. Complete follow-up behavioural data were available for 151 children. The final sample consisted of 129 very preterm born participants (mean GA = 30.3 weeks (24–32.9)) with neonatal resting-state functional, T1, and T2 weighted MRI at TEA (mean age at scan = 42.2 weeks (SD = 1.44)) and subsequent childhood follow-up assessment (mean age at assessment = 4.64 years (SD = 4.18–7.17)).

Written informed consent was obtained from participants' carer(s) following procedures approved by the National Research Ethics Committee (14/LO/0677). The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

6.2.2 Perinatal socio-demographic and clinical data

Perinatal socio-demographic and clinical data were collected, with permission, from the Standardised Electronic Neonatal Database. Index of Multiple Deprivation (IMD) score, a proxy for socioeconomic status, was computed from parental postcode at the time of infant birth (Department for Communities and Local Government, 2011; https://tools.npeu.ox.ac.uk/imd/). The IMD measures social risk by comparing each neighbourhood to all others in the country and is based on seven domains of deprivation: income, employment, education skills and training, health and disability, barriers to housing and services, living environment and crime. Maternal education was defined as age upon leaving full-time education, divided into two categories: a) at or before 19 years, b) after 19 years (Kleine et al., 2020). Clinical data were summarised into a 'neonatal sickness index' (please refer to Kanel et al. (2021b) for further details) which consisted of the following five variables: GA, days on total parenteral nutrition, days on continuous positive airway pressure, days on mechanical ventilation and surfactant administration. Higher values reflected greater clinical risk.

Sample characteristics for the original neonatal sample and follow-up subsamples, with available behavioural and MRI + behavioural data, are shown in Table 6.1. The current complete sample (resting-state fMRI + behavioural data) did not differ from the baseline neonatal sample (complete resting-state fMRI data, n = 298) in terms of GA (t = 0.727, p = 0.468), PMA (t = -0.607, p = 0.544),

neonatal sickness index (t = -0.112, p = 0.911), IMD (t = 1.360, p = 0.175), sex (χ^2 = 0.16, p = 0.691), or maternal education (t = 1.87, p = 0.062). The current complete sample also did not differ from the behavioural follow-up subsample in terms of age at childhood assessment (t = -1.221, p = 0.231) or full-scale IQ (t = 0.124, p = 0.902).

Table 6.1. Socio-demographic sample characteristics

		Baseline (MRI) sample (N=298)	**Follow-up (behavioural) sample (N=151)**	**Complete (MRI + behavioural) sample (N=129)**
GA (weeks), median (range)		30.43 (23.57–32.86)	30.14 (24–32.86)	30.3 (24.00–32.90)
PMA (weeks), mean (SD)		42.12 (1.53)	42.22 (1.42)	42.2 (1.44)
Neonatal sickness index, median (range)		-0.29 (-1.34–2.55)	-0.32 (-1.34–2.05)	-0.29 (-1.34–2.05)
IMD score quintiles, n (%)	1 (Least Deprived)	60 (20.1)	36 (23.8)	30 (23.3)
	2	43 (14.4)	26 (17.2)	23 (17.8)
	3	61 (20.5)	37 (24.5)	32 (24.8)
	4	66 (22.1)	35 (23.2)	31 (24.0)
	5 (Most Deprived)	68 (22.8)	17 (11.3)	13 (10.0)
Maternal education ≥19 years, number (%)		200 (67.11)	117 (77.5)	95 (73.64)
Female (number, %)		146 (49.0)	69 (45.7)	61 (47.3)
Age at assessment (years), median (range)			4.63 (4.18–7.17)	4.64 (4.18–7.17)
Full-scale IQ at assessment, mean (SD)			108.03 (17.00)	108.00 (16.60)

MRI = magnetic resonance imaging; GA = gestational age; PMA = postmenstrual age at scan; IMD = index of multiple deprivation

6.2.3 MR imaging data

6.2.3.1 MRI acquisition

Infants underwent MR imaging at TEA on a 3-Tesla system (Philips Medical Systems, Best, The Netherlands) sited on the neonatal intensive care unit using an eight-channel phased array head coil. A paediatrician experienced in MRI procedures supervised the care of the infant during MR imaging. Pulse oximetry, temperature, and electrocardiography data were monitored throughout the session. Silicone-based putty (President Putty, Coltene Whaledent, Mahwah, NJ, USA), as well as neonatal earmuffs (MiniMuffs, Natus Medical Inc., San Carlos, CA, USA), were used for ear

protection. Oral chloral hydrate (25–50 mg kg^{-1}) was administered to infants whose parents chose sedation for the procedure (87% of infants were sedated). Whole brain functional imaging was performed using a T2* gradient echo planar image acquisition (sequence parameters: TR = 1500 ms; TE = 45 ms; flip angle = 90°; field-of-view: 200 mm; matrix: 80 × 80 (voxel size: 2.5 × 2.5 × 4 mm), 256 volumes (total scan time = 6 min 24 s). High-resolution anatomical images were acquired with pulse sequence parameters: T2 weighted fast-spin echo imaging: TR = 8670 ms, TE = 160 ms, flip angle 90°, slice thickness 2 mm with 1 mm overlap, in-plane resolution 0.86x0.86mm.

6.2.3.2 Image preprocessing

MR images were visually inspected to detect and exclude those with visible motion artefacts. Functional images then underwent single-subject independent component analysis (ICA) using FSL MELODIC (Beckmann and Smith, 2004) followed by FIX (Salimi-Khorshidi et al., 2014) for automatic de-noising and artefact removal. ICA was performed following removal of the first 6 volumes (allowing for T1 equilibration), motion correction with MCFLIRT, high-pass filtering (125s cutoff, 0.008 Hz) and automatic dimensionality estimation. No slice timing correction or spatial smoothing was applied at this stage. The standard FIX processing steps were modified to allow for standard-space masking using a population-specific neonatal template with tissue priors (Serag et al., 2012). The FIX algorithm was trained on hand-classified fMRI datasets, collected on the same scanner, from a sample of 40 preterm subjects aged 28-44 weeks GA, including both low-motion and high-motion subjects (see Ball et al. (2016), for further details).

Components were automatically classified as signal or noise (as described in Ball et al. (2016)), after which the unique variance of each noise component as well as the full variance of the motion parameters and derivatives were regressed out of the data (Griffanti et al., 2014; Satterthwaite et al., 2013). Standardised DVARS, a framewise data quality index (Power et al., 2012), was calculated before and after applying FIX. DVARS was significantly reduced following FIX clean-up ($t(315) = 9.01$, $p < .001$). Finally, datasets with more than two standard deviations above the mean number of volumes were detected as corrupted, as implemented by FSL Motion Outliers (calculated from DVARS), were

removed, resulting in a final sample of 298 infants, of whom 129 (who had complete behavioural follow-up data) were included in further analysis.

Cleaned functional images from the remaining sample were resampled to 2mm isotropic voxels and registered to a study-specific T2-weighted template using boundary-based registration. The template was generated from a subset of 161 participants using Advanced Normalization Tools (ANTS) software as described in Lautarescu et al. (2021). Data were spatially smoothed with a 4mm full-width half-maximum Gaussian kernel.

6.2.3.3 Seed-based connectivity

Seed-based connectivity refers to the correlation between voxels within one region of interest (or 'seed') and the rest of the brain. It requires a priori determination of the seed, usually based on a specific hypothesis. As discussed in the introduction, the amygdalae have been shown to be implicated in the development of socio-emotional outcomes in very preterm children (Rogers et al., 2017). Therefore, here we focus on their specific connectivity to the rest of the brain through a seed-based approach.

For each participant, the mean raw signal timeseries were extracted from the left and right amygdalae, respectively, as defined by the neonatal Automated Anatomical Labelling (AAL) atlas (Shi et al., 2011; Tzourio-Mazoyer et al., 2002). First-level general linear models (GLM) were constructed using FSL FEAT (Woolrich et al., 2001). separately for the left and right amygdalae, entering the mean seed timeseries as a regressor. Global signal regression was included to improve the specificity of positive signal correlations by adding mean whole-brain timeseries as an additional covariate.

6.2.4 Neurodevelopmental outcomes

Participants completed the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) (Wechsler, 2012) to estimate their full-scale IQ, and a facial emotion recognition task developed in-house (described in detail in Kanel et al. (2021b)). In short, this task used static stimuli from the Dartmouth database of children's faces (Dalrymple et al., 2013), consisting of four boys and four girls

displaying six emotions (happy, surprise, fear, anger, disgust and sadness) and neutral expressions. Each emotion had two levels of intensity: either 100% (the original) or 50% (a morphed image of the emotional face with a neutral face). Children were asked to correctly determine which emotion each image was representing, and the total number of correct responses were added up to create a total emotion recognition score.

The following parental behavioural questionnaires were administered: the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), measuring general childhood psychopathology (25 items categorised into five subscales: Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Relationship Problems, and Prosocial Behaviour); the Children's Behaviour Questionnaire – Very Short Form (CBQ-VSF) (Putnam and Rothbart, 2006), assessing children's temperament, summarised into three broad scales (Negative Affectivity, Effortful Control, and Surgency); the Empathy Questionnaire (EmQue) (Rieffe et al., 2010), measuring empathy-related behaviours, summarised into three scales: Emotion Contagion, Attention to Others' Emotions, and Prosocial Actions; and the Social Responsiveness Scale (SRS-2) (Constantino and Gruber, 2012), assessing social impairments associated with autism-spectrum behaviours, which provides subscales for Social Communication/Interaction (SCI) and Restricted Interests and Repetitive Behaviour (RRB).

6.2.5 Statistical Analyses

Statistical analyses were performed in R (R Core Team, 2013) and FSL FEAT. Factor analyses included data on 151 participants with complete neurodevelopmental data, using the following socio-emotional outcome variables: four SDQ subscales (Emotional Symptoms, Conduct Problems, Peer Relationship Problems and Prosocial Behaviour), three CBQ subscales (Negative Affectivity, Effortful Control and Surgency), three EmQue subscales (Emotion Contagion, Attention to Others' Emotions and Prosocial Actions); the SRS-2 SCI subscale and accuracy on the emotion recognition task. The resulting three factors (*Emotion Moderation*, *Social Function* & *Empathy*) were used in subsequent analyses (see Kanel et al. (2021b)).

For each factor, two general linear models were built (for left and right amygdalae, separately), probing the association between whole-brain amygdalae rs-FC and each socio-emotional outcome factor controlling for sex, neonatal sickness index, PMA at scan, and socioeconomic status (i.e., IMD) (as maternal age at leaving education and IMD were correlated ($r = -0.15$, $p = 0.05$), we chose IMD as a measure of social risk). Z-scores were used for all continuous variables. Whole-brain activation was determined by a voxelwise z-threshold of 3.1 and a cluster significance threshold of $p = 0.05$ (whole-brain family-wise error corrected). Clusters were labelled according to the Automated Anatomical Labelling (AAL) atlas (Shi et al., 2011; Tzourio-Mazoyer et al., 2002).

Where a significant association was found between a socio-emotional outcome factor and amygdalae rs-FC, post-hoc analyses were carried out to investigate associations between cluster-specific connectivity (i.e., mean extracted Beta values from the significant clusters) and individual variables contributing to the relevant socio-emotional outcome factor. We repeated all analyses after removal of outliers in terms of both behavioural outcomes and Beta rs-fMRI values, defined as values more than 1.5 times the value of the interquartile range beyond the quartiles. A Bonferroni-corrected significance threshold of $p = .05 / 6 = .008$ (accounting for two lateralities and three outcome factors) was used for all follow-up analyses.

Finally, due to previous findings showing an association between neonatal fractional anisotropy in the right uncinate fasciculus and childhood *Emotion Moderation* scores in the same participant sample (Kanel et al., 2021b), structure-function associations were explored by calculating Spearman's rank order correlations between mean fractional anisotropy of the uncinate fasciculus and amygdalae rs-FC Beta values from specific clusters spatially located in brain regions known to be structurally connected to the amygdalae via the uncinate fasciculus (Von Der Heide et al., 2013).

6.3 Results

6.3.1 Socio-emotional factors

As previously reported, factor analyses conducted on socio-emotional outcome variables revealed a 3-factor structure: *Emotion moderation*, *Social Function* & *Empathy* (Kanel et al., 2021b). *Emotion Moderation* had positive loadings for CBQ-VSF Negative Affectivity and CBQ-VSF Effortful Control scores; *Social Function* included positive loadings for higher SDQ Emotional Symptoms, SDQ Conduct Problems, SDQ Peer Relationship Problems scores and SRS-2 SCI; as well as negative loadings for SDQ Prosocial Behaviour, EmQue Prosocial Actions and CBQ-VSF Surgency; and *Empathy* had positive loadings for EmQue Emotion Contagion and EmQue Attention to Others' Emotions scores. Emotion recognition scores did not substantially load onto any of the factors. A high score for *Emotion Moderation* indicates a more negative affect, as well as a stronger ability to effortfully control emotions. A high score for *Social Function* indicates more socialising difficulties, and a high score for *Empathy* indicates more displays of empathy in the child.

6.3.2 Association between neonatal amygdala connectivity and socio-emotional factors

6.3.2.1 *Emotion Moderation*

After outlier deletion and Bonferroni-correction, significant associations were identified between neonatal rs-FC of the right amygdala with two distinct clusters, depicted in whole brain voxel-wise maps, and childhood *Emotion Moderation* scores (Figure 6.1). Neonatal rs-FC of the right amygdala with a cluster with local maxima in the right middle occipital gyrus (MOG), extending to the right angular gyrus, was positively associated with *Emotion Moderation* scores ($n = 120$, $\beta = 3.546$, $p = 0.001$). Neonatal rs-FC of the right amygdala with a cluster in the right parahippocampal gyrus (PHG) extending to the right orbitofrontal cortex (OFC), the bilateral olfactory cortex, left gyrus rectus and right superior temporal pole, was negatively associated with *Emotion Moderation* scores ($n = 123$, $\beta = -2.743$, $p = 0.003$) (Table 6.2).

A positive association was identified between neonatal rs-FC of the left amygdala with a cluster in the right thalamus and childhood *Emotion Moderation* scores (n = 122, β = 2.848, p = 0.003) (Figure 6.1, Table 6.2).

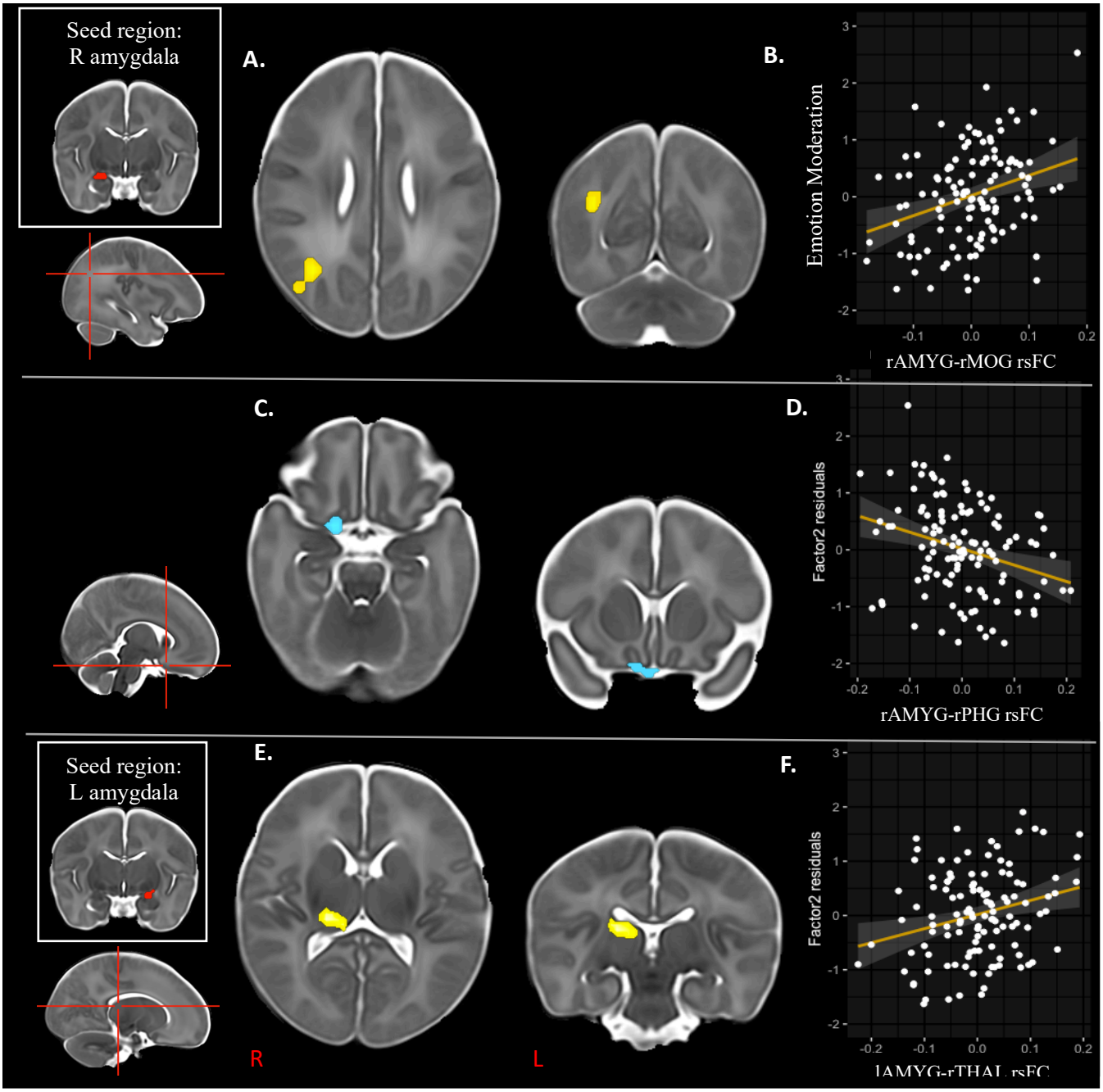


Figure 6.1. Whole brain voxel-wise statistical maps (whole-brain family-wise error corrected) and regression partial plots, depicting significant associations between amygdalae rs-FC and *Emotion Moderation* scores. Right amygdala (rAMYG) - Right middle occipital gyrus (rMOG): **A.** statistical map of rMOG cluster; **B.** association between rAMYG-rMOG and *Emotion Moderation* score. rAMYG - right parahippocampal gyrus (rPHG): **C.** statistical map of rPHG cluster; **D.** association between rAMYG-rPHG and *Emotion Moderation* score. Left amygdala (lAMYG) – right thalamus (rTHAL): **E.** statistical map of rTHAL cluster; **H**: association

between lAMYG-rTHAL and *Emotion Moderation* score. All regression partial plots were created after outlier deletion. Yellow = positive associations, blue = negative associations.

Table 6.2. Neonatal amygdalae resting state functional connectivity and childhood Emotion Moderation scores.

Amygdala seed laterality	Max Z	Location	Cluster size	Coverage	Association
Right	4.32	R middle occipital gyrus	40	R angular gyrus, R middle occipital gyrus	Positive
Right	4.33	R parahippocampal gyrus	55	B olfactory cortex, R orbitofrontal cortex, L gyrus rectus, R superior temporal pole	Negative
Left	4.27	R thalamus	41		Positive

Results remained significant after Bonferroni correction and outlier deletion
Seed: left or right amygdalae. Max Z: Fisher's Z-transformed correlation measure at cluster peak. Location: AAL area associated with cluster peak. Cluster size: number of voxels within cluster. Coverage: AAL areas included in cluster extent. Association: direction of association between rs-FC and '*Emotion Moderation'* outcome. R = right, L = left, B = bilateral.

In order to aid interpretation of contributing variables driving the association between childhood *Emotion Moderation* scores and neonatal amygdalae rs-FC, we further analysed the two variables that meaningfully loaded onto the *Emotion Moderation* factor into (CBQ-VSF Negative Affectivity and Effortful Control scores) and ran further regression analyses, adjusting for sex, neonatal sickness, PMA and IMD (retaining a significance threshold of p = .008).

After correcting for multiple comparisons, all three clusters identified in the *Emotion Moderation* analysis were also significantly associated with Negative Affectivity scores, i.e., rs-FC of the right amygdala with the right MOG and right PHG, and rs-FC between the left amygdala and the right thalamus (Table 6.3). After removing outliers, all associations between amygdalae rs-FC and Negative Affectivity scores remained significant.

Table 6.3. Associations between Negative Affectivity scores and mean amygdalae rs-FC in significant clusters

Amygdala seed	rs-FC cluster	Beta	*p*-value
Right	Right middle occipital gyrus	2.206	<0.001
Right	Right parahippocampal gyrus	-2.623	<0.001
Left	Right thalamus	2.119	<0.001

All models control for sex, PMA, neonatal sickness index & IMD
All analyses significant after Bonferroni correction (adjusted p-value threshold = 0.008).
rs-FC = Resting-state functional connectivity

Only rs-FC of the right amygdala with the right PHG was significantly associated with Effortful Control scores, after controlling for multiple comparisons (Table 6.4). This association was no longer significant after outlier removal.

Table 6.4. Associations between Effortful Control scores and mean amygdalae rs-FC in significant clusters

Amygdala seed	**rs-FC cluster**	**Beta**	***p*-value**
Right	Right middle occipital gyrus	1.030	0.059
Right	Right parahippocampal gyrus	-1.836	0.003*
Left	Right thalamus	1.429	0.011

All models control for sex, PMA, neonatal sickness index & IMD
*Analyses significant after Bonferroni correction (adjusted p-value threshold = 0.008).
rs-FC = Resting-state functional connectivity

6.3.2.2 *Social Function*

No significant associations were found between *Social Function* scores and neonatal amygdalae rs-FC.

6.3.2.3 *Empathy*

No significant associations were found between *Empathy* scores and neonatal amygdalae rs-FC.

6.3.3 Structure-function relationship

No significant correlations were found between participants' fractional anisotropy values in the right UF and Beta values representing rs-FC between the right amygdala and right PHG (putatively connected to the amygdalae via the UF (Von Der Heide et al., 2013)) (r_s = -.1, p = .2748).

6.4 Discussion

The amygdalae are central to the brain's emotional processing networks (LeDoux, 2003; LeDoux, 2000; Pessoa and Adolphs, 2010; Price, 2003) and investigating its functional connectivity early in life is critical for understanding the socio-emotional development of children who are vulnerable to affective disorders. Here we studied rs-FC of the amygdalae at TEA and childhood emotional outcomes following very preterm birth. We show that both stronger and weaker amygdalae rs-FC with cortical areas (middle occipital gyrus), and other sub-cortical regions that form the limbic system (parahippocampal gyrus and thalamus) was associated with specific aspects of emotion regulation in middle childhood. As emotion regulation is potentially modifiable (Tang et al., 2017), establishing criteria to identify target groups for intervention has the potential to contribute to supporting very preterm children's mental health.

6.4.1 *Emotion Moderation*

In this work, emotional development was summarised by a factor labelled '*Emotion Moderation*', consisting of higher Negative Affectivity and Effortful Control scores. Negative Affectivity encompasses emotions such as anger, fear, anxiety, shame and disgust, and reflects a disposition to experience aversive affective states (Watson et al., 1988). Effortful control refers to a self-regulatory temperamental trait which facilitates the modulation of reactivity by focusing attention or inhibiting/activating a behavioural response (Eisenberg et al., 2011; Rothbart et al., 2011). Higher values reflect better Effortful Control ability. Although the combination of positive loadings of both Negative Affectivity and Effortful Control onto the *Emotion Moderation* factor may seem counterintuitive in the first instance, we have previously suggested that this factor may reflect an adaptive strategy, in that preterm children could employ regulatory skills to moderate the impact of reactive system (Kanel et al., 2021b). Effortful Control has been suggested to act as a buffer against the development of psychiatric problems, by allowing individuals to use effective emotional responses to counter negative distortions or perceived threats (Loukas and Murphy, 2007). Indeed, children who score high on Effortful Control have been showed to have better social competence and prosocial

behaviour, whereas those who score low tend to display negative emotionality (Calkins and Dedmon, 2000; Eisenberg et al., 2001), although findings from the literature have been inconsistent (Eisenberg et al., 1998; Murray and Kochanska, 2002).

We would like to propose an alternative interpretation to the *Emotion Moderation* construct. Early definitions of internalising problems include difficulties based on overcontrolled symptoms that manifest when individuals attempt to maintain maladaptive control or regulation of internal emotional and cognitive states (Cicchetti and Toth, 2014; Merrell, 2008). Further, as part of Rothbart & Bates' conceptualisation of this trait (Rothbart and Bates, 1998), Effortful Control is formed by two regulatory processes: attentional control, or the ability to focus and shift attention (Derryberry and Reed, 2001) and inhibitory control, or the ability to appropriately inhibit behaviour (Eisenberg et al., 2011). These two processes should be considered separately when considering the role of Effortful Control in internalising problems (Liu and Bell, 2020). Specifically, response inhibition has been positively associated with internalising problems (Moore et al., 2008; Murray and Kochanska, 2002; Oosterlaan and Sergeant, 1998), possibly because what appears to be good inhibitory control may in fact reflect an overall inhibited, shy behaviour as a consequence of fear and anxiety (Derryberry and Rothbart, 1997; Eggum-Wilkens et al., 2015). In their developmental model, Aksan and Kochanska (2004) posit that a fearful temperament in early childhood could facilitate the development of effortful inhibition in the future. Our study used the CBQ-VSF (Putnam and Rothbart, 2006) to measure Effortful Control, which focuses on complying to rules and exercising caution – typical of the cooperative and compliant shy child (Rudasill and Konold, 2008). Importantly, the combination of high Negative Affectivity *and* Effortful Control possibly due to an inhibited, shy personality resulting from fear and anxiety, may capture the behavioural profile of a typical preterm child: more internalised, less extroverted, shyer and more cautious (Allin et al., 2006; Eryigit-Madzwamuse et al., 2015; Hack et al., 1995; Hertz et al., 2013; Schmidt et al., 2008), in line with the definition of 'preterm phenotype' (Arpi and Ferrari, 2013; Johnson and Marlow, 2011).

6.4.2 Neonatal amygdala rs-fMRI & childhood *Emotion Moderation*

We found that *Emotion Moderation* scores in childhood were associated with neonatal rs-FC between the right amygdala and two regions: PHG (negative association) and right MOG (positive association). *Emotion Moderation* scores were also positively related to rs-FC between left amygdala and right thalamus. Post-hoc analyses revealed these associations were mainly driven by Negative Affectivity scores.

The association of *Emotion Moderation* scores with rs-FC between right amygdala and a cluster with local maxima in PHG, and including OFC and temporal pole, is of particular interest given the importance of these regions in partially overlapping networks of the limbic system supporting emotion, memory (Catani et al., 2013; Leppänen and Nelson, 2009) and emotional memory (Greenberg et al., 2005; Smith et al., 2006). Functional connectivity between amygdalae and PHG has also been studied as a predictor of emotion regulation in school-aged children (Pagliaccio et al., 2015). The OFC modulates the amygdalae's response to external stimuli (Quirk et al., 2003) through inhibitory influences (Rempel-Clower, 2007). Therefore, connectivity between the OFC and amygdalae is important in evaluating the affective significance of events (Rudebeck et al., 2013; Salzman and Fusi, 2010). This regulatory mechanism may also apply to internal stimuli, as suggested by findings indicating an association between decreased amygdalae-OFC connectivity and increased anger (Fulwiler et al., 2012), negative affect (Banks et al., 2007), and anxiety (Hahn et al., 2011).

Decreased functional connectivity between the amygdalae and OFC (Cheng et al., 2018) and temporal pole (Cullen et al., 2014; Ramasubbu et al., 2014) has been reported in depression. Similarly, weaker amygdalae-PHG connectivity has been observed in individuals with depression (Chen et al., 2008; Cullen et al., 2014; Zeng et al., 2012) and anxiety disorder (Hariri et al., 2002). Taken together, our results suggest that rs-FC alterations in a network including amygdalae, PHG, and OFC might represent an underlying biological mechanism linking preterm birth, impairments in processes involving emotion-regulation, and the vulnerability to develop anxiety problems (Papini et al., 2016). Such altered rs-FC patterns in very preterm infants can already be observed at term

equivalent age and could be used as a connectivity fingerprint to predict later socio-emotional outcomes.

At a structural brain level, our findings are supported by diffusion MRI studies, which have shown an association between altered neonatal white matter microstructure in the right OFC and childhood socio-emotional problems (Rogers et al., 2012). Further, the current results are in line with our previous work which assessed the relationship between neonatal diffusion characteristics of the uncinate fasciculus (UF) and childhood *Emotion Moderation* scores (Kanel et al., 2021b). Anatomically, the UF connects cortical and subcortical regions including the amygdalae, PHG, OFC, and temporal pole (Von Der Heide et al., 2013). Importantly, both Negative Affectivity and Effortful Control contributed to the association between *Emotion Moderation* scores and amygdala-PHG connectivity, suggesting that it is indeed the combination of these two temperamental traits that is particularly sensitive to changes in early connectivity between these regions.

Connectivity between the right amygdala and right MOG, extending to angular gyrus, was positively associated to childhood *Emotion Moderation* scores; an association which appeared to be driven by an underlying association with Negative Affectivity. In line with this, Scheinost et al. (2016a) previously showed that very preterm neonates exhibited stronger functional connectivity between the right amygdala and right occipital lobe compared to term-born controls. Of note, the angular gyrus is part of the default mode network (DMN), which has been implicated in affective regulation associated with anxiety and mood (Sylvester et al., 2018b). Enhanced rs-FC between the amygdalae and several DMN brain regions has been observed in internalising disorders (Li et al., 2016; Li et al., 2015b), and has been further associated with altered self-referential thought processes and negative rumination (Buckner et al., 2008; Li et al., 2015b). These findings could aid the interpretation of the observed association between amygdala-DMN rs-FC and Negative Affectivity scores in our sample.

Finally, we found a positive association between left amygdala-right thalamus rs-FC and childhood *Emotion Moderation* scores, with this association once again being driven primarily by Negative Affectivity scores. It has been postulated that sensory information is relayed through thalamic connections to the amygdalae for emotional appraisal (Jones, 2000), and animal studies have

highlighted regulatory mechanisms of the thalami on the amygdalae and the importance of this connection for negative emotions and memories (Li et al., 2010; Penzo et al., 2015). A direct connection between the amygdalae and thalami has also been identified in humans (Abivardi and Bach, 2017), and altered connectivity between the two regions has been associated with social impairments and depressive symptoms in adolescents with autism (Guo et al., 2016). The interhemispheric pattern observed here (i.e., increased rs-FC between left amygdala and right thalamus and higher *Emotion Moderation* scores) is surprising; however, future research could elucidate these findings by considering previous observations of volumetric hemispheric asymmetries of both the amygdalae and the thalami following preterm birth (Cismaru et al., 2016; Lao et al., 2016).

6.4.3 Neonatal structural and functional associations

Our current and previous results (Kanel et al., 2021b) suggest that both structural and functional connectivity between right amygdala and right PHG could be useful for gaining insight into typical and atypical socio-emotional development. However, when investigating the relationship between the two modalities, we did not observe a significant association between functional and structural connectivity of the right amygdala and right PHG at TEA, despite both being separately associated with later *Emotion Moderation* scores. Although the anatomical structure of the human cerebral cortex constrains function (Honey et al., 2009), structure-function couplings are not always evident and exhibit age-related changes (Baum et al., 2020). For example, the DMN was found to show disproportionately large increases in structure-function coupling over childhood and young adulthood when compared to other functional systems (Baum et al., 2020). Further, while high level agreement of structure-function connectivity within the DMN has been reported in adults (Horn et al., 2014), such clear associations are not observed in children, who despite exhibiting adult-like DMN functional connectivity, display weak structural connectivity (Supekar et al., 2010). Such age-dependent patterns of structure-function connectivity could explain our results of non-significant association between functional and structural connectivity between right amygdala and right PHG at term.

6.4.4 Limitations

A limitation to the current study is that amygdalae connectivity was only measured at one time point at TEA. A recent study in term-born infants indicated that whilst some connections between the amygdalae and both subcortical (e.g. caudate, putamen, thalamus) and limbic regions (e.g. hippocampus, parahippocampus) were already present just after birth, some adult-like amygdalae rs-FC patterns (including connections with prefrontal and parietal cortices) developed over the first year of life (Salzwedel et al., 2019). Future research in preterm samples could further elucidate longitudinal changes in amygdalae rs-FC in the first few years of life. Another limitation is that our study did not include a control group, which limits the ability to draw conclusions as to the specificity of these results to preterm cohorts.

Differences in IMD between the baseline sample, who showed a relatively even distribution between the five IMD quintiles and the final sample, with only 10% of participants belonging to the 'most deprived' IMD quintile, may also limit our findings. This suggests that those participants who were not followed-up in childhood were likely to be at higher social risk than those who were assessed (Teixeira et al., 2021).

Another limitation of this study is the use of sedation in some of the infants prior to the MRI scan. The use of sedation with chloral hydrate in neonates (used in the current study) has been reported to have no significant effect on rs-FC or global cerebral blood flow (Arichi et al., 2012; Ball et al., 2016; Doria et al., 2010). Nevertheless, the use of sedatives that alter consciousness might affect neural activity, and in turn alter functional networks (Zhang et al., 2019). Indeed, previous studies in healthy adults have reported an effect of the sedative Midazolam on rs-FC (Kiviniemi et al., 2005; Liang et al., 2015). Sedation status might ultimately alter rs-FC pattern identification due to its influence on participants' level of head motion, known to alter functional neural patterns recorded (Power et al., 2012; Van Dijk et al., 2012). Since the time of data collection for the current study (2010-2013), protocols for motion-resistant image acquisition have been further developed to allow increased completion rates and decreased motion artefacts within neonatal imaging (Hughes et al.,

2017). Additionally, novel processing techniques have allowed optimised motion correction of highly confounded neonatal fMRI data (Fitzgibbon et al., 2020). When this study was conducted, sedation with chloral hydrate was the current practice when performing MRI in neonates, while this is no longer the case in contemporary research.

Conclusions

The current rs-FC study complements our previous structural findings of a relationship between neonatal amygdalae connectivity and childhood emotional development. In particular, the important regulatory effects of specific brain regions (including the orbitofrontal cortex, parahippocampal gyrus, and thalamus) on the reactive amygdalae are highlighted here. Communication within the limbic system and between the limbic system and the cortex is important for higher-order cognitive affective functions, such as emotion regulation, which has direct implications on psychiatric outcomes (Buhle et al., 2014; Kohn et al., 2014; Paschke et al., 2016). Our results suggest that the functional connectivity associated with socio-emotional outcomes in very preterm children are already evident at the earliest stages of life. These findings could be used as a connectivity fingerprint to predict later socio-emotional outcomes, which in turn could inform preventative therapies aimed at preventing and targeting emerging emotional disorders.

Chapter 7: Investigating white matter structure and behavioural outcomes in very preterm and term-born children

7.1 Introduction

Very preterm children tend to exhibit altered behavioural development when compared with full-term controls, encompassing both cognitive and socio-emotional outcomes. This population displays an impaired general intellectual development, showing average IQ scores that are 0.7–0.8 SD lower than those of controls (Bhutta et al., 2002; Kerr-Wilson et al., 2012). Specific cognitive deficits have also been reported in the literature, encompassing verbal comprehension (Barre et al., 2011; Foster-Cohen et al., 2010; Reidy et al., 2013), processing speed (Rose and Feldman, 1996; Rose et al., 2002), and working memory abilities, in both visuo-spatial (Baron et al., 2010; Rose et al., 2011) and verbal (Aarnoudse-Moens et al., 2009b; Hutchinson et al., 2013; Mulder et al., 2009) modalities. Additionally, VPT children are more likely to experience socio-emotional problems compared to full-term children, typically exhibiting diminished social competence and self-esteem, emotion dysregulation, shyness, and timidity (Fitzallen et al., 2020; Montagna and Nosarti, 2016). Temperament refers to a set of stable individual traits that determine emotional reactivity and regulation, and is an important measure of socio-emotional development, as it has been shown to predict later clinical and subclinical psychopathology (Carthy et al., 2010; Cassiano et al., 2019; Forbes et al., 2017; Gartstein et al., 2012; Laceulle et al., 2014; Martins et al., 2021). Very preterm children have been shown to display significantly different temperamental profiles to their term-born peers, including increased NA and decreased EC levels (Caravale et al., 2017; Lejeune et al., 2015).

Behavioural deficits in preterm children might be at least partly explained by altered neurodevelopment as described in Chapter 2. DTI studies report group differences between preterm and term-born children in WM microstructure, with many identifying decreased FA and increased diffusivities in preterm children and adolescents compared to term controls (Constable et al., 2008; Dodson et al., 2017; Dubner et al., 2019; Duerden et al., 2013; Groeschel et al., 2014; Jo et al., 2012; Kelly et al., 2016a; Li et al., 2015a; Mullen et al., 2011; Murray et al., 2016; Pieterman et al., 2018; Travis et al., 2015; Travis et al., 2019; Young et al., 2018). However, some conflicting results have been reported showing no alterations in DTI metrics (Bruckert et al., 2019; Sølsnes et al., 2016), as well as increased FA and decreased diffusivities in preterm children (Dodson et al., 2017; Tokariev et al., 2019). Altered FA values could be interpreted in different ways and may reflect several inter- and intra- tract variations (Travis et al., 2015). These include factors such as number of crossing fibres within the voxel and myelin content of individual fibre populations. Distinguishing amongst these interpretations of FA could be problematic and may require additional neuroimaging techniques.

Neuroimaging studies have also investigated the direct association between WM structure and behavioural outcomes. Preterm children exhibit associations between increased FA and decreased diffusivity values in widespread WM and higher IQ scores (Dubner et al., 2019; Kennedy et al., 2021; Skranes et al., 2007; Vollmer et al., 2017; Wang et al., 2013; Young et al., 2019; Yung et al., 2007). More specifically, higher FA and lower diffusivity values have been associated with better language skills (Andrews et al., 2010; Bruckert et al., 2019; Feldman et al., 2012; Mullen et al., 2011; Mürner-Lavanchy et al., 2018; Travis et al., 2016), working memory (Loe et al., 2018), and visuospatial processing abilities (Skranes et al., 2007; Tokariev et al., 2019). Conflicting results are also reported here, with some studies finding no such associations (Bruckert et al., 2019; Tokariev et al., 2019; Young et al., 2018), whilst others have found a negative relationship between FA values and language development (Dubner et al., 2020; Feldman et al., 2012; Travis et al., 2015). Additionally, DTI studies have reported associations between decreased FA and increased emotional difficulties (Kelly et al., 2016b; Loe et al., 2013) and social processing deficits (Skranes et al., 2007). As part of this PhD I have reported an association between neonatal WM DTI metrics and childhood temperament in a cohort of VPT individuals (Kanel et al., 2021b).

FBA is a diffusion imaging technique that allows for a differentiation between multiple fibres within a voxel. A 'fixel' refers to a single fibre population within a voxel, and through FBA, total intra-axonal volume of individual fibres may be calculated, thought to relate to the WM tracts' ability to relay information (Raffelt et al., 2017; Tournier et al., 2011). This metric considers both the microstructure (fibre density, FD) and macrostructure (fibre cross-section, FC) of WM tracts. Recent studies utilising FBA have reported significantly altered tract microstructure and macrostructure in widespread WM in preterm neonates (Pannek et al., 2018) and children (Kelly et al., 2020), when compared to full-term controls. Brain-behaviour associations have also been investigated, with neonatal FBA metrics showing an association with cognitive development in preterm toddlers (Pannek et al., 2020), whilst FBA metrics correlated with math computation ability in a group of preterm and term-born children (Collins et al., 2021). So far, no studies have investigated associations between FBA metrics and cognitive and socio-emotional outcomes in preterm and full-term children.

In the current study, my aim was to explore white matter structure, as measured by FBA, and behavioural outcomes in VPT and term-born children. I tested the hypothesis that VPT children perform worse on IQ tests and display altered temperamental traits, when compared to term-born controls. I also hypothesised that VPT children would exhibit altered WM structure, displaying a smaller total intra-axonal volume (i.e., smaller microstructure and macrostructure), when compared to full-term controls. Further, I investigated brain-behaviour associations between WM structure, as measured by FBA, and behavioural outcomes in VPT and term-born children. Specifically, I tested the hypothesis that WM total intra-axonal volume would show a positive association with cognitive outcomes, as well as favourable temperamental outcomes, in all participants, and that the VPT group will show altered brain-behaviour associations, when compared to full-term controls. Finally, I repeated all WM analyses using voxel-based DTI analysis. Based on previous literature, I hypothesised VPT children would display decreased FA and increased RD compared to full-term controls. I also tested the hypothesis that this pattern of decreased FA and increased RD would be associated with worse cognitive and socio-emotional outcomes.

7.2 Methods

7.2.1 Participants

Preterm children were recruited from a cohort of 251 very preterm neonates originally recruited as part of a large study called the Evaluation of Preterm Imaging study (ePrime, Eudra: CT 2009-011602-42) (2018). They were recruited at birth in 2010-2013 from hospitals within the North and Southwest London Perinatal Network. Inclusion criteria were birth before 33 weeks gestational age (GA) and maternal age over 16 years. Exclusion criteria included the presence of major congenital malformation, prior magnetic resonance imaging (MRI), metallic implants, parents unable to speak English, or being subject to child protection proceedings.

At 8–10 years, children were invited back for follow-up assessments and an MRI scan at the Centre for the Developing Brain, St Thomas' Hospital, London, as part of the follow-up at Timepoint 2. Invitations were sent in chronological order of birth to all children past their eighth birthday, and this study is currently ongoing. Written informed consent was obtained from participants' carer(s) following procedures approved by the Stanmore Research Ethics Committee (18/LO/0048). The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). At the time of writing, 64 VPT children were successfully recruited for assessments. Of those, 52 completed a full MRI scan.

Additionally, full-term control children were recruited from the community. Inclusion criterion was birth occurring between 38-42 weeks gestational age. Exclusion criteria included disabilities, clinically diagnosed psychological and physical disorders, and previous procedures that included the insertion of metal objects, such as a mesh. Altogether 46 control participants were recruited, and 42 completed a full MRI scan.

Statistical analyses indicated that children who underwent MRI (n = 94) did not differ significantly from those who did not (n = 16) in terms of their age (W = 782, $p = 0.547$), sex (Chi-square = 0.032, $p = 0.859$) or group (i.e., preterm vs controls) (Chi-square = 0.997, $p = 0.318$). However, those children who underwent MRI did show significantly higher total IQ scores than those who did not (W = 319, $p = 0.002$).

A further 14 children were excluded due to having motion artefacts in their diffusion MRI (details of which are in the following section). The number of children excluded due to excessive motion did not differ significantly between the two groups (Chi-square = 0.242, $p = 0.622$). Also, excluded children did not differ to those included in terms of their age (W = 570.5, $p = 0.767$), sex (Chi-square = 2.075, $p = 0.150$), or IQ score (W = 761, $p = 0.101$).

The final sample consisted of 80 children (46 very preterm, 34 control) who had complete T1-weighted MRI and dMRI, as well as complete neuropsychological assessments, at 7–10 years (median = 8.50 (IQR = 8.17–8.92)). Figure 7.1 provides a summary of excluded participants.

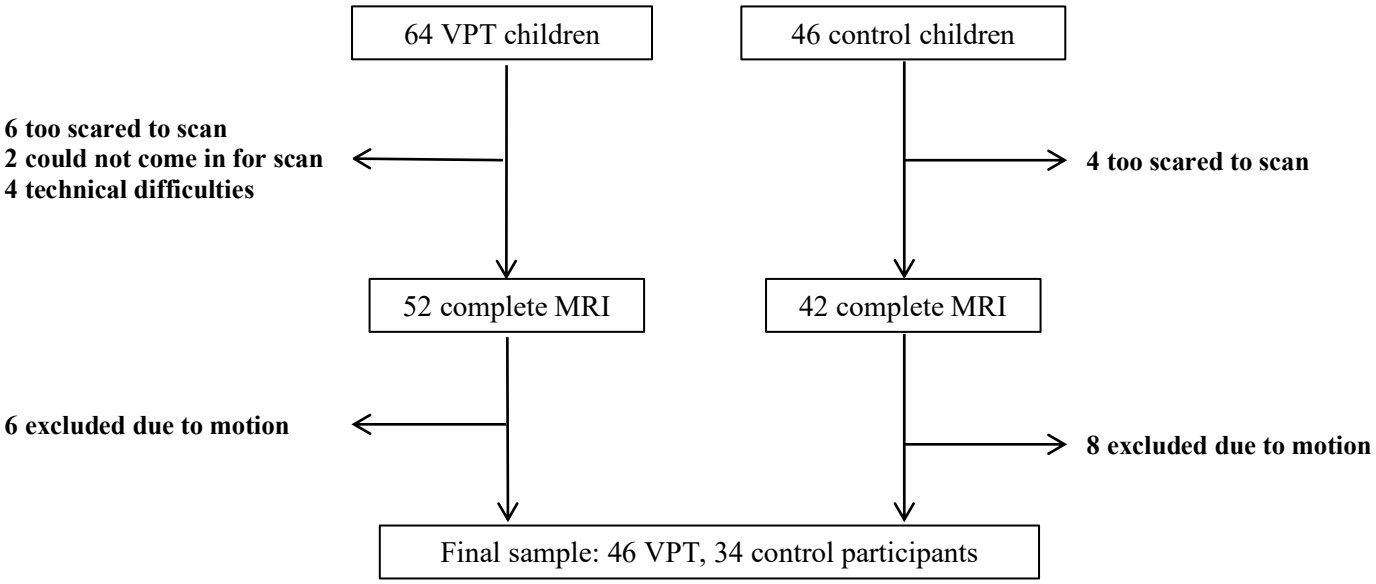


Figure 7.1. Inclusion/exclusion flowchart for follow-up at Timepoint 3.
VPT = very preterm

7.2.2 Procedure

7.2.2.1 Socio-demographic data

IMD score was computed from the parents' postcode (Department for Communities and Local Government, 2011; https://imd-by-postcode.opendatacommunities.org/imd/2019) and provided a proxy for family SES. The IMD measures social risk by comparing each neighbourhood to all others in the country and is based on seven domains of deprivation (with varying weighting, as follows):

income (22.5%), employment (22.5%), education skills and training (13.5%), health and disability (13.5%), barriers to housing and services (9.3%), living environment (9.3%) and crime (9.3%). Participants' ethnicity data were also collected, and grouped according to classification by the Office of National Statistics (ONS) (2016) (for further details please see Section 4.1.2).

7.2.2.2 MRI data acquisition

MR images were acquired on a Philips 3 Tesla Achieva (Philips Medical Systems, Best, The Netherlands) system at the Evalina Newborn Imaging Centre using a 32-channel phased array head coil. Children were given paediatric earplugs, which were placed in the external auditory meatus, as well as noise cancelling headphones.

High resolution 3D T1 and T2 weighted imaging were acquired, as well as a FLAIR for clinical reporting. MPRAGE T1-weighted images were acquired using: TR = 7.894 ms, TE = 3.595 ms, TI = 900 ms; flip angle = 8°, field of view = 240 x 220 x 160 mm3 with an isotropic resolution of 1 x 1 x 1 mm3. The data were acquired with a SENSE factor of 1.5 along the first PE direction and 2 along the second PE direction.

Participants also underwent a diffusion sequence, which included 108 diffusion-weighted volumes: 12 non-collinear directions with b value 0 s/mm^2, 32 directions with b value 700 s/mm^2, and 64 directions with b value 2500 s/mm^2 using the following parameters: TR = 3800 ms, TE = 94 ms, flip angle = 90°, field of view = 240 x 240 x 50 mm^3, and voxel size = 2 x 2 x 2 mm^3. The data were acquired with a SENSE factor of 1.5.

7.2.2.3 MRI data processing

Structural MR images

Structural images were processed using FreeSurfer, software allowing the segmentation of subcortical structures (Dale et al., 1999; Reuter et al., 2010). FreeSurfer pipeline includes motion correction, removal of non-brain tissue, intensity normalisation, topology correction and the

parcellation of cerebral cortex using geometric information. Using volumetric segmentation, intracranial volumes (ICV) for each participant were calculated (Buckner et al., 2004).

Diffusion MR images: preprocessing

Images were primarily analysed using FMRIB's Diffusion Toolbox (FSL, Oxford, fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). Non-brain tissue was removed with BET (Smith, 2002), images were corrected for susceptibility induced distortions using *topup* (Andersson et al., 2003; Smith et al., 2004), and eddy current artefacts using *eddy* (Andersson and Sotiropoulos, 2016). Diffusion-weighted images were then visually inspected by an expert in neonatal neuroimaging in 3 orthogonal planes for the presence of motion artefact and corrupt diffusion weighted volumes were excluded. All participants included in analyses had 21 or fewer excluded volumes (< 20% volumes motion corrupted). An average number of volumes deleted per participant was 12.2, just over 10% of the total 107 diffusion volumes (VPT average = 12.9, control average = 11.6). Number of discarded diffusion volumes did not differ significantly between VPT and control groups (W = 1157.5, $p = 0.7409$).

Diffusion MRI: Fixel-based analysis

After exclusion of corrupted volumes, images were re-processed with *eddy* and *topup*, and then processed with MRTrix3 (version 3.0_RC3) (Tournier et al., 2019) using steps from multi-shell, multi-tissue constrained spherical deconvolution (CSD) in order to perform fixel-based analysis (FBA) (Raffelt et al., 2017). Briefly, images were corrected for bias fields (Tustison et al., 2010), underwent global intensity normalisation, and upsampled voxel size to 1.25 mm. We then performed 3-tissue CSD (Jeurissen et al., 2014), which estimates the orientation of fibres (fibre orientation distributions, FOD) in each voxel by using an average response function from all images (Tournier et al., 2007; Tournier et al., 2004). Each child's FOD image was registered to a group average FOD template, created from a subset of 40 subjects (20 VPT, 20 control) without focal brain injury. Those who's brain images were used for the template (n = 40) did not differ from the rest (n = 40) in terms of their age (W = 683.5, $p = 0.264$), sex (Chi-square = 2.506, $p = 0.113$), or WISC scores (W = 931, $p = 0.209$).

The following metrics were calculated. a) Fibre density (FD): an estimate of the density of axons within a fibre population in a voxel; b) Fibre cross-section (FC): a morphological measure of the cross-sectional area in the direction perpendicular to the orientation of a fixel. Each subject's FC is calculated in relation to the template, and so a FC > 1 represents a larger fibre bundle in the subject than in the template. C) Fibre density and Cross-section (FDC): a combined measure of changes in both microscopic density (FD) and macroscopic morphology (FC), calculated as FD multiplied by FC (Raffelt et al., 2017).

Whole brain tractography was performed on the FOD templates, with spherical-deconvolution informed filtering of tractograms (SIFT) (Smith et al., 2013), required for statistical analysis using the connectivity-based fixel enhancement (CFE) method (Raffelt et al., 2015).

Diffusion MRI: Voxel-based analyses

All analyses were performed using MRtrix3 and based on methodology originally performed by Mito and colleagues (2018). Diffusion tensor metrics were derived for each subject's pre-processed DWI data (Veraart et al., 2016). FA & RD maps were generated in individual subjects' space, and then transformed to the population template space by using the subject-to-template warps generated during the FOD registration step for FBA. Statistical analyses were then performed in template space on voxel-wise metrics (FA & RD).

7.2.2.4 Neurodevelopmental outcomes

Participants completed the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003), a cohort of tests that calculate a general intelligence score. The WISC-IV outputs a score for full-scale IQ, as well as several subscales that represent the major components of intelligence. These include Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Raw scores are transformed into scaled scores according to age-appropriate norms.

VCI includes the following subtests: Similarities measures verbal reasoning and the development of concepts; Vocabulary measures word knowledge and verbal concept formation;

Comprehension measures an individual's ability to understand complex questions and formulate answers. PRI includes the following subtests: Block Design assesses ability to understand complex visual information; Picture Concepts assesses ability to categorise items; Matrix Reasoning measures non-verbal problem solving. WMI includes the following subtests: Digit Span measures verbal short-term memory and attention; Letter-Number Sequencing measures ability to hold verbal information in memory while manipulating it. PSI includes the following subtests: Coding measures speed of processing but is also affected by learning, short-term memory, and concentration; Symbol Search measures processing speed but is also affected by visual-motor coordination and concentration.

Parents also completed a questionnaire probing children's socio-emotional development. The Temperament in Middle Childhood Questionnaire (TMCQ) (Simonds and Rothbart, 2004) is a validated measure assessing children's temperament and summarises outcomes into three subscales: Negative Affectivity (NA), Effortful Control (EC), and Surgency (Surg). See Section 4.3.2.2, Table 4.12, for more information on this measure.

7.2.3 Statistical analyses

In order to analyse differences in cognitive outcomes (WISC subscale scores for: VCI, PRI, WMI, and PSI), ANOVAs were run with group as independent variable, controlling for age and sex. Results were corrected for multiple testing using Bonferroni correction with an adjusted *p*-value threshold (4 WISC subscales: $p = 0.05 / 4 = 0.125$). In order to explore differences in socio-emotional outcomes (TMCQ subscale scores for: NA, EC, Surg), ANOVAs were performed with group as independent variable, controlling for age and sex. Results were corrected for multiple testing using Bonferroni correction with an adjusted *p*-value threshold (3 TMCQ subscales: $p = 0.05 / 3 = 0.0167$).

At each fixel, FBA metrics (FD, FC and FDC) were compared between the VPT and control groups using a general linear model (GLM) in template space. All comparisons were adjusted for age and sex, and comparisons of FC and FDC were also adjusted for ICV. Connectivity-based smoothing and statistical inference were performed using CFE (Raffelt et al., 2015). Non-parametric permutation testing (5000 permutations) generated a family-wise error rate (FWE)-corrected *p*-value for every

individual fixel. Fixels were considered statistically significant at $p < 0.05$, FWE rate corrected. Average FD, FC, and FDC were obtained from regions including all significant fixels of between-group analyses.

Fixel-based brain-behaviour associations were examined using separate GLMs assessing associations between the WISC subscales (VCI, PRI, WMI, PSI) and whole-brain FD, FC, and FDC at each fixel. Associations were also investigated between the TMCQ subscales (NA, EC, Surg) and whole-brain FD, FC, and FDC at each fixel. All comparisons were adjusted for age and sex, and comparisons of FC and FDC were also adjusted for ICV. Contrasts of interest included positive and negative main effect of outcome (in all participants), as well as interactions between outcome and group. We corrected our results for multiple testing using Bonferroni correction. For the WISC subscales, four GLMs were run, with an adjusted *p*-value threshold of 0.0125, and fixels were considered statistically significant at a $p < 0.0125$, FWE-corrected. For the TMCQ subscales, three GLMs were run, and fixels were considered statistically significant at $p < 0.0167$, FWE-corrected. Average FD, FC, and FDC were obtained from regions, including all significant fixels of brain-behaviour associations.

Voxel-based statistical analyses utilised the same GLMs as those used for FBA, and were performed using threshold-free cluster enhancement with default parameters ($dh = 0.1$, $E = 0.5$, $H = 2$) (Smith and Nichols, 2009). Between group analyses compared DTI metrics (FA and RD) between VPT and control groups. Brain-behaviour associations were examined for whole-brain FA and RD, using GLMs for four WISC subscales (adjusted *p*-value = 0.0125) and three TMCQ subscales (adjusted $p = 0.0167$), adjusting for age and sex. Contrasts included main effect of outcomes and interactions between outcome and group. Mean DTI metrics were obtained from voxels within regions of significant between-group differences and brain-behaviour associations.

7.3 Results

7.3.1 Participant characteristics

Characteristics of participants included in the final sample are summarised in Table 7.1.

Table 7.1. Participants' characteristics

Characteristic		**All participants (n = 80)**	**Preterm group (n = 46)**	**Term group (n = 34)**	**Between-group analyses**
GA at birth (weeks), median (IQR)		32.36 (28.86–40.00)	29.36 (27.68–30.93)	40 (39.04–40.82)	–
Age at assessment, median (IQR)		8.50 (8.17–8.92)	8.46 (8.25–8.90)	8.67 (8.08–9.00)	t = -0.444, p = 0.659
Female, n (%)		46 (57.5%)	25 (54.35)	21 (61.76)	c^2 = 0.189, p = 0.664
Full IQ score, mean (± SD)		109.69 (13.51)	106.59 (14.08)	113.89 (11.63)	t = -2.534, p = 0.013
IMD score quintiles, n (%)	1 (Least Deprived)	26 (32.50)	15 (32.60)	11 (32.35)	–
	2	13 (16.25)	8 (17.40)	5 (14.71)	–
	3	17 (21.25)	12 (26.09)	5 (14.71)	–
	4	21 (26.25)	9 (19.57)	12 (35.29)	–
	5 (Most Deprived)	3 (3.75)	2 (4.35)	1 (2.94)	–
Ethnicity, n (%)	White	51 (63.75)	27 (58.70)	24 (70.59)	–
	Mixed/Multiple ethnic groups	8 (10.00)	5 (10.87)	3 (8.82)	–
	Asian/Asian British	10 (12.50)	9 (19.57)	1 (2.94)	–
	Black/African/ Caribbean/Black British	5 (6.25)	5 (10.87)	0 (0.00)	–

IMD = Index of Multiple Deprivation; IQR = Interquartile range; SD = standard deviation
Ethnicity was grouped according to ONS classification; 6 Participants had missing ethnicity data.

Seventy-seven out of 80 participants had complete socio-emotional outcome data. The removal of 3 participants did not significantly alter mean GA at birth (p = 0.704), age at assessment (p = 0.806), sex (p = 0.747), full-scale IQ (p = 0.251), IMD score (p = 0.435), or ethnicity (p = 0.819). Data on these 77 participants are shown in Table 7.2.

Table 7.2. Characteristics of participants with available socio-emotional data.

Characteristic		All participants (n = 77)
GA at birth (weeks), median (IQR)		32.43 (28.86–40.00)
Age at assessment, median (IQR)		8.50 (8.25–8.91)
Female, n (%)		44 (57.1%)
Full IQ score, mean (± SD)		109.35 (13.61)
IMD score quintiles, n (%)	1 (Least Deprived)	24 (31.2)
	2	13 (16.9)
	3	17 (22.1)
	4	20 (26.0)
	5 (Most Deprived)	3 (3.9)
Ethnicity, n (%)	White	49 (63.6)
	Mixed/Multiple ethnic groups	8 (10.4)
	Asian/Asian British	10 (13.0)
	Black/African/Caribbean/Black British	5 (6.5)

IMD = Index of Multiple Deprivation; IQR = Interquartile range; SD = standard deviation
Ethnicity was grouped according to ONS classification; number (%); 5 participants had missing ethnicity data.

7.3.2 Between-group behavioural outcomes

No significant differences in cognitive outcomes were observed after correcting for multiple comparisons using Bonferroni correction (adjusted *p*-value threshold = 0.0125) (Table 7.3).

Table 7.3. Statistical analyses of group differences in WISC scores

Variable	Outcome	Group mean (SD)		F value	*p*-value
		Preterm	Control		
WISC |(n = 80)	VCI	107 (12.1)	112 (12.8)	3.189	0.078
	PRI	105 (14.6)	113 (14.5)	5.267	0.025
	WMI	100 (16.1)	106 (12.7)	3.139	0.080
	PSI	104 (13.8)	109 (12.6)	3.768	0.056

PRI = Perceptual Reasoning Index; PSI = Processing Speed Index; VCI = Verbal Comprehension Index; WMI = Working Memory Index.

No significant differences in temperamental traits were observed after correcting for multiple comparisons using Bonferroni correction (adjusted *p*-value threshold = 0.0167) (Table 7.4).

Table 7.4. Statistical analyses of group differences in TMCQ scores

Variable	Outcome	Group mean (SD)		F value	*p*-value
		Preterm	Control		
TMCQ (n = 77)	NA	2.38 (0.7)	2.20 (0.5)	1.621	0.207
	EC	3.32 (0.5)	3.49 (0.4)	2.624	0.109

	Surg	3.19 (0.5)	3.08 (0.4)	1.141	0.289

EC = Effortful Control; NA = Negative Affectivity; Surg = Surgency; TMCQ = Temperament in Middle Childhood Questionnaire.

7.3.3 Between-group FBA differences

VPT children had significantly lower FD, FC and FDC than control children in several WM tracts (all $p_{FWE} < 0.05$). Figure 7.2 shows between-group differences in FBA metrics. Table 7.5 includes all WM regions with significant fixels of different FBA metrics between the two groups.

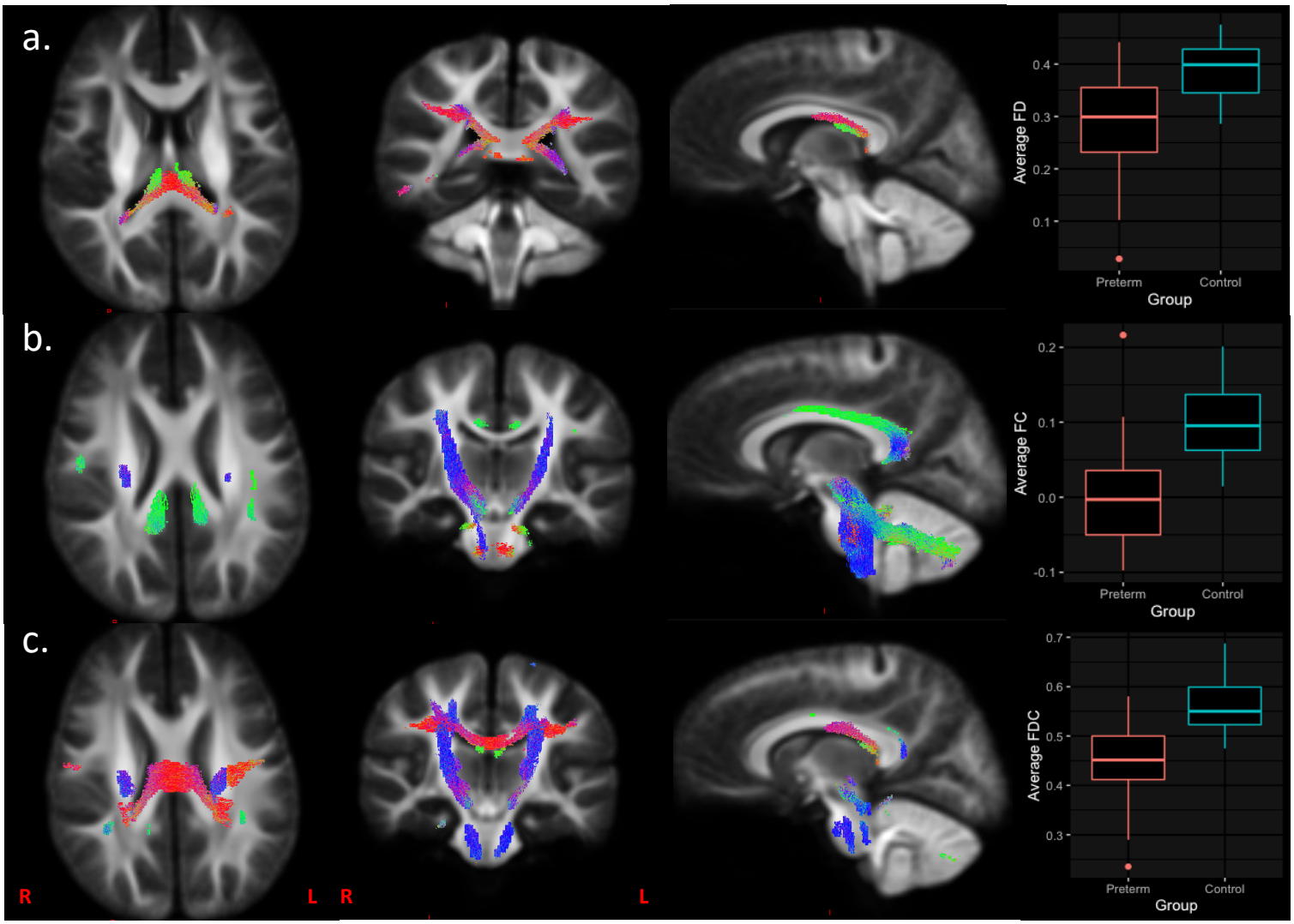


Figure 7.2. Between group differences (VPT < full-term) in a. fibre density (FD); b. fibre cross-section (FC); and c. fibre density & cross-section (FDC), controlling for age and sex (as well as ICV for FC and FDC).

Generated by cropping whole-brain template-derived tractogram such that it included only streamline segments that pass through significant fixels ($p < 0.05$, family-wise error rate-corrected). Streamline segments were coloured by direction (anterior-posterior = green; superior-inferior = blue; left-right = red). Figures show boxplots representing group differences in the relevant metric within significant regions.

Table 7.5. White matter regions including significant fixels in between-group FBA models

FBA metric (covariates)	Direction	WM regions
FD (age, sex)	VPT<FT	Bilateral: Fornix, anterior commissure, body and splenium of the corpus callosum, tapetum; right superior longitudinal fasciculus
FC (age, ex, ICV)	VPT<FT	Bilateral: superior longitudinal fasciculus, corticospinal tract, middle cerebellar peduncle, superior cerebellar peduncle, cingulum
FDC (age, sex, ICV)	VPT<FT	Bilateral: Forceps minor, anterior corona radiata, fornix, anterior commissure, corticospinal tract, cerebral peduncle, superior longitudinal fasciculus, body and splenium of the corpus callosum; right: uncinate fasciculus/inferior longitudinal fasciculus, cingulum, cerebellum, superior cerebellar peduncle.

FC = fibre cross-section; FD = fibre density; FDC = fibre density & cross-section; FT = full-term group; ICV = intracranial volume; VPT = very preterm group.

7.3.4 Brain-cognition associations between FBA metrics and cognitive outcomes

7.3.4.1 Verbal Comprehension

After controlling for age, sex and ICV, verbal comprehension scores were significantly positively associated with FDC in fixels located in the corpus callosum and corticospinal tract (CST) (all $p_{FWE} < 0.0125$, Figure 7.3).

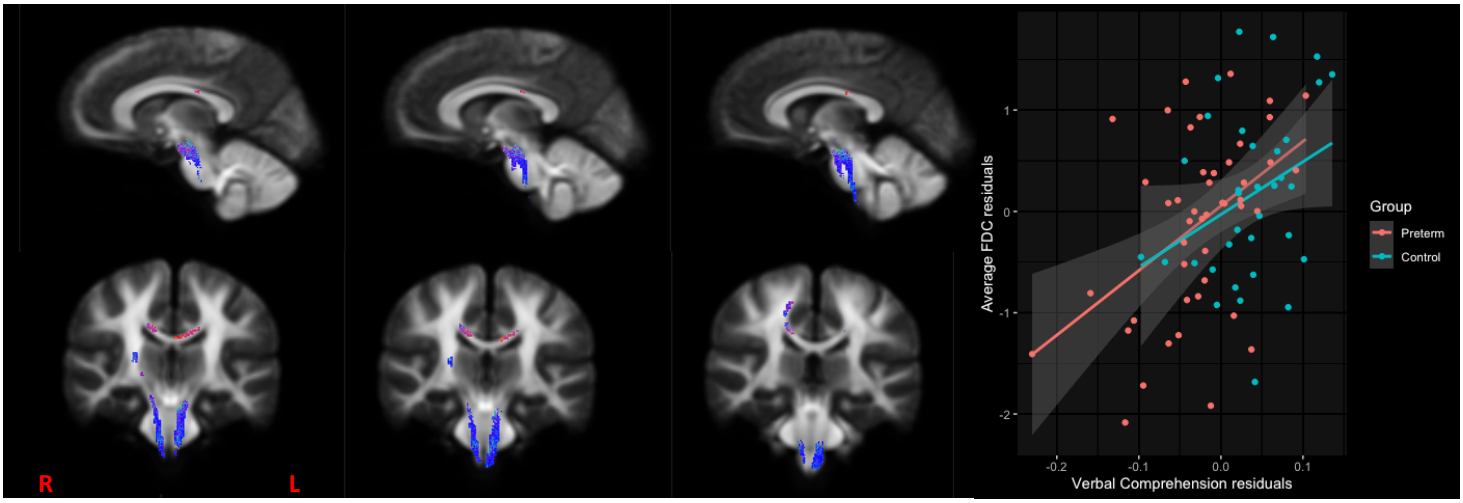


Figure 7.3. Spatial maps depicting associations between FDC values and verbal comprehension scores, after controlling for age, sex and ICV.

Figures were generated by cropping the whole-brain template-derived tractogram such that it included only streamline segments that pass through significant fixels ($p < 0.0125$, family-wise error rate-corrected). Streamline segments were coloured by direction (anterior-posterior = green; superior-inferior = blue; left-right = red). Scatterplot shows partial plot correlation between verbal comprehension scores and FDC values averaged over all significant fixels, for the two separate groups, corrected for age, sex and ICV.

No significant associations were found between VCI scores and FC or FD (all $p_{FWE} \geq 0.0125$). There was no significant interaction between VCI-FBA metric association and group.

7.3.4.2 Perceptual Reasoning

No significant associations were found between PRI scores and FC, FD, or FDC (all $p_{FWE} \geq 0.0125$). There was no significant interaction between PRI-FBA metric association and group.

7.3.4.3 Working Memory

No significant associations were found between WMI scores and FC, FD, or FDC (all $p_{FWE} \geq 0.0125$). There was no significant interaction between WMI-FBA metric association and group.

7.3.4.4 Processing Speed

No significant associations were found between PSI scores and FC, FD, or FDC (all $p_{FWE} \geq 0.0125$). There was no significant interaction between PSI-FBA metric association and group.

7.3.5 Brain-behaviour associations between FBA metrics and temperamental traits

No significant associations were found between NA, EC, and Surg scores and FC, FD, or FDC (all $p_{FWE} \geq 0.0167$). There were no significant interactions between temperamental trait–FBA metric association and group.

7.3.6 Voxel-based DTI analyses

7.3.6.1 Between-group analyses

No significant differences in FA values were found between the VPT and control groups. VPT children had significantly higher RD than control children in WM tracts listed in Table 7.6, displayed in Figure 7.4 (all $p_{FWE} < 0.05$).

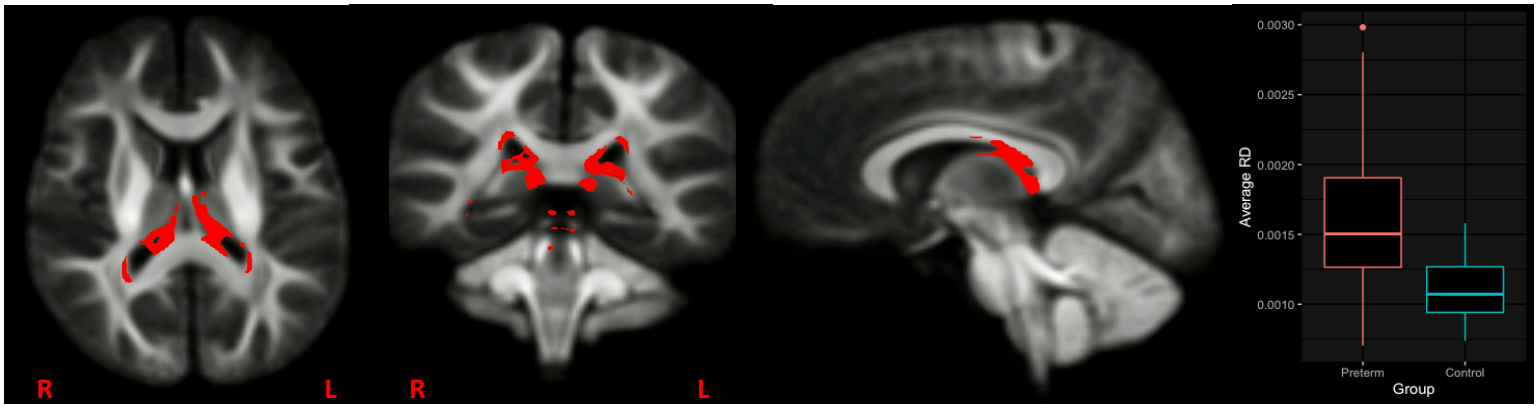


Figure 7.4. Voxel-based analyses of radial diffusivity (RD).
Significant regions (shown in red) indicate significantly higher RD in VPT compared to full-term groups, after controlling for age and sex. Figures show boxplots representing group differences in RD within significant regions.

Table 7.6. Voxel-wise RD differences between VPT children and controls.

DTI metric (covariates)	Direction	WM regions
RD (age, sex)	VPT<FT	Bilateral: Fornix, stria terminalis, body of the corpus callosum, tapetum

FT = full-term group; RD = radial diffusivity; VPT = very preterm group.

7.3.6.2 DTI brain-behaviour associations

No significant associations were found between DTI metrics (FA and RD) and any of the behavioural outcomes: WISC subscales (VCI, PRI, WMI, PSI) and TMCQ subscales (NA, EC, Surg).

7.4 Discussion

This study investigated associations between white matter structure and behavioural outcomes in VPT and term-born children. We found no significant differences in cognitive or socio-emotional outcomes between the VPT and control groups. Fixel-based diffusion imaging analyses indicated axonal reductions in VPT children when compared with full-term controls in several WM tracts, in the form of decreased FD, FC, and FDC. Voxel-based analyses also revealed increases in RD in the preterm group in overlapping WM tracts. Finally, we found a positive association between FDC values in the corpus callosum and CST and verbal comprehension scores, in the whole participant sample (VPT and full-term children). We did not find a moderation of this brain-behaviour association by preterm group status. Results indicated no associations between FBA metrics and temperamental traits. DTI analyses revealed no associations between FA or RD and behavioural outcomes.

7.4.1 Behavioural differences

In the current study we did not observe significant differences between the preterm and term-born control groups in terms of Verbal Comprehension, Perceptual Reasoning, Working Memory, or Processing Speed scores when correcting for multiple comparisons. Therefore our results are not in line with previous findings indicating significantly worse performance of preterm children on various cognitive tests measuring general intelligence (Anderson, 2014; Mangin et al., 2017), working memory (Aarnoudse-Moens et al., 2009b; Omizzolo et al., 2014), language abilities (Barre et al., 2011; Reidy et al., 2013), processing speed (Rose et al., 2002), and visuo-spatial skills (Ornstein et al., 1991; Torrioli et al., 2000). Further, our results indicated no differences in temperamental traits between VPT and control children, contrary to findings from studies indicating increased negative affect (Caravale et al., 2017; Lejeune et al., 2015) and decreased self-regulatory behaviours (Spittle et al., 2009; Wolf et al., 2002) in preterm children.

In terms of processing speed, previous research has indicated that performance differences between VPT and term-born children in this domain are primarily due to a greater proportion of

extremely slow responses, as opposed to generally lower average processing speed (de Kieviet et al., 2012b), resulting in difficulties when attempting to maintain a high level of efficiency with increased task complexity. Given the short and relatively easy nature of the processing speed tasks within the WISC-IV, this may explain the lack of group differences in this domain.

As stated in Chapter 4, VPT children followed-up at Timepoint 2, and those who completed a full MRI scan at Timepoint 3, showed higher IQ scores when compared to those not followed-up, or with an incomplete MRI scan. Therefore, our results are likely to be skewed and therefore underestimate the cognitive deficits seen in VPT children, possibly explaining the lack of differences with the full-term controls. Furthermore, despite many findings indicating significant differences in cognitive development between preterm and term-born children and adolescents, there is also evidence to suggest these two groups score comparably on various cognitive tests, including vocabulary comprehension, working memory and processing speed tasks (Pérez-Pereira et al., 2020; Saavalainen et al., 2007). It has also been suggested that preterm children might be able to 'catch-up' to their term-born peers by late childhood and overcome some of their difficulties. This is supported by findings indicating preterm individuals perform better on working memory tasks in early adolescence than at eight years (Curtis et al., 2002).

Similar to the cohort studied by Perez-Pereira and colleagues (2020), our participants could be considered as 'low-risk' as they did not show serious additional medical conditions. Furthermore, the current cohort have a relatively favourable socio-economic background, with around a third of participants coming from regions in England considered to be within the least socially deprived quintile. As coming from a higher socio-economic background is well known to be associated with better cognitive outcomes (Duncan and Magnuson, 2012; Sarsour et al., 2011), this might help explain the lack of cognitive deficits seen in the VPT group. Our results are supported by previous literature indicating that VPT children at both clinical and socio-demographical low risk develop behavioural skills similar to full-term children (Pérez-Pereira and Cruz, 2017; Pérez-Pereira et al., 2014).

These findings might also help explain the lack of differences in temperamental traits between the two groups. Results from Voigt and colleagues (2013) indicated that whilst there was no direct association between preterm birth and temperamental traits in toddlers, environmental variables,

specifically parenting stress, had an influence on toddlers' NA scores. This is supported by previous research highlighting the effects of parenting characteristics on socio-emotional development in VPT children (Gracioli and Linhares, 2019; Vinall and Grunau, 2014). As such parental characteristics, including sensitivity and temperament, are known to be directly influenced by a family's socioeconomic position (Booth et al., 2018; Kalil et al., 2012; McLoyd et al., 1994; Vaccaro et al., 2021), a lack of differences in childhood temperament between the VPT and control groups in this study could also be attributed to the fact that the VPT group who was followed up at Timepoint 3 was less socially deprived than the group who was not followed-up, i.e., had higher SES.

7.4.2 Between-group white matter differences

7.4.2.1 FBA findings

VPT children exhibited lower FD, FC and FDC in central WM regions compared with full-term controls. Although both FD and FC represent the capacity to transfer information, lower FD represents the fraction of space occupied by axons in every voxel (or intra-axonal volume), while lower FC indicates a smaller cross-sectional area of fibre tracts (Raffelt et al., 2017). The former could be indicative of individual axonal diameters, or the number of axons that occupy the space. An apparent decrease in the volume of intra-axonal compartment (lower FD) is indicative of increased exchange of water between the intra-axonal and extra-axonal spaces, which has been suggested to be caused by lower myelin content (Pannek et al., 2018). Therefore, a decrease in FD in VPT children could suggest lower myelin content in this population compared to full-term controls, in regions including the corpus callosum and fornix.

Further, a difference in FC signifies altered macrostructure, whereby a larger cross-section will be seen in 'thicker' fibre bundles that contain a higher number of neurons compared to 'thinner' bundles (Raffelt et al., 2017). Therefore, our results indicate that VPT children have fewer axons within specific fibre bundles (including the cingulum, SLF, CST, and cerebellar peduncles) compared to full-term controls.

Our results indicate varying spatial specificity for FD and FC differences between preterm and full-term children. Specifically, FD was predominantly affected in the corpus callosum (body and splenium), tapetum, and fornix. This is in line with a recent study showing similar altered FD patterns in preterm children at 7 and 13 years (Kelly et al., 2020). VPT children may have axonal reductions in these developmentally sensitive fibre tracts, known to be rapidly developing during childhood (Lebel and Beaulieu, 2011). The current results showed more group differences in FC, indicating alterations in the CST, middle and superior cerebellar peduncles, cingulum, and SLF. Our results indicate that FC and FDC differences between the two groups remained significant even after controlling for ICV, suggesting that such differences are unlikely to be driven exclusively by whole-brain volume differences.

In a previous study, our group examined diffusion MR images of the current cohort at TEA age using FBA. Whilst not directly comparing the preterm neonates with full-term controls, Pecheva and colleagues (2019) identified associations between FBA metrics and GA, highlighting altered macrostructural (FC) alterations in similar regions to the current study, including tracts within the CST, cerebellum, and pons.

Similar results have been reported in a further cohort of preterm neonates. Pannek and colleagues (2018) identified altered microstructure (FD) in the body of the corpus callosum, whilst brain macrostructure (FC) was altered within the cerebellar peduncles and cingulum, amongst other WM tracts. Similar to Pannek and colleagues, the current study identified reduced FD, but not FC, in the anterior commissure in a preterm cohort when compared to full-term controls. However, due to partial volume effects as described by Raffelt and colleagues (2017), differences in the cross-section of the anterior commissure are likely to manifest as alterations in within-voxel intra-axonal volume (FD), and therefore it is difficult to differentiate between FD and FC alterations in this structure.

Finally, FDC showed reductions primarily in regions showing reductions in FD and FC, including the bilateral fornix, CST, cerebral peduncles, corpus callosum and SLF. FDC is influenced by both microstructural and macrostructural properties, and it has been suggested that this metric, compared to FD or FC alone, is a better representation of ‘the ability to transfer information’ (Raffelt et al., 2017). FDC was also reduced in the right side only within the superior cerebellar peduncle and

cingulum. Increased alterations in preterm individuals on the right, compared to the left, hemisphere is in line with previous literature indicating structural asymmetries of WM tracts in this population. For example, favourable diffusion characteristics, including higher FA and lower diffusivities, are reported in the left CST (Liu et al., 2010; van Pul et al., 2012b) and parietotemporal SLF (Liu et al., 2010). It has been suggested that such structural asymmetries, which are already present at TEA, might be a reflection of advanced myelination in the left hemisphere (Liu et al., 2010). Later maturation of the right hemisphere could therefore mean it is more susceptible to alterations resulting from preterm birth.

7.4.2.2 DTI findings

VPT children displayed higher RD values, when compared to controls, in voxels located within several WM tracts, including the fornix and corpus callosum. RD-based group differences overlapped with regions displaying FD differences, in opposite directions: higher RD was predominantly found in regions where VPT children showed lower FD than controls. Higher RD reflects heightened diffusivity perpendicular to the direction of axonal fibres, which might indicate increased membrane permeability of the axon. As described above, changes in FD are also thought to be indicative of membrane permeability. Taken together, these DTI results further support our findings of increased membrane permeability within specific WM tracts in VPT children compared to full-term controls.

7.4.3 Brain-behaviour associations

The current study found a positive association between scores on a subscale of the WISC-IV (VCI) and FDC in the bilateral CST and in the body of the corpus callosum, in the whole participant group (VPT and full-term children). Previous DTI studies have reported associations between cognition and diffusion characteristics in the CST and corpus callosum in children (Duerden et al., 2015; Kennedy et al., 2021; Moreno et al., 2014; Young et al., 2017). More specifically, our results showed an association between WM structure and verbal comprehension, as no associations were

found between FBA metrics and any of the other WISC-IV subscales. Similar findings have been reported in DTI studies of children, whereby brain-behaviour associations are identified between language abilities and diffusion characteristics in various WM tracts, including the CST and corpus callosum (Andrews et al., 2010; Feldman et al., 2012; Mürner-Lavanchy et al., 2018; Suprano et al., 2020; Young et al., 2017). Recently, FBA has been used to assess associations between WM properties and cognitive outcomes in children. In a VPT cohort, neonatal FBA metrics (FD, FC and FDC) of the corpus callosum and CST were shown to be significantly associated with cognitive outcomes at 1 and 2 years (Pannek et al., 2020), in line with results from the current analyses. Further, in a combined group of VPT and full-term children, math computation was associated with FBA metrics predominantly in the CST and the corpus callosum (Collins et al., 2021).

The development of the corpus callosum has long been implicated in language outcomes, with smaller tract volumes showing associations with lower verbal intelligence measures in preterm children (Caldú et al., 2006; Narberhaus et al., 2008; Nosarti et al., 2004). The corpus callosum is thought to influence language development through its involvement in language network organisation and integration (Bartha-Doering et al., 2021; Friederici and Alter, 2004). The functional relevance of CST for verbal comprehension, however, is less clear, and requires further investigation. Although previous research has indicated specific associations between diffusion characteristics of the CST and verbal comprehension (Jung et al., 2019), it remains possible that effects seen in the current analyses reflect associations with widespread WM, that are more evident in larger tracts.

Associations between FBA metrics and VCI scores were similar in VPT and full-term children. No significant interaction was found between group status and cognitive performance on WM structure. Previous literature has yielded conflicting results for associations between language-related skills and WM structure in preterm children, with some studies reporting altered WM systems in this group (Bruckert et al., 2019; Feldman et al., 2012; Thompson et al., 2020; Travis et al., 2016), whilst others suggest similar associations to full-term children (Andrews et al., 2010; Mürner-Lavanchy et al., 2018).

7.4.4 Limitations and future directions

The VPT children followed-up for the current study had a significantly higher IMD score than those who were not followed up at Timepoint 3 (see Chapter 4). Furthermore, of the children who were followed-up, those who had complete MRI scans showed significantly higher IQ scores than those who did not complete the MRI scan. Therefore, our VPT group includes children coming from a relatively high socio-economic background, with relatively good cognitive development. Therefore, our results may not be generalisable to all VPT children.

Further, the language measure used in the current study is thought to depend on various cognitive processes, including attention, working memory, and the development of complex concepts, and therefore it is difficult to claim an association between diffusion characteristics of these WM tracts and language comprehension only. Future research could focus on determining brain-behaviour associations between WM structure and 'purer' language tasks.

The socio-emotional measures used here included temperamental traits as measured by pre-defined subscales from one parental questionnaire, the TMCQ. Whilst these traits have been validated in various populations, parents' reports are likely to be biased by their own characteristics, and based specifically on parent–child relationship (Kagan and Fox, 2006). A more robust approach of measuring temperament might include the direct observation of children's behaviour, whereby assessors rate children's reactions to stimuli that elicit emotional reactivity (e.g., Durbin et al., 2007).

Finally, the current cross-sectional analyses included one time-point for both brain and behavioural data. Future research could employ longitudinal methodologies including multiple time-points, in order to disentangle this relationship further and tap into true developmental effects.

The current FBA findings support previous DTI literature indicating altered WM development in VPT children compared to full term controls. Our results indicate decreased fibre density (i.e., microstructure) in several WM tracts, overlapping with regions of increased RD, which is in line with previous DTI findings in VPT children. Further, the current results supplement these findings by also reporting reduced fibre cross-section (i.e., macrostructure) in this population. Results

from the current FBA study also support previous DTI findings of associations between diffusion characteristics of WM tracts and verbal comprehension in VPT and full-term children. We report here a positive association, suggesting that better verbal outcomes correlate with an improved ability of WM tracts to transfer information. As this ability is shown to be diminished in VPT children (Kelly et al., 2020; Pannek et al., 2018; Pecheva et al., 2019), this may aid in understanding cognitive deficits exhibited by VPT children. The ability to pinpoint such altered WM diffusion characteristics could help in the early detection of cognitive problems so often experienced by this population, allowing for potential preventative measures to be implemented.

Chapter 8: General Discussion

8.1 Overview of thesis

The aim of this thesis was to increase our understanding of white matter development and its associations with behavioural outcomes in VPT neonates and children.

This thesis first investigated associations between neonatal structural and functional connectivity and socio-emotional outcomes in a group of VPT children. In Chapter 5, structural connectivity was quantified using tract-specific DTI metrics, and this was shown to be related to childhood socio-emotional outcome factors. In Chapter 6, neonatal functional connectivity of the amygdalae, measured using resting-state fMRI, was assessed in relation to these same socio-emotional outcomes. While previous research has demonstrated associations between neonatal structural and functional connectivity and cognitive outcomes in childhood, associations with socio-emotional outcomes in VPT children have not been studied as extensively. The present work aimed to explore whether altered brain connectivity in preterm neonates is associated with childhood socio-emotional outcomes.

Chapter 7 explored the differences in diffusion characteristics between VPT and term-born children and their association with behavioural outcomes. Whilst previous research has explored this association in VPT children, this thesis differs in utilising the advanced FBA method, which correlates more specifically with tissue microstructure than traditional diffusion imaging methods. These findings have improved our understanding of alterations in WM structure in VPT children and their associations with cognition.

8.2 Summary of findings

8.2.1 Socio-emotional profile in VPT children

In both Chapters 5 and 6, socio-emotional outcomes were reflected by three factors: *Emotion Moderation*, *Social Function*, and *Empathy*. In the analysis of each chapter, only *Emotion Moderation* revealed an association with brain connectivity. Results from Chapter 5 demonstrated that those with better cognition were more likely to exhibit good social functioning, indicating *Social Function* was moderated by IQ. This dependency of social functioning on cognition is reflected in previous literature (Adolphs, 2001; Watson et al., 1999). *Empathy,* on the other hand, was seen to be related to sex, with girls demonstrating higher scores on the Empathy Questionnaire than boys, a tendency also in line with previous literature (Auyeung et al., 2009; Mestre et al., 2009). Sex differences in empathy may be heightened by an individual's environment, where influence from parents, teachers, and caregivers is thought to reinforce stereotypical gender roles and expectations. An evolutionary perspective can also be considered, where sex differences in empathy are promoted by differential natural selection and sexual selection pressures (Di Tella et al., 2020). With women bearing costs in the selection of a poorly suited mate – and disproportionate costs in raising children – greater empathy and thus an ability to understand another's feelings and intentions allows for the selection of partners who will be more likely to provide assistance in child rearing (Vongas and Al Hajj, 2015).

Lastly, childhood *Emotion Moderation* was shown to be negatively associated with both structural and functional neonatal connectivity in a VPT cohort, with high scores on this factor indicating a tendency for increased Negative Affectivity and Effortful Control. As discussed in Chapter 6, although the combination of these two temperamental traits may appear counterintuitive, it is possible to interpret *Emotion Moderation* as the *maladaptive* control or regulation of internal emotional and cognitive states (Cicchetti and Toth, 2014; Merrell, 2008). Increased Effortful Control could be predominantly driven by increased inhibitory control, reflecting an overall inhibited and shy behaviour as a consequence of fear and anxiety (Derryberry and Rothbart, 1997; Eggum-Wilkens et al., 2015). Such a temperamental profile corresponds with the 'preterm phenotype' (Arpi and Ferrari, 2013; Johnson and Marlow, 2011) and conforms with a temperament model developed by Robins et

al. (1996) which postulates that individuals can be divided into groups of temperament typologies, namely 'overcontrolled' (individuals are shy, compliant, and dependent), 'under-controlled' (individuals are active, aggressive, resistant, and demonstrate difficulties regulating emotions), and 'resilient' (individuals are compliant, cooperative, display positive emotions and well-developed social skills, and are adaptive in stressful situations). Developed with a sample of American adolescents, this model has since been replicated in other countries and age groups (Asendorpf and van Aken, 1999; Hart et al., 2003; Hart et al., 1997). In revealing the negative association between neonatal connectivity and *Emotion Moderation*, we present a possible biological precursor for the 'overcontrolled' temperamental typology, commonly seen in VPT children.

8.2.2 Neonatal frontal-temporal connectivity and socio-emotional outcomes

The UF connects the orbitofrontal cortex and parts of the limbic system, including the amygdalae, temporal pole, and parahippocampal gyrus (Von Der Heide et al., 2013). Findings from Chapters 5 & 6 indicate that early alterations of structural and functional connectivity between the anterior temporal lobe and the orbitofrontal region represent a possible biological mechanism underlying the association reported between VPT birth and emotion dysregulation in childhood and beyond. Decreased structural and functional connectivity were independently associated with poorer Emotion Moderation.

The anterior temporal lobe is implicated in the processing of social concepts, including facial emotion recognition and theory of mind (Olson et al., 2007; Simmons et al., 2010; Zahn et al., 2007). Within the anterior temporal lobes, the amygdalae play a key role in socio-emotional processing (Adolphs, 2001) and is involved in evaluating the significance of and arousal from emotional stimuli (Pessoa and Adolphs, 2010; Phelps and LeDoux, 2005). The orbitofrontal cortex plays a role in reward-based decision making and in assigning value to external stimuli (Grabenhorst and Rolls, 2011). Considering the functions of these brain regions, it is possible that their connectivity facilitates the transmission of neural representations of salient stimuli, a process required for the formulation of reactions to these stimuli. Such reactions will be based on an evaluation of the stimuli's importance, which may include an analysis of its emotional tone or incentive value (Von Der Heide et al., 2013).

The association between anterior temporal – orbitofrontal connectivity and temperament reported in Chapters 5 & 6 may be attributable to the mediating effect of altered stimuli processing. Previous literature has demonstrated associations between temperament and information processing, specifically a relationship between negative affect and altered processing of salient stimuli (Lonigan et al., 2004; Mauer and Borkenau, 2007). Moreover, altered information processing has been shown to be associated with anxiety in children, with anxious individuals exhibiting processing biases towards threatening stimuli (Hadwin and Field, 2010; Hadwin et al., 2006). As such, high *Emotion Moderation* scores, which we may be exhibited as more inhibited, shy, and anxious behavioural responses, could be underpinned by altered processing of representations of emotional stimuli.

Our results indicated an association between connectivity of the anterior temporal and orbitofrontal cortices and socio-emotional outcomes in the right hemisphere only. Asymmetric associations such as this have been demonstrated in previous literature, including associations between the right anterior temporal lobe and emotional memory (Olson et al., 2007) and asymmetric outcomes of temporal atrophy in individuals with frontotemporal dementia (e.g., Thompson et al., 2003). Moreover, a recent review of behavioural studies investigating patients with frontotemporal lobar degeneration suggested a general dominance of the right hemisphere for emotional functions (Gainotti, 2019).

The developmental sequalae of socio-emotional difficulties warrants further investigation, with future studies characterising the mediating effect of information processing on the relationship between altered brain development and behavioural outcomes.

8.2.3 White matter development in VPT children

This thesis improves our understanding of WM development in VPT children by identifying altered tracts exhibiting decreases in microstructure and macrostructure when compared to full-term controls. Altered microstructural diffusion characteristics reflected in decreased FD and increased RD in VPT children might indicate elevated membrane permeability, as a result of reduced myelin content. This was mostly seen in commissural WM regions encompassing the fornix and body of the

corpus callosum. Macrostructural alterations exhibited as decreases in FC in the VPT group suggests this population develops 'thinner' fibre bundles containing fewer axons when compared to full-term controls. This was specifically seen in projection and association fibres tracts including the cingulum, SLF, CST, and cerebellar peduncles. Alterations in the combined measure of FD and FC, FDC, were also reported in VPT children. This metric is thought to represent total intra-axonal volume more precisely than each of the two metrics alone. Reductions in FDC were found in similar regions to those indicating reduced FD and FC only, including the fornix, corpus callosum, CST, and SLF.

8.2.4 Childhood diffusion characteristics and behavioural outcomes

The accurate interpretation of changes in FA can be problematic as they occur secondary to a variety of inter- and intra-tract mechanisms. The usage of traditional MRI techniques such as DTI can introduce these difficulties in interpretation as it conveys only a limited amount of information on WM tract structure. Indeed, the DTI literature has revealed conflicting results, with both negative and positive associations with language outcomes reported in separate studies (e.g., Bruckert et al., 2019; Mürner-Lavanchy et al., 2018). As such, a more advanced MRI technique, FBA — which can identify multiple specific fibre pathways within a voxel — was employed in analyses in Chapter 7.

Preterm children showed significantly reduced FD, FC and FDC values in central WM when compared to term-born controls. We found that tract microstructure (FD) is likely to be affected by prematurity mainly within the corpus callosum and fornix. Tract macrostructure (FC), on the other hand, showed alterations in more WM tracts, including CST, cerebellar peduncles, cingulum, and SLF. Such differences were in line with previous results from FBA studies of preterm neonates and children (Kelly et al., 2020; Pannek et al., 2018; Pecheva et al., 2019).

Further, total intra-axonal volume (FDC) within the body of the corpus callosum and the CST was associated with verbal comprehension. Neonatal FDC in the corpus callosum and CST has recently been related to cognitive development of VPT toddlers (Pannek et al., 2020), suggesting such associations remain consistent along the lifespan. This is important as it suggests that early alterations in WM development may be indicative of later development and behavioural outcomes. In order to

confirm this hypothesis, future research should focus on assessing similar associations within the same cohort at different timepoints through the use of longitudinal study designs.

Finally, despite performing marginally worse on all subscales of the WISC, VPT children did not show significant differences in performance to term-born controls after controlling for multiple comparisons. This result is reflected in previous literature (e.g., Pérez-Pereira et al., 2020; Saavalainen et al., 2007), although findings have been conflicting, with certain studies observing a significantly worse performance on cognitive tests by VPT children than full-term controls (e.g., Anderson, 2014; Hua et al., 2008; Reidy et al., 2013). Such disparity might be explained by variations in cohort characteristics that ultimately affect their performance. For example, the present cohort of VPT children followed-up as part of the ePrime study were shown to have a lower average IMD score when compared to those not followed-up (Chapter 4). This suggests a sampling bias whereby those children from a relatively higher socioeconomic background are more likely to take part in follow-up studies. The comparable performance on the WISC by this VPT cohort could thus be a product of better cognitive development seen in individuals from higher socio-economic background (Duncan and Magnuson, 2012; Sarsour et al., 2011). Similarly, the fact that the followed-up VPT group was less socially deprived than the group who was not followed-up might also help explain the lack of differences in temperament between the VPT and full-term children. Previous research has reported the influence of SES on behavioural problems (Costello et al., 2003; Piotrowska et al., 2015), and therefore, sampling behaviour from a VPT group with a relatively high socioeconomic background could result in more favourable outcomes compared to those that would have been observed in a more representative group of VPT children.

8.3 Limitations

8.3.1 Data collection

8.3.1.1 Behavioural measures

The practice of intelligence testing has been criticised for its instruments being biased towards the cultural context in which they have been developed. Cultural differences in lifestyles and child-

rearing practices may affect equal access to knowledge assessed by IQ tests (Cocodia, 2014), which is most often specific to white, Western society (Ford, 2005), and should therefore be taken into account when analysing the results of intelligence tests. One major limitation of the present IQ test analyses is that they did not control for ethnicity. We are therefore unable to conclude whether our results contain bias.

An additional limitation of the measures used in the present thesis concerns the use of parental questionnaires assessing children's socio-emotional development. Parental reporting on their children's social and emotional well-being has been shown to be biased, with parents estimating a child's happiness in relation to their own self-reported happiness (López-Pérez and Wilson, 2015). Further, behavioural competencies are developed in the context of family and community, with cultural differences influencing developmental concepts such as temperament and attachment (Bricker et al., 2004). As such cultural differences may be more apparent in some contexts compared to others, such as at home compared to school settings, gathering information across multiple environments and sources is an important consideration when assessing childhood development (Chen, 2011; Yates et al., 2008). Nevertheless, the parental questionnaires used in the current analyses (see Section 4.2.2.2) have been shown to be valid and reliable tools for behavioural data collection concerning aspects that can be difficult to measure through performance-based testing. Moreover, not only were parental ratings of the SDQ recently shown to be in line with the self-reported behaviour of adolescents, they also provided additional information necessary for the identification of emotional and behavioural difficulties, especially with respect to externalising problems (Theunissen et al., 2019).

However, even participants' own self-reported measures of childhood development are subject to biases, such as response biases and social desirability. Alternative behavioural measures that aim to explore participants' understanding and interpretation of social phenomena might include presenting participants with a scenario of fictional characters, or 'vignettes', and qualitatively analysing their responses and commentary (Jenkins et al., 2010). These methods have been previously shown to engage children, particularly in discussing sensitive topics (Barter and Renold, 2000).

Further objective measures of childhood behaviour include more unbiased, direct observations that are rated by trained assessors. Children's behaviours can be rated in response to

structured situations, such as separation or frustration paradigms, allowing the direct comparisons of regulatory strategies in the face of specific stressors (e.g., McConnell et al., 2003). Unstructured observations might illustrate more natural, day-to-day regulatory challenges (e.g., Fantuzzo and McWayne, 2002). Parent-child interactions might also be assessed with this method in order to characterise behaviour in the home context (Gardner, 2000), whilst observations within school settings might allow researchers to analyse teacher-child interactions (La Paro et al., 2004). The combined use of multiple methods and reporters, that tap into different aspects of childhood development, are likely to provide the most comprehensive assessment of childhood development (Smith-Donald et al., 2007; Wakschlag et al., 2005).

8.3.1.2 Socio-demographic measures

The current thesis used area-based deprivation as a sociodemographic measure, the IMD, which is a useful method of quantifying SES that is UK-specific. As the IMD was calculated on the basis of maternal address at the time of infant birth, families were not required to answer questions about personal matters that may have made them feel uncomfortable, such as income. However, such area-based socio-economic indicators do have their limitations, as they assume a level of homogeneity, despite findings reporting heterogenous income and education levels within a geographic unit (Diez-Roux et al., 2001). Alternative methods of collecting data that are more specific to the individual are available, including systematic categorisations of occupation, annual household income, and more in-depth questionnaires that focus on material affluence, such as the Family Affluence Scale, which includes questions about material possessions, family holidays, and number of rooms in the home (Currie et al., 2008).

The current thesis also collected data on maternal education, which was quantified as the age at leaving school, and was binarized rather than treated as a continuous variable. The binarization – (i) at or before 19 years and (ii) after 19 years - aimed to subdivide the group into those finishing education at secondary school, and those continuing to study at degree level (Belfield et al., 2018). Dichotomization of maternal education represents a limitation of the current study as this non-fine

grade categorisation may lead to loss of information about individual differences and potential overlooking of non-linear relationships, hence loss of measurement reliability (MacCallum et al., 2002). Preferable alternative methods of collecting data on maternal education might include specifying attained educational levels (Bonthrone et al., 2021). The use of other systems of maternal education classification, for instance the CASMIN (Comparative Analysis of Social Mobility in Industrial Nations) (Brauns et al., 2003) which uses three educational levels: primary, secondary and tertiary, could allow comparisons of findings between different countries and educational systems.

8.3.1.3 Measuring neonatal illness

As detailed in Section 4.1.3, in this work I used a neonatal sickness index computed from clinical data regarding participants' health during the perinatal period. Other validated measures of neonatal critical illness are also available, including scoring systems that use neonatal physiological and/or clinical data. For instance, the Critical Risk Index for Babies (CRIB-I and CRIB-II) were developed in the UK, are simple and rapid to use, and CRIB-II only contains objective parameters, avoiding potential problems of bias (Cockburn et al., 1993; Parry et al., 2003; Tarnow-Mordi et al., 1990). The CRIB-II can successfully predict neonatal mortality in preterm infants (Ezz-Eldin et al., 2015; Faridpour et al., 2020; Rastogi et al., 2010), although it did not perform better than GA or BW in predicting functional disability and is therefore not advised to be used in predicting long-term outcomes (Greenwood et al., 2012). Another set of commonly used measures are two versions of the Score for Neonatal Acute Physiology (SNAP-I and SNAP-II) (Richardson et al., 2001; Richardson et al., 1993). These measures, which were developed in the US, focus on the neonates' physiological wellbeing, and are highly predictive of neonatal mortality in preterm infants (Beltempo et al., 2019; Dammann et al., 2009; Maiya et al., 2001). SNAP-II scores are also used to predict neurodevelopmental outcomes (Dammann et al., 2010), as well as altered brain development (Ranger et al., 2013; Zwicker et al., 2013). A comparison between the CRIB and SNAP measures showed no significant differences in their abilities to predict neonatal mortality, and all were significantly better at predicting mortality than BW alone (Zardo and Procianoy, 2003).

Whilst these illness severity scores are useful tools that allow for standardised comparisons between populations and healthcare providers, their use does have its limitations. The use of an existing score may not represent the most accurate approach of quantifying illness severity within a specific population due to variations in clinical care between different countries and clinical units. Therefore, the use of a particular scoring system should include careful consideration of the measure's specific purpose and population (Dorling et al., 2005). Further, due to constant improvements in neonatal intensive care, these scores were developed at a time that involved different preterm neonatal care to the current practice, as well as differing survival rates. This highlights the need for the formulation of new sickness severity scores that are more in line with current practice, taking into account advances in neonatology (Garg et al., 2018). The neonatal sickness score used in the current analyses is specific to the time and place of birth of the cohort, and therefore to the clinical practice experienced by neonates recruited into in the study.

8.3.2 Generalisability of findings

8.3.2.1 Socio-demographic characteristics

As no control groups were included in Chapters 5 & 6, the current findings may not be generalised to term-born children. Previous research has mostly focussed on comparing preterm children to controls in a variable-centred approach, for example through the examination of broad temperamental traits. Whilst these traits are a useful way of categorising behaviour and allow for more manageable data analysis, disadvantages remain. This approach does not consider the multiple temperamental dimensions exhibited by individuals, such that more nuanced individual differences may go unnoticed (Zentner and Shiner, 2012). Through methodologies such as factor analysis, a person-centred approach is possible that considers the individual as the unit of analysis, best understood by considering all variables simultaneously (von Eye and Bergman, 2003). In childhood temperament research, the combination of such variables allows for identification of typologies used to differentiate between individuals (Hart et al., 2003), and may improve our understanding of child behaviour by considering the multifaceted nature of temperament. Here, we utilised multiple variables

and captured a temperamental profile that is in line with both the preterm phenotype, as well as a previous model of temperamental typologies (Hart et al., 2003).

Further, and as previously mentioned, the cohort of preterm children followed-up at both Timepoints 2 and 3 came from less deprived socio-economic groups compared to children who were not followed-up, highlighting a possible sampling bias. The trend of losing the more socially disadvantaged participants to follow-up in longitudinal research has been previously reported in both full-term (Cameron et al., 2017; Eisner et al., 2019) and preterm paediatric samples (MacBean et al., 2019; Piedvache et al., 2021). Indeed, individuals from disadvantaged backgrounds may experience more adverse consequences associated with preterm birth due to a lack of protective factors such as sensitive parenting and improved education (Benavente-Fernández et al., 2019; Wolke, 2019). Therefore, the relative socio-economic advantage of the followed-up VPT cohort is likely to be linked to the observed outcomes in this group (e.g., no differences from full-term controls in terms of cognition or socio-emotional outcomes, see Section 7.3.2) – and thus lead to an underestimation of the difficulties experienced by VPT children as a whole.

The preterm cohort was also limited in its lack of ethnic diversity, with an underrepresentation of children from minority groups. Firstly, non-English speaking families were excluded from the original ePrime study. This was necessary as the use of interpreters would have made it difficult to be certain whether the structured interview was administered appropriately (Edwards et al., 2018). Therefore, results from all ePrime studies can only be generalised to English-speaking families. One way of preventing such biased samples could involve the recruitment of non-English speaking families with the use of validated data collection methods that include versions of standardised measures in multiple languages.

Furthermore, the current analyses included a convenience sample recruited from the ePrime cohort, and therefore the sample is not necessarily representative of the ethnic distribution within the wider preterm population. Previous research has highlighted differences in temperament and psychiatric outcomes among ethnically diverse children (de Boo and Kolk, 2007), with an emphasis on worse outcomes in those experiencing ethnic discrimination (Zare et al., 2018). Future studies

should consider utilising stratified random sampling for a more representative sample of the population, or including ethnicity as a covariate in analyses of behavioural outcomes.

More generally, the wider research community is failing to include individuals from ethnic minorities, with findings indicating that disproportionally fewer individuals from minority groups are invited to participate in research, when considering the prevalence of these groups in the population (Wendler et al., 2006). Therefore, strategies to increase ethnic minority representation in medical research is essential to tackle the root causes of underrepresentation (Redwood and Gill, 2013). Some examples of such design-level changes are limiting exclusion criteria on personal characteristics, such as age or geography, as well as implementing recruitment through as wide a range of routes as possible (Witham et al., 2020).

8.3.2.2 Brain injury exclusion

It is important to note the implications of excluding all participants with major lesions for the generalization of our findings to representative samples of very preterm individuals. As reported at the end of Chapter 5, significant differences were seen in the DTI metrics (FA & RD) of the right ILF between those excluded due to major lesions and those with no brain injuries seen at TEA. Therefore, excluding participants with major brain lesions from statistical analyses limits generalizability of findings to those very preterm infants with more favourable neonatal MRI. However, the exclusion of participants with major brain lesions is unlikely to have biased the measurement of socio-emotional outcomes, as these were not different between the three brain injury groups: major injury, minor injury, and no injury.

Future research could aim to include infants with major lesions in their analyses, although this presents several challenges. Primarily, those with a major lesion represent a minority of the population, more likely to show the most pronounced brain alterations (Nosarti et al., 2008), in turn biasing results away from the main body of the population. On a more practical level, the inclusion of major lesions may lead to problems in the registration of brain images (Brett et al., 2001).

8.4 Directions for future research

Future research should prioritise recruitment of a representative sample of the community, with a focus on including children from lower socio-economic backgrounds. This would allow for non-biased results that could be better generalised to the wider population. Additionally, in order to better understand the behavioural profiles of VPT children, research in this field could employ similar factor analysis techniques on socio-emotional outcomes in groups of children with varying gestational ages, in order to understand the contribution of preterm birth to differences in behavioural profiles.

Future research could also focus on studying the socio-emotional development of children through data collection from multiple informants, such as parents, teachers, and children themselves, in order to limit bias. It has been suggested that discrepancies between informants' answers may be interpreted as a measurement error (Achenbach, 2011), although these themselves may be uniquely informative on their origin and causes (De Los Reyes, 2011).

Further, the collection of multimodal data would increase our understanding of neurodevelopmental alterations in VPT children through the integration of findings that may not be captured by studies utilising one modality. For example, understanding how specific properties of WM tracts may influence BOLD signals, and vice versa, may offer further insight into the downstream effects of injury in preterm neonates. One example of research using multimodal neuroimaging techniques in a VPT paediatric sample has revealed associations between both structural and functional alterations in the right frontoparietal regions and socio-emotional development (Urbain et al., 2019). This study reported that when observing angry faces, preterm children exhibited diminished functional responses in regions including the right angular gyrus. Structurally, this region also showed reduced cortical thickness in this group, when compared to full-term controls. Thus, reduced functional brain responses associated with altered socio-emotional processing rely on atypical structural brain maturation (Urbain et al., 2019).

Finally, as longitudinal WM development is non-linear (Lebel and Beaulieu, 2011), it is assumed that findings of associations between WM structure and behavioural outcomes are not

constant throughout participants' lives. To understand these relationships and their trajectories, comprehensive longitudinal studies with multiple time points are required. There are difficulties with such studies that often lie beyond the control of even large research teams, such as upgrades to scanners and software midway through, but novel methods of data collection, such as accelerated longitudinal designs (Galbraith et al., 2017) have been proposed, to resolve these issues. Future work should aim to utilise such methods to produce a comprehensive characterisation of the link between brain alterations and behavioural outcomes in typical and atypical developmental populations.

8.5 Conclusions

This thesis provides evidence for associations between structural and functional properties of the limbic system at TEA and socio-emotional outcomes in childhood in a VPT cohort. Advanced diffusion MRI techniques are used to characterise specific properties of WM that have rarely been studied before in a group of VPT and term-born children. Imaging results show significant WM structural alterations in VPT children, and importantly, differentiate between regions of altered microstructure, and macrostructure, in this population. Specific WM tracts associated with verbal cognitive outcomes in VPT and term-born children were also characterised.

With improvements in both perinatal neuroimaging protocols and processing methods, research in this field could aim for a more accurate and detailed characterisation of altered neural development in VPT samples, as well as its associations with behavioural outcomes. Early characterisation of such altered development may help identify those children at risk of neurodevelopmental sequelae and highlight possible therapeutic targets for intervention.

References

Aanes, S., Bjuland, K.J., Skranes, J., et al., 2015. Memory function and hippocampal volumes in preterm born very-low-birth-weight (vlbw) young adults. *Neuroimage* 105, 76-83.

Aarnoudse-Moens, C.S., Duivenvoorden, H.J., Weisglas-Kuperus, N., et al., 2012. The profile of executive function in very preterm children at 4 to 12 years. *Dev Med Child Neurol* 54, 247-253.

Aarnoudse-Moens, C.S., Smidts, D.P., Oosterlaan, J., et al., 2009a. Executive function in very preterm children at early school age. *J Abnorm Child Psychol* 37, 981-993.

Aarnoudse-Moens, C.S., Weisglas-Kuperus, N., van Goudoever, J.B., et al., 2009b. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics* 124, 717-728.

Aarnoudse-Moens, C.S.H., Weisglas-Kuperus, N., Duivenvoorden, H.J., et al., 2013. Executive function and iq predict mathematical and attention problems in very preterm children. *PLoS One* 8, e55994.

Abernethy, L.J., Cooke, R.W., Foulder-Hughes, L., 2004. Caudate and hippocampal volumes, intelligence, and motor impairment in 7-year-old children who were born preterm. *Pediatr Res* 55, 884-893.

Abivardi, A., Bach, D.R., 2017. Deconstructing white matter connectivity of human amygdala nuclei with thalamus and cortex subdivisions in vivo. *Hum Brain Mapp* 38, 3927-3940.

Achenbach, T.M., 1991. Manual for the child behaviour checklist/4-18 and 1991 profile University of Vermont Department of Psychiatry, Burlington, VT.

Achenbach, T.M., 2011. Commentary: Definitely more than measurement error: But how should we understand and deal with informant discrepancies? *Clin Child Adolesc Psychol* 40, 80-86.

Achenbach, T.M., Edelbrock, C.S., 1981. Behavioral-problems and competencies reported by parents of normal and disturbed-children aged 4 through 16. *Monogr Soc Res Child Dev* 46, 1-82.

Achenbach, T.M., Rescorla, L., 2000. Aseba preschool forms & profiles. Burlington, VT: Research Center for Children, Youth and Families, University of Vermont.

Adams, E., Chau, V., Poskitt, K.J., et al., 2010. Tractography-based quantitation of corticospinal tract development in premature newborns. *J Pediatr* 156, 882-888.e881.

Adams, M.M., Read, J.A., Rawlings, J.S., et al., 1993. Preterm delivery among black and white enlisted women in the united states army. *Obstet Gynecol* 81, 65-71.

Adams, R., Mercer, M., Courage, M., 2004. Ontogenetic development of visual acuity over the first three postnatal years. *Ophthalmic Genet* 25, 199-203.

Adén, U., Favrais, G., Plaisant, F., et al., 2010. Systemic inflammation sensitizes the neonatal brain to excitotoxicity through a pro-/anti-inflammatory imbalance: Key role of tnfalpha pathway and protection by etanercept. *Brain Behav Immun* 24, 747-758.

Adolphs, R., 2001. The neurobiology of social cognition. *Curr Opin Neurobiol* 11, 231-239.

Aeby, A., De Tiège, X., Creuzil, M., et al., 2013. Language development at 2 years is correlated to brain microstructure in the left superior temporal gyrus at term equivalent age: A diffusion tensor imaging study. *Neuroimage* 78, 145-151.

Ahmad, S., Waldie, K.E., Morton, S.M.B., et al., 2021. Do patterns of levels of socio-emotional competence during early childhood predict executive function at 4.5 years? *Child Psychiatry Hum Dev*.

Ajayi-Obe, M., Saeed, N., Cowan, F.M., et al., 2000. Reduced development of cerebral cortex in extremely preterm infants. *Lancet* 356, 1162-1163.

Aksan, N., Kochanska, G., 2004. Links between systems of inhibition from infancy to preschool years. *Child Dev* 75, 1477-1490.

Albaugh, M.D., Ducharme, S., Karama, S., et al., 2017a. Anxious/depressed symptoms are related to microstructural maturation of white matter in typically developing youths. *Dev Psychopathol* 29, 751-758.

Albaugh, M.D., Nguyen, T.-V., Ducharme, S., et al., 2017b. Age-related volumetric change of limbic structures and subclinical anxious/depressed symptomatology in typically developing children and adolescents. *Biol Psychol* 124, 133-140.

Alcauter, S., Lin, W., Smith, J.K., et al., 2014. Development of thalamocortical connectivity during infancy and its cognitive correlations. *J Neurosci* 34, 9067.

Alexander, B., Kelly, C.E., Adamson, C., et al., 2019. Changes in neonatal regional brain volume associated with preterm birth and perinatal factors. *Neuroimage* 185, 654-663.

Alexandrou, G., Mårtensson, G., Skiöld, B., et al., 2014. White matter microstructure is influenced by extremely preterm birth and neonatal respiratory factors. *Acta Paediatr* 103, 48-56.

Alix, J.J., Zammit, C., Riddle, A., et al., 2012. Central axons preparing to myelinate are highly sensitive [corrected] to ischemic injury. *Ann Neurol* 72, 936-951.

Allievi, A.G., Arichi, T., Tusor, N., et al., 2016. Maturation of sensori-motor functional responses in the preterm brain. *Cereb Cortex* 26, 402-413.

Allin, M., Matsumoto, H., Santhouse, A.M., et al., 2001. Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. *Brain* 124, 60-66.

Allin, M., Rooney, M., Cuddy, M., et al., 2006. Personality in young adults who are born preterm. *Pediatrics* 117, 309-316.

Anbeek, P., Vincken, K.L., Groenendaal, F., et al., 2008. Probabilistic brain tissue segmentation in neonatal magnetic resonance imaging. *Pediatr Res* 63, 158-163.

Anblagan, D., Pataky, R., Evans, M.J., et al., 2016. Association between preterm brain injury and exposure to chorioamnionitis during fetal life. *Scientific reports* 6, 37932.

Anderson, A.W., Marois, R., Colson, E.R., et al., 2001. Neonatal auditory activation detected by functional magnetic resonance imaging. *Magn Reson Imaging* 19, 1-5.

Anderson, I.M., Shippen, C., Juhasz, G., et al., 2011a. State-dependent alteration in face emotion recognition in depression. *Br J Psychiatry* 198, 302-308.

Anderson, J.W., Johnstone, B.M., Remley, D.T., 1999. Breast-feeding and cognitive development: A meta-analysis. *Am J Clin Nutr* 70, 525-535.

Anderson, P.J., 2014. Neuropsychological outcomes of children born very preterm. *Semin Fetal Neonatal Med* 19, 90-96.

Anderson, P.J., De Luca, C.R., Hutchinson, E., et al., 2010. Underestimation of developmental delay by the new bayley-iii scale. *Arch Pediatr Adolesc Med* 164, 352-356.

Anderson, P.J., De Luca, C.R., Hutchinson, E., et al., 2011b. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. *Dev Neuropsychol* 36, 57-73.

Anderson, P.J., Doyle, L.W., 2004. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. *Pediatrics* 114, 50-57.

Anderson, P.J., Reidy, N., 2012. Assessing executive function in preschoolers. *Neuropsychology review* 22, 345-360.

Andersson, J.L., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: Application to diffusion tensor imaging. *Neuroimage* 20, 870-888.

Andersson, J.L.R., Sotiropoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion mr imaging. *Neuroimage* 125, 1063-1078.

Andre, Q.R., Geeraert, B.L., Lebel, C., 2020. Brain structure and internalizing and externalizing behavior in typically developing children and adolescents. *Brain Struct Funct* 225, 1369-1378.

Andrews, J.S., Ben-Shachar, M., Yeatman, J.D., et al., 2010. Reading performance correlates with white-matter properties in preterm and term children. *Dev Med Child Neurol* 52, e94-100.

Anjari, M., Srinivasan, L., Allsop, J.M., et al., 2007. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. *Neuroimage* 35, 1021-1027.

Arichi, T., Fagiolo, G., Varela, M., et al., 2012. Development of bold signal hemodynamic responses in the human brain. *Neuroimage* 63, 663-673.

Arichi, T., Gordon-Williams, R., Allievi, A., et al., 2013. Computer-controlled stimulation for functional magnetic resonance imaging studies of the neonatal olfactory system. *Acta Paediatr* 102, 868-875.

Arichi, T., Moraux, A., Melendez, A., et al., 2010. Somatosensory cortical activation identified by functional mri in preterm and term infants. *Neuroimage* 49, 2063-2071.

Arpi, E., Ferrari, F., 2013. Preterm birth and behaviour problems in infants and preschool-age children: A review of the recent literature. *Dev Med Child Neurol* 55, 788-796.

Asato, M.R., Terwilliger, R., Woo, J., et al., 2010. White matter development in adolescence: A dti study. *Cereb Cortex* 20, 2122-2131.

Asendorpf, J.B., van Aken, M.A., 1999. Resilient, overcontrolled, and undercontroleed personality prototypes in childhood: Replicability, predictive power, and the trait-type issue. *Journal of personality and social psychology* 77, 815.

Ashburner, J., Csernansk, J.G., Davatzikos, C., et al., 2003. Computer-assisted imaging to assess brain structure in healthy and diseased brains. *Lancet Neurol* 2, 79-88.

Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry--the methods. *Neuroimage* 11, 805-821.

Ashburner, J., Hutton, C., Frackowiak, R., et al., 1998. Identifying global anatomical differences: Deformation‐based morphometry. *Hum Brain Mapp* 6, 348-357.

Association, A.P., 2013. Diagnostic and statistical manual of mental disorders (dsm-5®). American Psychiatric Pub.

Atkinson, R.C., Shiffrin, R.M., 1968. Human memory: A proposed system and its control processes. *Psychol Learn Motiv* 2, 89-195.

Auyeung, B., Wheelwright, S., Allison, C., et al., 2009. The children's empathy quotient and systemizing quotient: Sex differences in typical development and in autism spectrum conditions. *Journal of autism and developmental disorders* 39, 1509.

Back, S.A., 2017. White matter injury in the preterm infant: Pathology and mechanisms. *Acta Neuropathol* 134, 331-349.

Back, S.A., Han, B.H., Luo, N.L., et al., 2002. Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. *J Neurosci* 22, 455-463.

Back, S.A., Miller, S.P., 2014. Brain injury in premature neonates: A primary cerebral dysmaturation disorder? *Ann Neurol* 75, 469-486.

Baddeley, A., 1992. Working memory. *Science* 255, 556-559.

Baddeley, A., 1996. The fractionation of working memory. *Proc Natl Acad Sci U S A* 93, 13468-13472.

Baddeley, A.D., Hitch, G., Bower, G.H., 1974. Working memory, Psychol learn motiv, pp. 47-89.

Ball, G., Aljabar, P., Arichi, T., et al., 2016. Machine-learning to characterise neonatal functional connectivity in the preterm brain. *Neuroimage* 124, 267-275.

Ball, G., Aljabar, P., Nongena, P., et al., 2017. Multimodal image analysis of clinical influences on preterm brain development. *Ann Neurol* 82, 233-246.

Ball, G., Boardman, J.P., Aljabar, P., et al., 2013a. The influence of preterm birth on the developing thalamocortical connectome. *Cortex; a journal devoted to the study of the nervous system and behavior* 49, 1711-1721.

Ball, G., Boardman, J.P., Rueckert, D., et al., 2012. The effect of preterm birth on thalamic and cortical development. *Cereb Cortex* 22, 1016-1024.

Ball, G., Pazderova, L., Chew, A., et al., 2015. Thalamocortical connectivity predicts cognition in children born preterm. *Cereb Cortex* 25, 4310-4318.

Ball, G., Srinivasan, L., Aljabar, P., et al., 2013b. Development of cortical microstructure in the preterm human brain. *Proc Natl Acad Sci U S A* 110, 9541-9546.

Ballabh, P., 2010. Intraventricular hemorrhage in premature infants: Mechanism of disease. *Pediatr Res* 67, 1-8.

Ballabh, P., 2014. Pathogenesis and prevention of intraventricular hemorrhage. *Clin Perinatol* 41, 47-67.

Banks, S.J., Eddy, K.T., Angstadt, M., et al., 2007. Amygdala–frontal connectivity during emotion regulation. *Social cognitive and affective neuroscience* 2, 303-312.

Barnea-Goraly, N., Menon, V., Eckert, M., et al., 2005. White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. *Cereb cortex* 15, 1848-1854.

Barnett, M.L., Tusor, N., Ball, G., et al., 2018. Exploring the multiple-hit hypothesis of preterm white matter damage using diffusion mri. *Neuroimage Clin* 17, 596-606.

Baron, I.S., Erickson, K., Ahronovich, M.D., et al., 2010. Spatial location memory discriminates children born at extremely low birth weight and late-preterm at age three. *Neuropsychology* 24, 787-794.

Baron, I.S., Kerns, K.A., Muller, U., et al., 2012. Executive functions in extremely low birth weight and late-preterm preschoolers: Effects on working memory and response inhibition. *Child Neuropsychol* 18, 586-599.

Barre, N., Morgan, A., Doyle, L.W., et al., 2011. Language abilities in children who were very preterm and/or very low birth weight: A meta-analysis. *J Pediatr* 158, 766-774.e761.

Barter, C., Renold, E., 2000. 'I wanna tell you a story': Exploring the application of vignettes in qualitative research with children and young people. *Int J Soc Res Methodol* 3, 307-323.

Bartha-Doering, L., Kollndorfer, K., Schwartz, E., et al., 2021. The role of the corpus callosum in language network connectivity in children. *Developmental science* 24, e13031.

Bartocci, M., Bergqvist, L.L., Lagercrantz, H., et al., 2006. Pain activates cortical areas in the preterm newborn brain. *Pain* 122, 109-117.

Basser, P.J., Mattiello, J., LeBihan, D., 1994. Mr diffusion tensor spectroscopy and imaging. *Biophysical journal* 66, 259-267.

Batalle, D., Hughes, E.J., Zhang, H., et al., 2017. Early development of structural networks and the impact of prematurity on brain connectivity. *Neuroimage* 149, 379-392.

Batalle, D., O'Muircheartaigh, J., Makropoulos, A., et al., 2019. Different patterns of cortical maturation before and after 38 weeks gestational age demonstrated by diffusion mri in vivo. *Neuroimage* 185, 764-775.

Bates, E., Dale, P.S., Thal, D., 1995. Individual differences and their implications for theories of language development, The handbook of child language, vol. 30. Blackwell, Oxford, pp. 96-151.

Baum, G.L., Cui, Z., Roalf, D.R., et al., 2020. Development of structure–function coupling in human brain networks during youth. *Proc Natl Acad Sci U S A* 117, 771.

Bayet, L., Pascalis, O., Gentaz, É., 2014. Le développement de la discrimination des expressions faciales émotionnelles chez les nourrissons dans la première année. *Annee Psychol* 114, 469-500.

Bayless, S., Pit-ten Cate, I.M., Stevenson, J., 2008. Behaviour difficulties and cognitive function in children born very prematurely. *Int J Behav Dev* 32, 206.

Bayless, S., Stevenson, J., 2006. Executive functions in school-age children born very prematurely. *Early Hum Dev* 83, 247-254.

Bayley, N., 2006. Bayley scales of infant and toddler development, Third edition ed. Harcourt Assessment Inc, San Antonio, TX.

Beaino, G., Khoshnood, B., Kaminski, M., et al., 2011. Predictors of the risk of cognitive deficiency in very preterm infants: The epipage prospective cohort. *Acta Paediatr* 100, 370-378.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system–a technical review. *NMR Biomed* 15, 435-455.

Beauport, L., Schneider, J., Faouzi, M., et al., 2017. Impact of early nutritional intake on preterm brain: A magnetic resonance imaging study. *J Pediatr* 181, 29-36.e21.

Beauregard, J.L., Drews-Botsch, C., Sales, J.M., et al., 2018. Does socioeconomic status modify the association between preterm birth and children's early cognitive ability and kindergarten academic achievement in the united states? *Am J Epidemiol* 187, 1704-1713.

Beckmann, C.F., Smith, S.M., 2004. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging* 23, 137-152.

Belfield, C., Goll, D., Sibieta, L., 2018. Socio-economic differences in total education spending in england: Middleclass welfare no more., IFS Briefing Note BN242 ed. The Institute for Fiscal Studies.

Beltempo, M., Shah, P.S., Ye, X.Y., et al., 2019. Snap-ii for prediction of mortality and morbidity in extremely preterm infants. *J Matern Fetal Neonatal Med* 32, 2694-2701.

Benavente-Fernández, I., Synnes, A., Grunau, R.E., et al., 2019. Association of socioeconomic status and brain injury with neurodevelopmental outcomes of very preterm children. *JAMA Netw Open* 2, e192914-e192914.

Bennet, L., Dhillon, S., Lear, C.A., et al., 2018. Chronic inflammation and impaired development of the preterm brain. *J Reprod Immunol* 125, 45-55.

Berger, R., Söder, S., 2015. Neuroprotection in preterm infants. *Biomed Res Int* 2015, 257139-257139.

Bernier, A., Carlson, S.M., Deschênes, M., et al., 2012. Social factors in the development of early executive functioning: A closer look at the caregiving environment. *Developmental science* 15, 12-24.

Best, J.R., Miller, P.H., Naglieri, J.A., 2011. Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. *Learn Individ Differ* 21, 327-336.

Bhutta, A.T., Cleves, M.A., Casey, P.H., et al., 2002. Cognitive and behavioral outcomes of school-aged children who were born preterm: A meta-analysis. *JAMA* 288, 728-737.

Bhutta, N., Chang, A.C., Dettling, L.J., 2020. Disparities in wealth by race and ethnicity in the 2019 survey of consumer finances.

Bierman, K.L., 2011. The promise and potential of studying the “invisible hand” of teacher influence on peer relations and student outcomes: A commentary. *J Appl Dev Psychol* 32, 297-303.

Bierstone, D., Wagenaar, N., Gano, D.L., et al., 2018. Association of histologic chorioamnionitis with perinatal brain injury and early childhood neurodevelopmental outcomes among preterm neonates. *JAMA Pediatr* 172, 534-541.

Biswal, B., Yetkin, F.Z., Haughton, V.M., et al., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magn Reson Med* 34, 537-541.

Blencowe, H., Cousens, S., Oestergaard, M.Z., et al., 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *Lancet* 379, 2162-2172.

Blesa, M., Sullivan, G., Anblagan, D., et al., 2019. Early breast milk exposure modifies brain connectivity in preterm infants. *Neuroimage* 184, 431-439.

Blondel, B., Macfarlane, A., Gissler, M., et al., 2006. Preterm birth and multiple pregnancy in european countries participating in the peristat project. *BJOG* 113, 528-535.

Boardman, J.P., Counsell, S.J., Rueckert, D., et al., 2007. Early growth in brain volume is preserved in the majority of preterm infants. *Ann Neurol* 62, 185-192.

Boardman, J.P., Counsell, S.J., Rueckert, D., et al., 2006. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. *Neuroimage* 32, 70-78.

Boardman, J.P., Craven, C., Valappil, S., et al., 2010. A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. *Neuroimage* 52, 409-414.

Bohnert, K.M., Breslau, N., 2008. Stability of psychiatric outcomes of low birth weight: A longitudinal investigation. *Arch Gen Psychiatry* 65, 1080-1086.

Bonifacio, S.L., Glass, H.C., Chau, V., et al., 2010. Extreme premature birth is not associated with impaired development of brain microstructure. *J Pediatr* 157, 726-732.e721.

Bonthrone, A.F., Chew, A., Kelly, C.J., et al., 2021. Cognitive function in toddlers with congenital heart disease: The impact of a stimulating home environment. *Infancy : the official journal of the International Society on Infant Studies* 26, 184-199.

Booth, A.T., Macdonald, J.A., Youssef, G.J., 2018. Contextual stress and maternal sensitivity: A meta-analytic review of stress associations with the maternal behavior q-sort in observational studies. *Dev Rev* 48, 145-177.

Born, A.P., Miranda, M.J., Rostrup, E., et al., 2000. Functional magnetic resonance imaging of the normal and abnormal visual system in early life. *Neuropediatrics* 31, 24-32.

Born, P., Leth, H., Miranda, M.J., et al., 1998. Visual activation in infants and young children studied by functional magnetic resonance imaging. *Pediatr Res* 44, 578-583.

Bornstein, M.H., Haynes, O.M., 1998. Vocabulary competence in early childhood: Measurement, latent construct, and predictive validity. *Child Dev* 69, 654-671.

Botting, N., Simkin, Z., Conti-Ramsden, G., 2006. Associated reading skills in children with a history of specific language impairment (sli). *Read Writ* 19, 77-98.

Bourke, C., Douglas, K., Porter, R., 2010. Processing of facial emotion expression in major depression: A review. *Aust N Z J Psychiatry* 44, 681-696.

Bouyssi-Kobar, M., Brossard-Racine, M., Jacobs, M., et al., 2018. Regional microstructural organization of the cerebral cortex is affected by preterm birth. *Neuroimage Clin* 18, 871-880.

Bouyssi-Kobar, M., De Asis-Cruz, J., Murnick, J., et al., 2019. Altered functional brain network integration, segregation, and modularity in infants born very preterm at term-equivalent age. *J Pediatr* 213, 13-21.e11.

Bouyssi-Kobar, M., du Plessis, A.J., McCarter, R., et al., 2016. Third trimester brain growth in preterm infants compared with in utero healthy fetuses. *Pediatrics* 138, e20161640.

Brauns, H., Scherer, S., Steinmann, S., 2003. The casmin educational classification in international comparative research, Advances in cross-national comparison. Springer, pp. 221-244.

Brenner, R.G., Smyser, C.D., Lean, R.E., et al., 2021. Microstructure of the dorsal anterior cingulum bundle in very preterm neonates predicts the preterm behavioral phenotype at 5 years of age. *Biol Psychiatry* 89, 433-442.

Brett, M., Leff, A.P., Rorden, C., et al., 2001. Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage* 14, 486-500.

Bricker, D., Davis, M.S., Squires, J., 2004. Mental health screening in young children. *Infants Young Child* 17, 129-144.

Briggs-Gowan, M.J., Carter, A.S., 2008. Social-emotional screening status in early childhood predicts elementary school outcomes. *Pediatrics* 121, 957-962.

Briggs-Gowan, M.J., Carter, A.S., Irwin, J.R., et al., 2004. The brief infant-toddler social and emotional assessment: Screening for social-emotional problems and delays in competence. *J Pediatr Psychol* 29, 143-155.

Brown, G., 2009. Nicu noise and the preterm infant. *Neonatal Netw* 28, 165-173.

Browne, J.V., 2004. Early relationship environments: Physiology of skin-to-skin contact for parents and their preterm infants. *Clin Perinatol* 31, 287-298.

Bruckert, L., Borchers, L.R., Dodson, C.K., et al., 2019. White matter plasticity in reading-related pathways differs in children born preterm and at term: A longitudinal analysis. *Front Hum Neurosci* 13, 139.

Brydges, C.R., Landes, J.K., Reid, C.L., et al., 2018. Cognitive outcomes in children and adolescents born very preterm: A meta‐analysis. *Dev Med Child Neurol* 60, 452-468.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: Anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124, 1-38.

Buckner, R.L., Head, D., Parker, J., et al., 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *Neuroimage* 23, 724-738.

Buckner, R.L., Vincent, J.L., 2007. Unrest at rest: Default activity and spontaneous network correlations. *Neuroimage* 37, 1091-1099.

Buhle, J.T., Silvers, J.A., Wager, T.D., et al., 2014. Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cereb Cortex* 24, 2981-2990.

Bull, R., Scerif, G., 2001. Executive functioning as a predictor of children's mathematics ability: Inhibition, switching, and working memory. *Dev Neuropsychol* 19, 273-293.

Burnett, A.C., Anderson, P.J., Lee, K.J., et al., 2018. Trends in executive functioning in extremely preterm children across 3 birth eras. *Pediatrics* 141, e20171958.

Burnett, A.C., Scratch, S.E., Anderson, P.J., 2013. Executive function outcome in preterm adolescents. *Early Hum Dev* 89, 215-220.

Buzsáki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. *Science* 304, 1926-1929.

Bystron, I., Blakemore, C., Rakic, P., 2008. Development of the human cerebral cortex: Boulder committee revisited. *Nat Rev Neurosci* 9, 110-122.

Caldú, X., Narberhaus, A., Junqué, C., et al., 2006. Corpus callosum size and neuropsychologic impairment in adolescents who were born preterm. *J Child Neurol* 21, 406-410.

Calkins, S.D., Dedmon, S.E., 2000. Physiological and behavioral regulation in two-year-old children with aggressive/destructive behavior problems. *J Abnorm Child Psychol* 28, 103-118.

Callanan, C., Doyle, L.W., Rickards, A.L., 2001. Children followed with difficulty: How do they differ? *Journal of paediatrics and child health* 37, 152-156.

Cameron, C.M., Osborne, J.M., Spinks, A.B., et al., 2017. Impact of participant attrition on child injury outcome estimates: A longitudinal birth cohort study in australia. *BMJ open* 7, e015584.

Campbell, S.B., Denham, S.A., Howarth, G.Z., et al., 2016. Commentary on the review of measures of early childhood social and emotional development: Conceptualization, critique, and recommendations. *J Appl Dev Psychol* 45, 19-41.

Cannon, M., Jones, P., Gilvarry, C., et al., 1997. Premorbid social functioning in schizophrenia and bipolar disorder: Similarities and differences. *Am J Psychiatry* 154, 1544-1550.

Caravale, B., Sette, S., Cannoni, E., et al., 2017. Sleep characteristics and temperament in preterm children at two years of age. *J Clin Sleep Med* 13, 1081-1088.

Carthy, T., Horesh, N., Apter, A., et al., 2010. Patterns of emotional reactivity and regulation in children with anxiety disorders. *Journal of psychopathology and behavioral assessment* 32, 23-36.

Casey, B.J., Getz, S., Galvan, A., 2008. The adolescent brain. *Dev Rev* 28, 62-77.

Casey, B.J., Giedd, J.N., Thomas, K.M., 2000. Structural and functional brain development and its relation to cognitive development. *Biol Psychol* 54, 241-257.

Casey, B.J., Heller, A.S., Gee, D.G., et al., 2019. Development of the emotional brain. *Neuroscience letters* 693, 29-34.

Cassiano, R.G.M., Gaspardo, C.M., Linhares, M.B.M., 2019. Temperament moderated by neonatal factors predicted behavioral problems in childhood: A prospective longitudinal study. *Early Hum Dev* 135, 37-43.

Catani, M., Dell'Acqua, F., De Schotten, M.T., 2013. A revised limbic system model for memory, emotion and behaviour. *Neuroscience and biobehavioral reviews* 37, 1724-1737.

Chau, V., Brant, R., Poskitt, K.J., et al., 2012. Postnatal infection is associated with widespread abnormalities of brain development in premature newborns. *Pediatr Res* 71, 274-279.

Chau, V., Poskitt, K.J., McFadden, D.E., et al., 2009. Effect of chorioamnionitis on brain development and injury in premature newborns. *Ann Neurol* 66, 155-164.

Chawanpaiboon, S., Vogel, J.P., Moller, A.B., et al., 2019. Global, regional, and national estimates of levels of preterm birth in 2014: A systematic review and modelling analysis. *Lancet Glob Health* 7, e37-e46.

Chen, C.-H., Suckling, J., Ooi, C., et al., 2008. Functional coupling of the amygdala in depressed patients treated with antidepressant medication. *Neuropsychopharmacology* 33, 1909-1918.

Chen, X., 2011. Culture and children's socioemotional functioning: A contextual-developmental perspective, in: Rubin, X.C.K.H. (Ed.), Socioemotional development in cultural context. The Guilford Press, pp. 29-53.

Chen, X.-K., Wen, S.W., Fleming, N., et al., 2007. Teenage pregnancy and adverse birth outcomes: A large population based retrospective cohort study. *Int J Epidemiol* 36, 368-373.

Cheng, W., Rolls, E.T., Qiu, J., et al., 2018. Functional connectivity of the human amygdala in health and in depression. *Social cognitive and affective neuroscience* 13, 557-568.

Chung, M.K., Worsley, K.J., Paus, T., et al., 2001. A unified statistical approach to deformation-based morphometry. *Neuroimage* 14, 595-606.

Cicchetti, D., 1997. Emotion regulation checklist : Ers. [Rochester, N.Y. : Mt. Hope Family Center], [publisher not identified], [1997] ©1997.

Cicchetti, D., Cannon, T.D., 1999. Neurodevelopmental processes in the ontogenesis and epigenesis of psychopathology. *Dev Psychopathol* 11, 375-393.

Cicchetti, D., Toth, S.L., 2014. Internalizing and externalizing expressions of dysfunction: Volume 2. Psychology Press.

Cisler, J.M., Olatunji, B.O., Feldner, M.T., et al., 2010. Emotion regulation and the anxiety disorders: An integrative review. *Journal of psychopathology and behavioral assessment* 32, 68-82.

Cismaru, A.L., Gui, L., Vasung, L., et al., 2016. Altered amygdala development and fear processing in prematurely born infants. *Front Neuroanat* 10, 55.

Clark, C.A., Woodward, L.J., Horwood, L.J., et al., 2008. Development of emotional and behavioral regulation in children born extremely preterm and very preterm: Biological and social influences. *Child Dev* 79, 1444-1462.

Clausson, B., Lichtenstein, P., Cnattingius, S., 2000. Genetic influence on birthweight and gestational length determined by studies in offspring of twins. *BJOG* 107, 375-381.

Cockburn, F., Cooke, R., Gamsu, H., et al., 1993. The crib (clinical risk index for babies) score: A tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. *Lancet* 342, 193-198.

Cocodia, E.A., 2014. Cultural perceptions of human intelligence. *J Intell* 2, 180-196.

Cohen-Gilbert, J.E., Thomas, K.M., 2013. Inhibitory control during emotional distraction across adolescence and early adulthood. *Child Dev* 84, 1954-1966.

Collins, J.W., Jr., David, R.J., Handler, A., et al., 2004. Very low birthweight in african american infants: The role of maternal exposure to interpersonal racial discrimination. *Am J Public Health* 94, 2132-2138.

Collins, J.W., Jr., David, R.J., Simon, D.M., et al., 2007. Preterm birth among african american and white women with a lifelong residence in high-income chicago neighborhoods: An exploratory study. *Ethn Dis* 17, 113-117.

Collins, S.E., Spencer-Smith, M., Mürner-Lavanchy, I., et al., 2019. White matter microstructure correlates with mathematics but not word reading performance in 13-year-old children born very preterm and full-term. *Neuroimage Clin* 24, 101944.

Collins, S.E., Thompson, D.K., Kelly, C.E., et al., 2021. Development of brain white matter and math computation ability in children born very preterm and full-term *Dev Cogn Neurosci* 51, 100987.

Constable, R.T., Ment, L.R., Vohr, B.R., et al., 2008. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: An investigation of group and gender effects. *Pediatrics* 121, 306-316.

Constantino, J.N., Gruber, C.P., 2002. The social responsiveness scale. Western Psychological Services, Los Angeles.

Constantino, J.N., Gruber, C.P., 2012. Social responsiveness scale second edition (srs-2): Manual. Western Psychological Services (WPS).

Conti‐Ramsden, G., Durkin, K., Simkin, Z., et al., 2009. Specific language impairment and school outcomes. I: Identifying and explaining variability at the end of compulsory education. *International journal of language & communication disorders / Royal College of Speech & Language Therapists* 44, 15-35.

Cooke, R.W., Abernethy, L.J., 1999. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. *Arch Dis Child Fetal Neonatal Ed* 81, F116-F121.

Cordeiro, C.N., Tsimis, M., Burd, I., 2015. Infections and brain development. *Obstet Gynecol Surv* 70, 644-655.

Costello, A.B., Osborne, J., 2005. Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical Assessment, Research & Evaluation* 10, 1-9.

Costello, E.J., Compton, S.N., Keeler, G., et al., 2003. Relationships between poverty and psychopathologya natural experiment. *JAMA* 290, 2023-2029.

Counsell, S.J., Boardman, J.P., 2005. Differential brain growth in the infant born preterm: Current knowledge and future developments from brain imaging. *Semin Fetal Neonatal Med* 10, 403-410.

Counsell, S.J., Edwards, A.D., Chew, A.T., et al., 2008. Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. *Brain* 131, 3201-3208.

Counsell, S.J., Shen, Y., Boardman, J.P., et al., 2006. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. *Pediatrics* 117, 376-386.

Cowan, N., 1997. The development of working memory, The development of memory in childhood Psychology Press/Erlbaum, Taylor & Francis. , pp. 163-199.

Cowan, N., 2008. What are the differences between long-term, short-term, and working memory? *Prog Brain Res* 169, 323-338.

Cowan, N., Wood, N.L., Wood, P.K., et al., 1998. Two separate verbal processing rates contributing to short-term memory span. *J Exp Psychol Gen* 127, 141.

Crosby Budinger, M., Drazdowski, T.K., Ginsburg, G.S., 2013. Anxiety-promoting parenting behaviors: A comparison of anxious parents with and without social anxiety disorder. *Child Psychiatry Hum Dev* 44, 412-418.

Cullen, K.R., Westlund, M.K., Klimes-Dougan, B., et al., 2014. Abnormal amygdala resting-state functional connectivity in adolescent depression. *JAMA Psychiatry* 71, 1138-1147.

Cummings, C.M., Caporino, N.E., Kendall, P.C., 2014. Comorbidity of anxiety and depression in children and adolescents: 20 years after. *Psychological bulletin* 140, 816-845.

Cummings, J.L., 1993. Frontal-subcortical circuits and human behavior. *Arch Neurol* 50, 873-880.

Currie, C., Molcho, M., Boyce, W., et al., 2008. Researching health inequalities in adolescents: The development of the health behaviour in school-aged children (hbsc) family affluence scale. *Soc Sci Med* 66, 1429-1436.

Curtis, W.J., Lindeke, L.L., Georgieff, M.K., et al., 2002. Neurobehavioural functioning in neonatal intensive care unit graduates in late childhood and early adolescence. *Brain* 125, 1646-1659.

Daamen, M., Bauml, J.G., Scheef, L., et al., 2014. Working memory in preterm-born adults: Load-dependent compensatory activity of the posterior default mode network. *Hum Brain Mapp* 36, 1121-1137.

Dahl, L.B., Kaaresen, P.I., Tunby, J., et al., 2006. Emotional, behavioral, social, and academic outcomes in adolescents born with very low birth weight. *Pediatrics* 118, e449-459.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9, 179-194.

Dale, A.M., Halgren, E., 2001. Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Curr Opin Neurobiol* 11, 202-208.

Dalrymple, K.A., Gomez, J., Duchaine, B., 2013. The dartmouth database of children's faces: Acquisition and validation of a new face stimulus set. *PLoS One* 8, e79131.

Damaraju, E., Phillips, J.R., Lowe, J.R., et al., 2010. Resting-state functional connectivity differences in premature children. *Front Syst Neurosci* 4, 23.

Dammann, O., Naples, M., Bednarek, F., et al., 2010. Snap-ii and snappe-ii and the risk of structural and functional brain disorders in extremely low gestational age newborns: The elgan study. *Neonatology* 97, 71-82.

Dammann, O., Shah, B., Naples, M., et al., 2009. Interinstitutional variation in prediction of death by snap-ii and snappe-ii among extremely preterm infants. *Pediatrics* 124, e1001-1006.

de Bie, H.M., Boersma, M., Adriaanse, S., et al., 2012. Resting-state networks in awake five- to eight-year old children. *Hum Brain Mapp* 33, 1189-1201.

de Boo, G.M., Kolk, A.M., 2007. Ethnic and gender differences in temperament, and the relationship between temperament and depressive and aggressive mood. *Pers Individ Dif* 43, 1756-1766.

de Kieviet, J.F., van Elburg, R.M., Lafeber, H.N., et al., 2012a. Attention problems of very preterm children compared with age-matched term controls at school-age. *J Pediatr* 161, 824-829.

de Kieviet, J.F., Zoetebier, L., van Elburg, R.M., et al., 2012b. Brain development of very preterm and very low-birthweight children in childhood and adolescence: A meta-analysis. *Dev Med Child Neurol* 54, 313-323.

De Los Reyes, A., 2011. Introduction to the special section: More than measurement error: Discovering meaning behind informant discrepancies in clinical assessments of children and adolescents. *Clin Child Adolesc Psychol* 40, 1-9.

Dean, B., Ginnell, L., Boardman, J.P., et al., 2021. Social cognition following preterm birth: A systematic review. *Neuroscience and biobehavioral reviews* 124, 151-167.

Dekaban, A.S., Sadowsky, D., 1978. Changes in brain weights during the span of human life: Relation of brain weights to body heights and body weights. *Annals of Neurology* 4, 345-356.

Delane, L., Campbell, C., Bayliss, D.M., et al., 2017. Poorer divided attention in children born very preterm can be explained by difficulty with each component task, not the executive requirement to dual-task. *Child Neuropsychol* 23, 510-522.

Delnord, M., Blondel, B., Zeitlin, J., 2015. What contributes to disparities in the preterm birth rate in european countries? *Curr Opin Obstet Gynecol* 27, 133-142.

Delobel-Ayoub, M., Arnaud, C., White-Koning, M., et al., 2009. Behavioral problems and cognitive performance at 5 years of age after very preterm birth: The epipage study. *Pediatrics* 123, 1485-1492.

Denham, S.A., 1998. Emotional development in young children. Guilford Press.

Derryberry, D., Reed, M.A., 2001. A multidisciplinary perspective on attentional control, in: Charles Folk, B.G. (Ed.), Attraction, distraction and action, vol. 133, p. 325.

Derryberry, D., Rothbart, M.K., 1997. Reactive and effortful processes in the organization of temperament. *Dev Psychopathol* 9, 633-652.

Di Tella, M., Miti, F., Ardito, R.B., et al., 2020. Social cognition and sex: Are men and women really different? *Pers Individ Dif* 162, 110045.

Dibben, C., Clemens, T., 2015. Place of work and residential exposure to ambient air pollution and birth outcomes in scotland, using geographically fine pollution climate mapping estimates. *Environ Res* 140, 535-541.

Diez-Roux, A.V., Kiefe, C.I., Jacobs, D.R., Jr., et al., 2001. Area characteristics and individual-level socioeconomic position indicators in three population-based epidemiologic studies. *Ann Epidemiol* 11, 395-405.

Dimitrova, R., Arulkumaran, S., Carney, O., et al., 2021. Phenotyping the preterm brain: Characterizing individual deviations from normative volumetric development in two large infant cohorts. *Cereb Cortex* 31, 3665-3677.

Dimitrova, R., Pietsch, M., Christiaens, D., et al., 2020. Heterogeneity in brain microstructural development following preterm birth. *Cereb Cortex* 30, 4800-4810.

Dodd, H.F., Rayson, H., Ryan, Z., et al., 2020. Trajectories of anxiety when children start school: The role of behavioral inhibition and attention bias to angry and happy faces. *J Abnorm Psychol* 129, 701-712.

Dodson, C.K., Travis, K.E., Ben-Shachar, M., et al., 2017. White matter microstructure of 6-year old children born preterm and full term. *Neuroimage Clin* 16, 268-275.

Doria, V., Beckmann, C.F., Arichi, T., et al., 2010. Emergence of resting state networks in the preterm human brain. *Proc Natl Acad Sci U S A* 107, 20015-20020.

Dorling, J., Field, D., Manktelow, B., 2005. Neonatal disease severity scoring systems. *Arch Dis Child Fetal Neonatal Ed* 90, F11-F16.

Doyle, L.W., Cheong, J.L., Burnett, A., et al., 2015. Biological and social influences on outcomes of extreme-preterm/low-birth weight adolescents. *Pediatrics* 136, e1513-e1520.

Dubner, S.E., Dodson, C.K., Marchman, V.A., et al., 2019. White matter microstructure and cognitive outcomes in relation to neonatal inflammation in 6-year-old children born preterm. *Neuroimage Clin* 23, 101832.

Dubner, S.E., Rose, J., Bruckert, L., et al., 2020. Neonatal white matter tract microstructure and 2-year language outcomes after preterm birth. *Neuroimage Clin* 28, 102446.

Dubois, J., Benders, M., Cachia, A., et al., 2008. Mapping the early cortical folding process in the preterm newborn brain. *Cereb Cortex* 18, 1444-1454.

Dubois, M., Legouhy, A., Corouge, I., et al., 2021a. Multiparametric analysis of cerebral development in preterm infants using magnetic resonance imaging. *Front Neurosci* 15, 658002-658002.

Dubois, M., Legouhy, A., Corouge, I., et al., 2021b. Multiparametric analysis of cerebral development in preterm infants using magnetic resonance imaging. *Front Neurosci* 15, 658002-658002.

Ducharme, S., Albaugh, M.D., Hudziak, J.J., et al., 2014. Anxious/depressed symptoms are linked to right ventromedial prefrontal cortical thickness maturation in healthy children and young adults. *Cereb Cortex* 24, 2941-2950.

Duerden, E.G., Card, D., Lax, I.D., et al., 2013. Alterations in frontostriatal pathways in children born very preterm. *Dev Med Child Neurol* 55, 952-958.

Duerden, E.G., Foong, J., Chau, V., et al., 2015. Tract-based spatial statistics in preterm-born neonates predicts cognitive and motor outcomes at 18 months. *AJNR Am J Neuroradiol* 36, 1565-1571.

Duerden, E.G., Grunau, R.E., Guo, T., et al., 2018. Early procedural pain is associated with regionally-specific alterations in thalamic development in preterm neonates. *J Neurosci* 38, 878-886.

Duerden, E.G., Guo, T., Dodbiba, L., et al., 2016. Midazolam dose correlates with abnormal hippocampal growth and neurodevelopmental outcome in preterm infants. *Ann Neurol* 79, 548-559.

Duncan, G.J., Magnuson, K., 2012. Socioeconomic status and cognitive functioning: Moving from correlation to causation. *Wiley Interdiscip Rev Cogn Sci* 3, 377-386.

DuPaul, G.J., Power, T.J., Anastopoulos, A.D., et al., 1998. Adhd rating scale—iv: Checklists, norms, and clinical interpretation. Guilford Press.

Durbin, C.E., Hayden, E.P., Klein, D.N., et al., 2007. Stability of laboratory-assessed temperamental emotionality traits from ages 3 to 7. *Emotion* 7, 388-399.

Durkin, K., Conti‐Ramsden, G., 2007. Language, social behavior, and the quality of friendships in adolescents with and without a history of specific language impairment. *Child Dev* 78, 1441-1457.

Dykas, M.J., Cassidy, J., 2011. Attachment and the processing of social information across the life span: Theory and evidence. *Psychological bulletin* 137, 19.

Eden, A.S., Schreiber, J., Anwander, A., et al., 2015. Emotion regulation and trait anxiety are predicted by the microstructure of fibers between amygdala and prefrontal cortex. *J Neurosci* 35, 6020-6027.

Edwards, A.D., Redshaw, M.E., Kennea, N., et al., 2018. Effect of mri on preterm infants and their families: A randomised trial with nested diagnostic and economic evaluation. *Arch Dis Child Fetal Neonatal Ed* 103, F15-F21.

Eggum-Wilkens, N.D., Lemery-Chalfant, K., Aksan, N., et al., 2015. Self-conscious shyness: Growth during toddlerhood, strong role of genetics, and no prediction from fearful shyness. *Infancy : the official journal of the International Society on Infant Studies* 20, 160-188.

Eisenberg, N., Cumberland, A., Spinrad, T.L., et al., 2001. The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Dev* 72, 1112-1134.

Eisenberg, N., Shepard, S.A., Fabes, R.A., et al., 1998. Shyness and children's emotionality, regulation, and coping: Contemporaneous, longitudinal, and across‐context relations. *Child dev* 69, 767-790.

Eisenberg, N., Smith, C.L., Spinrad, T.L., 2011. Effortful control: Relations with emotion regulation, adjustment, and socialization in childhood, Handbook of self-regulation: Research, theory, and applications, 2nd ed. Guilford Press, New York, NY, US, pp. 263-283.

Eisner, N.L., Murray, A.L., Eisner, M., et al., 2019. A practical guide to the analysis of non-response and attrition in longitudinal research using a real data example. *Int J Behav Dev* 43, 24-34.

Eklind, S., Mallard, C., Leverin, A.L., et al., 2001. Bacterial endotoxin sensitizes the immature brain to hypoxic--ischaemic injury. *The European journal of neuroscience* 13, 1101-1106.

Engle, R.W., Tuholski, S.W., Laughlin, J.E., et al., 1999. Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *J Exp Psychol Gen* 128, 309.

Epstein, N.B., Ryan, C.E., Bishop, D.S., et al., 2003. The mcmaster model: A view of healthy family functioning. The Guilford Press.

Erberich, S.G., Friedlich, P., Seri, I., et al., 2003. Functional mri in neonates using neonatal head coil and mr compatible incubator. *Neuroimage* 20, 683-692.

Erberich, S.G., Panigrahy, A., Friedlich, P., et al., 2006. Somatosensory lateralization in the newborn brain. *Neuroimage* 29, 155-161.

Eriksen, B.A., Eriksen, C.W., 1974. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & psychophysics* 16, 143-149.

Eryigit-Madzwamuse, S., Strauss, V., Baumann, N., et al., 2015. Personality of adults who were born very preterm. *Arch Dis Child Fetal Neonatal Ed* 100, F524-529.

Everitt, B.S., 1975. Multivariate analysis: The need for data, and other problems. *Br J Psychiatry* 126, 237-240.

Eyre, M., Fitzgibbon, S.P., Ciarrusta, J., et al., 2021. The developing human connectome project: Typical and disrupted perinatal functional connectivity. *Brain* 144, 2199-2213.

Ezz-Eldin, Z.M., Hamid, T.A.A., Youssef, M.R.L., et al., 2015. Clinical risk index for babies (crib ii) scoring system in prediction of mortality in premature babies. *JCDR* 9, SC08.

Fabes, R.A., Gaertner, B.M., Popp, T.K., 2006. Getting along with others: Social competence in early childhood, Blackwell handbook of early childhood development. Blackwell Publishing, pp. 297-316.

Fair, D.A., Cohen, A.L., Power, J.D., et al., 2009. Functional brain networks develop from a “local to distributed” organization. *PLoS Comput Biol* 5, e1000381.

Fan, F., Liao, X., Lei, T., et al., 2021. Development of the default-mode network during childhood and adolescence: A longitudinal resting-state fmri study. *Neuroimage* 226, 117581.

Fan, J., McCandliss, B.D., Fossella, J., et al., 2005. The activation of attentional networks. *Neuroimage* 26, 471-479.

Fan, J., McCandliss, B.D., Sommer, T., et al., 2002. Testing the efficiency and independence of attentional networks. *J Cogn Neurosci* 14, 340-347.

Fantuzzo, J., McWayne, C., 2002. The relationship between peer-play interactions in the family context and dimensions of school readiness for low-income preschool children. *J Educ Psychol* 94, 79.

Faridpour, F., Shirinabadi Farahani, A., Rassouli, M., et al., 2020. Clinical risk index for babies (crib-ii) scoring system in prediction of mortality risk in preterm neonates in the first 24 hour. *Evidence Based Care* 10, 58-63.

Feldman, H.M., Lee, E.S., Yeatman, J.D., et al., 2012. Language and reading skills in school-aged children and adolescents born preterm are associated with white matter properties on diffusion tensor imaging. *Neuropsychologia* 50, 3348-3362.

Fenchel, D., Dimitrova, R., Seidlitz, J., et al., 2020. Development of microstructural and morphological cortical profiles in the neonatal brain. *Cereb Cortex* 30, 5767-5779.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., et al., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience and biobehavioral reviews* 35, 573-588.

Fischi-Gomez, E., Vasung, L., Meskaldji, D.E., et al., 2014. Structural brain connectivity in school-age preterm infants provides evidence for impaired networks relevant for higher order cognitive skills and social cognition. *Cereb Cortex* 25, 2793-2805.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A* 97, 11050-11055.

Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis: Ii: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9, 195-207.

Fisher, A., Thiessen, E., Godwin, K., et al., 2013. Assessing selective sustained attention in 3- to 5-year-old children: Evidence from a new paradigm. *J Exp Child Psychol* 114, 275-294.

Fitzallen, G.C., Taylor, H.G., Bora, S., 2020. What do we know about the preterm behavioral phenotype? A narrative review. *Front Psychiatry* 11, 154.

Fitzgibbon, S.P., Harrison, S.J., Jenkinson, M., et al., 2020. The developing human connectome project (dhcp) automated resting-state functional processing framework for newborn infants. *Neuroimage* 223, 117303.

Forbes, M.K., Rapee, R.M., Camberis, A.L., et al., 2017. Unique associations between childhood temperament characteristics and subsequent psychopathology symptom trajectories from childhood to early adolescence. *J Abnorm Child Psychol* 45, 1221-1233.

Ford, D.Y., 2005. Intelligence testing and cultural diversity: Pitfalls and promises, Newsletter of National research Center on Gifted and talented.

Fornito, A., Bullmore, E.T., 2015. Connectomics: A new paradigm for understanding brain disease. *Eur Neuropsychopharmacol* 25, 733-748.

Foster-Cohen, S.H., Friesen, M.D., Champion, P.R., et al., 2010. High prevalence/low severity language delay in preschool children born very preterm. *J Dev Behav Pediatr* 31, 658-667.

Fransson, P., Åden, U., Blennow, M., et al., 2011. The functional architecture of the infant brain as revealed by resting-state fmri. *Cereb Cortex* 21, 145-154.

Fransson, P., Skiold, B., Horsch, S., et al., 2007. Resting-state networks in the infant brain. *Proc Natl Acad Sci U S A* 104, 15531-15536.

Freberg, M.E., Vandiver, B.J., Watkins, M.W., et al., 2008. Significant factor score variability and the validity of the wisc-iii full scale iq in predicting later academic achievement. *Appl Neuropsychol* 15, 131-139.

Freeman Duncan, A., Watterberg, K.L., Nolen, T.L., et al., 2012. Effect of ethnicity and race on cognitive and language testing at age 18-22 months in extremely preterm infants. *J Pediatr* 160, 966-971.e962.

Friederici, A.D., Alter, K., 2004. Lateralization of auditory language functions: A dynamic dual pathway model. *Brain Lang* 89, 267-276.

Fry, A.F., Hale, S., 2000. Relationships among processing speed, working memory, and fluid intelligence in children. *Biol Psychol* 54, 1-34.

Fuchs, F., Monet, B., Ducruet, T., et al., 2018. Effect of maternal age on the risk of preterm birth: A large cohort study. *PLoS One* 13, e0191002.

Fukunaga, M., Horovitz, S.G., van Gelderen, P., et al., 2006. Large-amplitude, spatially correlated fluctuations in bold fmri signals during extended rest and early sleep stages. *Magn Reson Imaging* 24, 979-992.

Fulwiler, C.E., King, J.A., Zhang, N., 2012. Amygdala-orbitofrontal resting state functional connectivity is associated with trait anger. *Neuroreport* 23, 606.

Gainotti, G., 2019. The role of the right hemisphere in emotional and behavioral disorders of patients with frontotemporal lobar degeneration: An updated review. *Front Aging Neurosci* 11, 55.

Gajamange, S., Raffelt, D., Dhollander, T., et al., 2018. Fibre-specific white matter changes in multiple sclerosis patients with optic neuritis. *Neuroimage Clin* 17, 60-68.

Galbraith, S., Bowden, J., Mander, A., 2017. Accelerated longitudinal designs: An overview of modelling, power, costs and handling missing data. *Stat Methods Med Res* 26, 374-398.

Galdi, P., Blesa, M., Stoye, D.Q., et al., 2020. Neonatal morphometric similarity mapping for predicting brain age and characterizing neuroanatomic variation associated with preterm birth. *Neuroimage Clin* 25, 102195.

Gao, W., Gilmore, J.H., Shen, D., et al., 2013. The synchronization within and interaction between the default and dorsal attention networks in early infancy. *Cereb Cortex* 23, 594-603.

Gao, W., Zhu, H., Giovanello, K.S., et al., 2009. Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proc Natl Acad Sci U S A* 106, 6790-6795.

Gao, X., Maurer, D., 2009. Influence of intensity on children's sensitivity to happy, sad, and fearful facial expressions. *J Exp Child Psychol* 102, 503-521.

Gao, X., Maurer, D., 2010. A happy story: Developmental changes in children's sensitivity to facial expressions of varying intensities. *J Exp Child Psychol* 107, 67-86.

Gardner, F., 2000. Methodological issues in the direct observation of parent–child interaction: Do observational findings reflect the natural behavior of participants? *Clin Child Fam Psychol Rev* 3, 185-198.

Gardner, M.O., Goldenberg, R.L., Cliver, S.P., et al., 1995. The origin and outcome of preterm twin pregnancies. *Obstet Gynecol* 85, 553-557.

Garg, B., Sharma, D., Farahbakhsh, N., 2018. Assessment of sickness severity of illness in neonates: Review of various neonatal illness scoring systems. *J Matern Fetal Neonatal Med* 31, 1373-1380.

Garon, N., Bryson, S.E., Smith, I.M., 2008. Executive function in preschoolers: A review using an integrative framework. *Psychological bulletin* 134, 31-60.

Gartstein, M.A., Putnam, S.P., Rothbart, M.K., 2012. Etiology of preschool behavior problems: Contributions of temperament attributes in early childhood. *Infant Ment Health J* 33, 197-211.

Gee, D.G., Humphreys, K.L., Flannery, J., et al., 2013. A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *J Neurosci* 33, 4584-4593.

Genc, S., Smith, R.E., Malpas, C.B., et al., 2018. Development of white matter fibre density and morphology over childhood: A longitudinal fixel-based analysis. *Neuroimage* 183, 666-676.

Genova, H.M., Rajagopalan, V., Chiaravalloti, N., et al., 2015. Facial affect recognition linked to damage in specific white matter tracts in traumatic brain injury. *Social neuroscience* 10, 27-34.

Gholipour, A., Estroff, J.A., Barnewolt, C.E., et al., 2011. Fetal brain volumetry through mri volumetric reconstruction and segmentation. *Int J Comput Assist Radiol Surg* 6, 329-339.

Gibson‐Davis, C., Keister, L.A., Gennetian, L.A., 2021. Net worth poverty in child households by race and ethnicity, 1989–2019. *J Marriage Fam* 83, 667-682.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., et al., 1999. Brain development during childhood and adolescence: A longitudinal mri study. *Nat Neurosci* 2, 861-863.

Giedd, J.N., Vaituzis, A.C., Hamburger, S.D., et al., 1996. Quantitative mri of the temporal lobe, amygdala, and hippocampus in normal human development: Ages 4-18 years. *J.Comp Neurol.* 366, 223-230.

Gilchrist, C.P., Thompson, D.K., Alexander, B., et al., 2021. Growth of prefrontal and limbic brain regions and anxiety disorders in children born very preterm. *Psychol Med* 9, 1-12.

Gimenez, M., Junque, C., Narberhaus, A., et al., 2006a. White matter volume and concentration reductions in adolescents with history of very preterm birth: A voxel-based morphometry study. *Neuroimage* 32, 1485-1498.

Giménez, M., Junqué, C., Narberhaus, A., et al., 2006. Correlations of thalamic reductions with verbal fluency impairment in those born prematurely. *Neuroreport* 17, 463-466.

Gimenez, M., Junque, C., Vendrell, P., et al., 2006b. Abnormal orbitofrontal development due to prematurity. *Neurology* 67, 1818-1822.

Gioia, G.A., Andrwes, K., Isquith, P.K., 1996. Behavior rating inventory of executive function-preschool version (brief-p). Psychological Assessment Resources Odessa, FL.

Gioia, G.A., Isquith, P.K., Guy, S.C., et al., 2000. Behavior rating inventory of executive function. *Child Neuropsychol* 6, 235-238.

Glinianaia, S.V., Ghosh, R., Rankin, J., et al., 2013. No improvement in socioeconomic inequalities in birthweight and preterm birth over four decades: A population-based cohort study. *BMC Public Health* 13, 345.

Goldenberg, R.L., Culhane, J.F., Iams, J.D., et al., 2008. Epidemiology and causes of preterm birth. *Lancet* 371, 75-84.

Good, C.D., Johnsrude, I.S., Ashburner, J., et al., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14, 21-36.

Goodman, A., Goodman, R., 2009. Strengths and difficulties questionnaire as a dimensional measure of child mental health. *Journal of the American Academy of Child and Adolescent Psychiatry* 48, 400-403.

Goodman, R., 1997. The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry* 38, 581-586.

Goodman, R., 2001. Psychometric properties of the strengths and difficulties questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry* 40, 1337-1345.

Goodman, R., Ford, T., Simmons, H., et al., 2000. Using the strengths and difficulties questionnaire (sdq) to screen for child psychiatric disorders in a community sample. *Br J Psychiatry* 177, 534-539.

Goodman, R., Scott, S., 1999. Comparing the strengths and difficulties questionnaire and the child behavior checklist: Is small beautiful? *J Abnorm Child Psychol* 27, 17-24.

Gosselin, P., 1995. Le développement de la reconnaissance des expressions faciales des émotions chez l'enfant. *Can J Behav Sci* 27, 107.

Gozzo, Y., Vohr, B., Lacadie, C., et al., 2009. Alterations in neural connectivity in preterm children at school age. *Neuroimage* 48, 458-463.

Grabenhorst, F., Rolls, E.T., 2011. Value, pleasure and choice in the ventral prefrontal cortex. *Trends Cogn Sci* 15, 56-67.

Gracioli, S.M.A., Linhares, M.B.M., 2019. Neonatal and temperament variables predict behavior problems of preterm children at toddlerhood. *J Hum Growth Devel* 29, 313-324.

Graven, S.N., 2000. Sound and the developing infant in the nicu: Conclusions and recommendations for care. *J Perinatol* 20, S88-93.

Grayson, D.S., Fair, D.A., 2017. Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature. *Neuroimage* 160, 15-31.

Greenberg, D.L., Rice, H.J., Cooper, J.J., et al., 2005. Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. *Neuropsychologia* 43, 659-674.

Greene, M.M., Patra, K., Nelson, M.N., et al., 2012. Evaluating preterm infants with the bayley-iii: Patterns and correlates of development. *Res Dev Disabil* 33, 1948-1956.

Greenwood, S., Abdel‐Latif, M.E., Bajuk, B., et al., 2012. Can the early condition at admission of a high‐risk infant aid in the prediction of mortality and poor neurodevelopmental outcome? A population study in australia. *Journal of paediatrics and child health* 48, 588-595.

Greicius, M.D., Kiviniemi, V., Tervonen, O., et al., 2008. Persistent default-mode network connectivity during light sedation. *Hum Brain Mapp* 29, 839-847.

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C.F., et al., 2014. Ica-based artefact removal and accelerated fmri acquisition for improved resting state network imaging. *Neuroimage* 95, 232-247.

Groenewegen, H.J., Voorn, P., Berendse, H.W., et al., 2009. The basal ganglia ix. Springer Science & Business Media.

Groeschel, S., Tournier, J.D., Northam, G.B., et al., 2014. Identification and interpretation of microstructural abnormalities in motor pathways in adolescents born preterm. *Neuroimage* 87, 209-219.

Groppo, M., Ricci, D., Bassi, L., et al., 2012. Development of the optic radiations and visual function after premature birth. *Cortex; a journal devoted to the study of the nervous system and behavior* 56, 30-37.

Gross, J., Baillet, S., Barnes, G.R., et al., 2013. Good practice for conducting and reporting meg research. *Neuroimage* 65, 349-363.

Gu, S., Satterthwaite, T.D., Medaglia, J.D., et al., 2015. Emergence of system roles in normative neurodevelopment. *Proc Natl Acad Sci U S A* 112, 13681-13686.

Guo, X., Duan, X., Long, Z., et al., 2016. Decreased amygdala functional connectivity in adolescents with autism: A resting-state fmri study. *Psychiatry Res Neuroimaging* 257, 47-56.

Hack, M., Klein, N.K., Taylor, H.G., 1995. Long-term developmental outcomes of low birth weight infants. *Future Child* 5, 176-196.

Hackman, D.A., Farah, M.J., 2009. Socioeconomic status and the developing brain. *Trends Cogn Sci* 13, 65-73.

Hadwin, J.A., Field, A.P., 2010. Information processing biases and anxiety: A developmental perspective. John Wiley & Sons.

Hadwin, J.A., Garner, M., Perez-Olivas, G., 2006. The development of information processing biases in childhood anxiety: A review and exploration of its origins in parenting. *Clin Psychol Rev* 26, 876-894.

Hagberg, H., Mallard, C., Ferriero, D.M., et al., 2015. The role of inflammation in perinatal brain injury. *Nat Rev Neurol* 11, 192-208.

Hahn, A., Stein, P., Windischberger, C., et al., 2011. Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *Neuroimage* 56, 881-889.

Hajat, A., Hsia, C., O'Neill, M.S., 2015. Socioeconomic disparities and air pollution exposure: A global review. *Curr Environ Health Rep* 2, 440-450.

Hall, J., Wolke, D., 2012. A comparison of prematurity and small for gestational age as risk factors for age 6-13 year emotional problems. *Early Hum Dev* 88, 797-804.

Hamilton, B.E., Minino, A.M., Martin, J.A., et al., 2007. Annual summary of vital statistics: 2005. *Pediatrics* 119, 345-360.

Hamrick, S.E., Miller, S.P., Leonard, C., et al., 2004. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: The role of cystic periventricular leukomalacia. *J Pediatr* 145, 593-599.

Hannam, K., McNamee, R., Baker, P., et al., 2014. Air pollution exposure and adverse pregnancy outcomes in a large uk birth cohort: Use of a novel spatio-temporal modelling technique. *Scand J Work Environ Health* 40, 518-530.

Hansen, C., Neller, A., Williams, G., et al., 2006. Maternal exposure to low levels of ambient air pollution and preterm birth in brisbane, australia. *BJOG* 113, 935-941.

Hariri, A.R., Tessitore, A., Mattay, V.S., et al., 2002. The amygdala response to emotional stimuli: A comparison of faces and scenes. *Neuroimage* 17, 317-323.

Hart, D., Atkins, R., Fegley, S., et al., 2003. Personality and development in childhood: A person-centered approach. *Monogr Soc Res Child Dev* 68, 1-109.

Hart, D., Hofmann, V., Edelstein, W., et al., 1997. The relation of childhood personality types to adolescent behavior and development: A longitudinal study of icelandic children. *Dev Psychol* 33, 195.

Hasegawa, T., Yamada, K., Morimoto, M., et al., 2011. Development of corpus callosum in preterm infants is affected by the prematurity: In vivo assessment of diffusion tensor imaging at term-equivalent age. *Pediatr Res* 69, 249-254.

Hasler, H.M., Akshoomoff, N., 2019. Mathematics ability and related skills in preschoolers born very preterm. *Child Neuropsychol* 25, 162-178.

Haynes, R.L., Folkerth, R.D., Keefe, R.J., et al., 2003. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 62, 441-450.

Healy, E., Reichenberg, A., Nam, K.W., et al., 2013. Preterm birth and adolescent social functioning-alterations in emotion-processing brain areas. *J Pediatr* 163, 1596-1604.

Hearne, B.N., Christie-Mizell, C.A., 2018. Educational attainment in young adulthood, depressive symptoms, and race-ethnicity: The long-reach of parenting styles in adolescence. *JSSW* 45, 91.

Heller, A.S., Cohen, A.O., Dreyfuss, M.F.W., et al., 2016. Changes in cortico-subcortical and subcortico-subcortical connectivity impact cognitive control to emotional cues across development. *Social cognitive and affective neuroscience* 11, 1910-1918.

Hertz, C.L., Mathiasen, R., Hansen, B.M., et al., 2013. Personality in adults who were born very preterm. *PLoS One* 8, e66881.

Hezel, D.M., McNally, R.J., 2014. Theory of mind impairments in social anxiety disorder. *Behav Ther* 45, 530-540.

Hill, N.E., 2006. Disentangling ethnicity, socioeconomic status and parenting: Interactions, influences and meaning. *Vulnerable Child Youth Stud* 1, 114-124.

Hille, E.T., den Ouden, A.L., Saigal, S., et al., 2001. Behavioural problems in children who weigh 1000 g or less at birth in four countries. *Lancet* 357, 1641-1643.

Hirshfeld-Becker, D.R., Micco, J.A., Simoes, N.A., et al., 2008. High risk studies and developmental antecedents of anxiety disorders. *American journal of medical genetics. Part C, Seminars in medical genetics* 148C, 99-117.

Hoffman, M.C., Jeffers, S., Carter, J., et al., 2007. Pregnancy at or beyond age 40 years is associated with an increased risk of fetal death and other adverse outcomes. *Am J Obstet Gynecol* 196, e11-13.

Honey, C.J., Sporns, O., Cammoun, L., et al., 2009. Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci U S A* 106, 2035-2040.

Horn, A., Ostwald, D., Reisert, M., et al., 2014. The structural–functional connectome and the default mode network of the human brain. *Neuroimage* 102, 142-151.

Horning, S.M., Cornwell, R.E., Davis, H.P., 2012. The recognition of facial expressions: An investigation of the influence of age and cognition. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 19, 657-676.

Hua, X., Leow, A.D., Lee, S., et al., 2008. 3d characterization of brain atrophy in alzheimer's disease and mild cognitive impairment using tensor-based morphometry. *Neuroimage* 41, 19-34.

Hughes, E.J., Winchman, T., Padormo, F., et al., 2017. A dedicated neonatal brain imaging system. *Magn Reson Med* 78, 794-804.

Huhtala, M., Korja, R., Lehtonen, L., et al., 2014. Associations between parental psychological well-being and socio-emotional development in 5-year-old preterm children. *Early Hum Dev* 90, 119-124.

Huppi, P.S., Maier, S.E., Peled, S., et al., 1998a. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatr Res* 44, 584-590.

Huppi, P.S., Warfield, S., Kikinis, R., et al., 1998b. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol* 43, 224-235.

Hutchinson, E.A., De Luca, C.R., Doyle, L.W., et al., 2013. School-age outcomes of extremely preterm or extremely low birth weight children. *Pediatrics* 131, e1053.

Hyson, M., 2004. The emotional development of young children: Building an emotion-centered curriculum. Teachers College Press.

Imafuku, M., Kawai, M., Niwa, F., et al., 2017. Preference for dynamic human images and gaze‐following abilities in preterm infants at 6 and 12 months of age: An eye‐tracking study. *Infancy : the official journal of the International Society on Infant Studies* 22, 223-239.

Inder, T.E., 2006. Neurodevelopmental impact of low-grade intraventricular hemorrhage in very preterm infants. *J Pediatr* 149, 152-154.

Inder, T.E., Huppi, P.S., Warfield, S., et al., 1999. Periventricular white matter injury in the premature infant is followed by reduced cerebral cortical gray matter volume at term. *Ann Neurol* 46, 755-760.

Inder, T.E., Warfield, S.K., Wang, H., et al., 2005. Abnormal cerebral structure is present at term in premature infants. *Pediatrics* 115, 286-294.

Inder, T.E., Wells, S.J., Mogridge, N.B., et al., 2003. Defining the nature of the cerebral abnormalities in the premature infant: A qualitative magnetic resonance imaging study. *J Pediatr* 143, 171-179.

Isaacs, E.B., Edmonds, C.J., Chong, W.K., et al., 2003. Cortical anomalies associated with visuospatial processing deficits. *Ann Neurol* 53, 768-773.

Isaacs, E.B., Edmonds, C.J., Chong, W.K., et al., 2004. Brain morphometry and iq measurements in preterm children. *Brain* 127, 2595-2607.

Isaacs, E.B., Edmonds, C.J., Lucas, A., et al., 2001. Calculation difficulties in children of very low birthweight: A neural correlate. *Brain* 124, 1701-1707.

Isaacs, E.B., Gadian, D.G., Sabatini, S., et al., 2008. The effect of early human diet on caudate volumes and iq. *Pediatr Res* 63, 308-314.

Isaacs, E.B., Lucas, A., Chong, W.K., et al., 2000. Hippocampal volume and everyday memory in children of very low birth weight. *Pediatr Res* 47, 713-720.

Iwata, S., Nakamura, T., Hizume, E., et al., 2012. Qualitative brain mri at term and cognitive outcomes at 9 years after very preterm birth. *Pediatrics* 129, e1138-1147.

Jardine, J., Walker, K., Gurol-Urganci, I., et al., 2021. Adverse pregnancy outcomes attributable to socioeconomic and ethnic inequalities in england: A national cohort study. *Lancet* 398, 1905-1912.

Jelescu, I.O., Veraart, J., Fieremans, E., et al., 2016. Degeneracy in model parameter estimation for multi-compartmental diffusion in neuronal tissue. *NMR Biomed* 29, 33-47.

Jenkins, N., Bloor, M., Fischer, J., et al., 2010. Putting it in context: The use of vignettes in qualitative interviewing. *Qual Res* 10, 175-198.

Jeurissen, B., Leemans, A., Tournier, J.D., et al., 2013. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Hum Brain Mapp* 34, 2747-2766.

Jeurissen, B., Tournier, J.-D., Dhollander, T., et al., 2014. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion mri data. *Neuroimage* 103, 411-426.

Jo, H.M., Cho, H.K., Jang, S.H., et al., 2012. A comparison of microstructural maturational changes of the corpus callosum in preterm and full-term children: A diffusion tensor imaging study. *Neuroradiology* 54, 997-1005.

Johansson, S., Cnattigius, S., 2010. Epidemiology of preterm birth, in: Nosarti, C., et al. (Eds.), Neurodevelopmental outcomes of preterm birth: From childhood to adult life. Cambridge University Press, Cambridge, pp. 1-16.

Johns, C.B., Lacadie, C., Vohr, B., et al., 2019. Amygdala functional connectivity is associated with social impairments in preterm born young adults. *Neuroimage Clin* 21, 101626-101626.

Johnson, S., 2007. Cognitive and behavioural outcomes following very preterm birth. *Semin Fetal Neonatal Med* 12, 363-373.

Johnson, S., Gilmore, C., Gallimore, I., et al., 2015. The long-term consequences of preterm birth: What do teachers know? *Dev Med Child Neurol* 57, 571-577.

Johnson, S., Hennessy, E., Smith, R., et al., 2009. Academic attainment and special educational needs in extremely preterm children at 11 years of age: The epicure study. *Arch Dis Child Fetal Neonatal Ed* 94, F283-289.

Johnson, S., Hollis, C., Kochhar, P., et al., 2010. Psychiatric disorders in extremely preterm children: Longitudinal finding at age 11 years in the epicure study. *J Am Acad Child Adolesc Psychiatry* 49, 453-463 e451.

Johnson, S., Hollis, C., Marlow, N., et al., 2014. Screening for childhood mental health disorders using the strengths and difficulties questionnaire: The validity of multi-informant reports. *Dev Med Child Neurol* 56, 453-459.

Johnson, S., Marlow, N., 2011. Preterm birth and childhood psychiatric disorders. *Pediatr Res* 69, 11R-18R.

Johnson, S., Wolke, D., 2013. Behavioural outcomes and psychopathology during adolescence. *Early Hum Dev* 89, 199-207.

Johnson, S., Wolke, D., Marlow, N., 2008. Developmental assessment of preterm infants at 2 years: Validity of parent reports. *Dev Med Child Neurol* 50, 58-62.

Jones, D.E., Greenberg, M., Crowley, M., 2015. Early social-emotional functioning and public health: The relationship between kindergarten social competence and future wellness. *Am J Public Health* 105, 2283-2290.

Jones, E.G., 2000. Cortical and subcortical contributions to activity-dependent plasticity in primate somatosensory cortex. *Annu Rev Neurosci* 23, 1-37.

Jones, K.M., Champion, P.R., Woodward, L.J., 2013. Social competence of preschool children born very preterm. *Early Hum Dev* 89, 795-802.

Joseph, K., Kramer, M.S., Marcoux, S., et al., 1998. Determinants of preterm birth rates in canada from 1981 through 1983 and from 1992 through 1994. *N Engl J Med* 339, 1434-1439.

Judaš, M., Sedmak, G., Pletikos, M., et al., 2010. Populations of subplate and interstitial neurons in fetal and adult human telencephalon. *J Anat* 217, 381-399.

Jung, M., Mody, M., Fujioka, T., et al., 2019. Sex differences in white matter pathways related to language ability. *Front Neurosci* 13, 898.

Kagan, J., Fox, N.A., 2006. Biology, culture, and temperamental biases, Handbook of child psychology.

Kalil, A., Ryan, R., Corey, M., 2012. Diverging destinies: Maternal education and the developmental gradient in time with children. *Demography* 49, 1361-1383.

Kanel, D., Counsell, S.J., Nosarti, C., 2021a. Advances in functional and diffusion neuroimaging research into the long-term consequences of very preterm birth. *J Perinatol* 41, 689-706.

Kanel, D., Vanes, L., Pecheva, D., et al., 2021b. Neonatal white matter microstructure and emotional development during the pre-school years in children who were born very preterm. *eNeuro*, ENEURO.0546-0520.2021.

Kanold, P.O., Shatz, C.J., 2006. Subplate neurons regulate maturation of cortical inhibition and outcome of ocular dominance plasticity. *Neuron* 51, 627-638.

Kapellou, O., Counsell, S.J., Kennea, N., et al., 2006. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 3, e265.

Karmiloff-Smith, A., D'Souza, D., Dekker, T.M., et al., 2012. Genetic and environmental vulnerabilities in children with neurodevelopmental disorders. *Proc Natl Acad Sci U S A* 109, 17261-17265.

Kelly, C.E., Cheong, J.L., Gabra Fam, L., et al., 2016a. Moderate and late preterm infants exhibit widespread brain white matter microstructure alterations at term-equivalent age relative to term-born controls. *Brain Imaging Behav* 10, 41-49.

Kelly, C.E., Thompson, D.K., Chen, J., et al., 2016b. Axon density and axon orientation dispersion in children born preterm. *Hum Brain Mapp* 37, 3080-3102.

Kelly, C.E., Thompson, D.K., Genc, S., et al., 2020. Long-term development of white matter fibre density and morphology up to 13 years after preterm birth: A fixel-based analysis. *Neuroimage* 220, 117068.

Kennedy, E., Poppe, T., Tottman, A., et al., 2021. Neurodevelopmental impairment is associated with altered white matter development in a cohort of school-aged children born very preterm. *Neuroimage Clin* 31, 102730.

Kent, A., Lomas, F., Hurrion, E., et al., 2005. Antenatal steroids may reduce adverse neurological outcome following chorioamnionitis: Neurodevelopmental outcome and chorioamnionitis in premature infants. *Paediatr Child Health* 41, 186-190.

Kerr-Wilson, C.O., Mackay, D.F., Smith, G.C., et al., 2012. Meta-analysis of the association between preterm delivery and intelligence. *J Public Health* 34, 209-216.

Kesler, S.R., Reiss, A.L., Vohr, B., et al., 2008. Brain volume reductions within multiple cognitive systems in male preterm children at age twelve. *J Pediatr* 152, 513-520, 520.

Kessels, R.P., Montagne, B., Hendriks, A.W., et al., 2014. Assessment of perception of morphed facial expressions using the emotion recognition task: Normative data from healthy participants aged 8-75. *J Neuropsychol* 8, 75-93.

Keunen, K., Counsell, S.J., Benders, M., 2017. The emergence of functional architecture during early brain development. *Neuroimage* 160, 2-14.

Khwaja, O., Volpe, J.J., 2008. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed* 93, F153-161.

Kim, D.J., Davis, E.P., Sandman, C.A., et al., 2014. Longer gestation is associated with more efficient brain networks in preadolescent children. *Neuroimage* 100C, 619-627.

Kim, S.G., Richter, W., Uğurbil, K., 1997. Limitations of temporal resolution in functional mri. *Magn Reson Med* 37, 631-636.

Kimpton, J.A., Batalle, D., Barnett, M.L., et al., 2021. Diffusion magnetic resonance imaging assessment of regional white matter maturation in preterm neonates. *Neuroradiology* 63, 573-583.

Kinney, H.C., Back, S.A., 1998. Human oligodendroglial development: Relationship to periventricular leukomalacia. *Semin Pediatr Neurol* 5, 180-189.

Kistka, Z.A., Palomar, L., Lee, K.A., et al., 2007. Racial disparity in the frequency of recurrence of preterm birth. *Am J Obstet Gynecol* 196, 131.e131-136.

Kistka, Z.A.F., DeFranco, E.A., Ligthart, L., et al., 2008. Heritability of parturition timing: An extended twin design analysis. *Am J Obstet Gynecol* 199, 43.e41-43.e45.

Kiviniemi, V.J., Haanpää, H., Kantola, J.-H., et al., 2005. Midazolam sedation increases fluctuation and synchrony of the resting brain bold signal. *Magn Reson Imaging* 23, 531-537.

Kleine, I., Falconer, S., Roth, S., et al., 2020. Early postnatal maternal trait anxiety is associated with the behavioural outcomes of children born preterm <33 weeks. *J Psychiatr Res* 131, 160-168.

Klin, A., 2000. Attributing social meaning to ambiguous visual stimuli in higher-functioning autism and asperger syndrome: The social attribution task. *J Child Psychol Psychiatry* 41, 831-846.

Knickmeyer, R.C., Xia, K., Lu, Z., et al., 2017. Impact of demographic and obstetric factors on infant brain volumes: A population neuroscience study. *Cereb Cortex* 27, 5616-5625.

Kohn, N., Eickhoff, S.B., Scheller, M., et al., 2014. Neural network of cognitive emotion regulation--an ale meta-analysis and macm analysis. *Neuroimage* 87, 345-355.

Korzeniewski, S.J., Joseph, R.M., Kim, S.H., et al., 2017. Social responsiveness scale assessment of the preterm behavioral phenotype in 10-year-olds born extremely preterm. *J Dev Behav Pediatr* 38, 697-705.

Kostović, I., Jovanov-Milosević, N., 2006. The development of cerebral connections during the first 20-45 weeks' gestation. *Semin Fetal Neonatal Med* 11, 415-422.

Kostović, I., Jovanov-Milošević, N., Radoš, M., et al., 2014. Perinatal and early postnatal reorganization of the subplate and related cellular compartments in the human cerebral wall as revealed by histological and mri approaches. *Brain Struct Funct* 219, 231-253.

Kostović, I., Judas, M., 2010. The development of the subplate and thalamocortical connections in the human foetal brain. *Acta Paediatr* 99, 1119-1127.

Kramer, M.S., McLean, F.H., Boyd, M.E., et al., 1988. The validity of gestational age estimation by menstrual dating in term, preterm, and postterm gestations. *JAMA* 260, 3306-3308.

Krogsrud, S.K., Fjell, A.M., Tamnes, C.K., et al., 2016. Changes in white matter microstructure in the developing brain—a longitudinal diffusion tensor imaging study of children from 4 to 11years of age. *Neuroimage* 124, 473-486.

Kroll, J., Karolis, V., Brittain, P.J., et al., 2019. Systematic assessment of perinatal and socio-demographic factors associated with iq from childhood to adult life following very preterm birth. *Intelligence* 77, 101401.

Kroll, J., Karolis, V., Brittain, P.J., et al., 2017. Real-life impact of executive function impairments in adults who were born very preterm. *J Int Neuropsychol Soc* 23, 381-389.

Kuklisova-Murgasova, M., Aljabar, P., Srinivasan, L., et al., 2011. A dynamic 4d probabilistic atlas of the developing brain. *Neuroimage* 54, 2750-2763.

Kwon, S.H., Scheinost, D., Lacadie, C., et al., 2015. Adaptive mechanisms of developing brain: Cerebral lateralization in the prematurely-born. *Neuroimage* 108, 144-150.

Kwong, K.K., Belliveau, J.W., Chesler, D.A., et al., 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A* 89, 5675-5679.

La Paro, K.M., Pianta, R.C., Stuhlman, M., 2004. The classroom assessment scoring system: Findings from the prekindergarten year. *Elem Sch J* 104, 409-426.

Laceulle, O.M., Ormel, J., Vollebergh, W.A., et al., 2014. A test of the vulnerability model: Temperament and temperament change as predictors of future mental disorders - the trails study. *J Child Psychol Psychiatry* 55, 227-236.

Lamichhane, D.K., Lee, S.-Y., Ahn, K., et al., 2020. Quantile regression analysis of the socioeconomic inequalities in air pollution and birth weight. *Environ Int* 142, 105875.

Lampinen, B., Szczepankiewicz, F., Mårtensson, J., et al., 2017. Neurite density imaging versus imaging of microscopic anisotropy in diffusion mri: A model comparison using spherical tensor encoding. *Neuroimage* 147, 517-531.

Langhoff-Roos, J., Kesmodel, U., Jacobsson, B., et al., 2006. Spontaneous preterm delivery in primiparous women at low risk in denmark: Population based study. *BMJ* 332, 937-939.

Lao, Y., Wang, Y., Shi, J., et al., 2016. Thalamic alterations in preterm neonates and their relation to ventral striatum disturbances revealed by a combined shape and pose analysis. *Brain Struct Funct* 221, 487-506.

Lautarescu, A., Hadaya, L., Craig, M.C., et al., 2021. Exploring the relationship between maternal prenatal stress and brain structure in premature neonates. *PLoS One* 16, e0250413.

Lawlor, D.A., Mortensen, L., Andersen, A.M., 2011. Mechanisms underlying the associations of maternal age with adverse perinatal outcomes: A sibling study of 264 695 danish women and their firstborn offspring. *Int J Epidemiol* 40, 1205-1214.

Lawrence, K., Campbell, R., Skuse, D., 2015. Age, gender, and puberty influence the development of facial emotion recognition. *Frontiers in psychology* 6, 761.

Le Bihan, D., 2013. Apparent diffusion coefficient and beyond: What diffusion mr imaging can tell us about tissue structure. *Radiology* 268, 318-322.

Le Bihan, D., Breton, E., Lallemand, D., et al., 1986. Mr imaging of intravoxel incoherent motions: Application to diffusion and perfusion in neurologic disorders. *Radiology* 161, 401-407.

Lean, R.E., Lessov-Shlaggar, C.N., Gerstein, E.D., et al., 2020. Maternal and family factors differentiate profiles of psychiatric impairments in very preterm children at age 5-years. *J Child Psychol Psychiatry* 61, 157-166.

Lean, R.E., Melzer, T.R., Bora, S., et al., 2017. Attention and regional gray matter development in very preterm children at age 12 years. *J Int Neuropsychol Soc* 23, 539-550.

Lebel, C., Beaulieu, C., 2011. Longitudinal development of human brain wiring continues from childhood into adulthood. *J Neurosci* 31, 10937-10947.

Lebel, C., Walker, L., Leemans, A., et al., 2008. Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage* 40, 1044-1055.

LeDoux, J., 2003. The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol* 23, 727-738.

LeDoux, J.E., 2000. Emotion circuits in the brain. *Annu Rev Neurosci* 23, 155-184.

Lee, H.J., Kwon, H., Kim, J.I., et al., 2021. The cingulum in very preterm infants relates to language and social-emotional impairment at 2 years of term-equivalent age. *Neuroimage Clin* 29, 102528.

Lee, I., Neil, J.J., Huettner, P.C., et al., 2014. The impact of prenatal and neonatal infection on neurodevelopmental outcomes in very preterm infants. *J Perinatol* 34, 741-747.

Lee, W., Donner, E.J., Nossin-Manor, R., et al., 2012. Visual functional magnetic resonance imaging of preterm infants. *Dev Med Child Neurol* 54, 724-729.

Lehto, J.E., Juujärvi, P., Kooistra, L., et al., 2003. Dimensions of executive functioning: Evidence from children. *Br J Dev Psychol* 21, 59-80.

Lejeune, F., Tolsa, C.B., Graz, M.B., et al., 2015. Emotion, attention, and effortful control in 24-month-old very preterm and full-term children. *LAnnee psychologique* 115, 241-264.

Lemola, S., Oser, N., Urfer-Maurer, N., et al., 2017. Effects of gestational age on brain volume and cognitive functions in generally healthy very preterm born children during school-age: A voxel-based morphometry study. *PLoS One* 12, e0183519.

Leppänen, J.M., Nelson, C.A., 2009. Tuning the developing brain to social signals of emotions. *Nat Rev Neurosci* 10, 37-47.

Levy, D.J., Heissel, J.A., Richeson, J.A., et al., 2016. Psychological and biological responses to race-based social stress as pathways to disparities in educational outcomes. *The American psychologist* 71, 455.

Li, K., Sun, Z., Han, Y., et al., 2015a. Fractional anisotropy alterations in individuals born preterm: A diffusion tensor imaging meta-analysis. *Dev Med Child Neurol* 57, 328-338.

Li, W., Cui, H., Zhu, Z., et al., 2016. Aberrant functional connectivity between the amygdala and the temporal pole in drug-free generalized anxiety disorder. *Front Hum Neurosci* 10, 549.

Li, W., Ward, B.D., Xie, C., et al., 2015b. Amygdala network dysfunction in late-life depression phenotypes: Relationships with symptom dimensions. *J Psychiatr Res* 70, 121-129.

Li, Y., Li, S., Wei, C., et al., 2010. Changes in emotional behavior produced by orexin microinjections in the paraventricular nucleus of the thalamus. *Pharmacol Biochem Behav* 95, 121-128.

Li, Y., Quigley, M.A., Macfarlane, A., et al., 2019. Ethnic differences in singleton preterm birth in england and wales, 2006 - 12: Analysis of national routinely collected data. *Paediatr Perinat Epidemiol* 33, 449-458.

Liang, P., Zhang, H., Xu, Y., et al., 2015. Disruption of cortical integration during midazolam-induced light sedation. *Hum Brain Mapp* 36, 4247-4261.

Limperopoulos, C., Benson, C.B., Bassan, H., et al., 2005a. Cerebellar hemorrhage in the preterm infant: Ultrasonographic findings and risk factors. *Pediatrics* 116, 717-724.

Limperopoulos, C., Soul, J.S., Gauvreau, K., et al., 2005b. Late gestation cerebellar growth is rapid and impeded by premature birth. *Pediatrics* 115, 688-695.

Lin, W., Zhu, Q., Gao, W., et al., 2008. Functional connectivity mr imaging reveals cortical functional connectivity in the developing brain. *AJNR Am J Neuroradiol* 29, 1883-1889.

Linsell, L., Johnson, S., Wolke, D., et al., 2018. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: A prospective, population-based cohort study. *Arch Dis Child* 103, 363-370.

Linsell, L., Malouf, R., Morris, J., et al., 2015. Prognostic factors for poor cognitive development in children born very preterm or with very low birth weight: A systematic review. *JAMA Pediatr* 169, 1162-1172.

Liu, R., Bell, M.A., 2020. Fearful temperament and the risk for child and adolescent anxiety: The role of attention biases and effortful control. *Clin Child Fam Psychol Rev* 23, 205-228.

Liu, Y., Aeby, A., Balériaux, D., et al., 2012. White matter abnormalities are related to microstructural changes in preterm neonates at term-equivalent age: A diffusion tensor imaging and probabilistic tractography study. *AJNR Am J Neuroradiol* 33, 839-845.

Liu, Y., Balériaux, D., Kavec, M., et al., 2010. Structural asymmetries in motor and language networks in a population of healthy preterm neonates at term equivalent age: A diffusion tensor imaging and probabilistic tractography study. *Neuroimage* 51, 783-788.

Liu, Y., Mendonça, M., Johnson, S., et al., 2021. Testing the neurodevelopmental, trauma and developmental risk factor models of psychosis using a naturalistic experiment. *Psychol Med* 51, 460-469.

Loe, I.M., Adams, J.N., Feldman, H.M., 2018. Executive function in relation to white matter in preterm and full term children. *Front Pediatr* 6, 418.

Loe, I.M., Lee, E.S., Feldman, H.M., 2013. Attention and internalizing behaviors in relation to white matter in children born preterm. *J Dev Behav Pediatr* 34, 156-164.

Lonigan, C.J., Carey, M.P., Finch, A.J., Jr., 1994. Anxiety and depression in children and adolescents: Negative affectivity and the utility of self-reports. *J Consult Clin Psychol* 62, 1000-1008.

Lonigan, C.J., Vasey, M.W., Phillips, B.M., et al., 2004. Temperament, anxiety, and the processing of threat-relevant stimuli. *Clin Child Adolesc Psychol* 33, 8-20.

López-Pérez, B., Wilson, E.L., 2015. Parent–child discrepancies in the assessment of children's and adolescents' happiness. *J Exp Child Psychol* 139, 249-255.

Loukas, A., Murphy, J.L., 2007. Middle school student perceptions of school climate: Examining protective functions on subsequent adjustment problems. *J Sch Psychol* 45, 293-309.

Lubsen, J., Vohr, B., Myers, E., et al., 2011. Microstructural and functional connectivity in the developing preterm brain. *Semin Perinatol* 35, 34-43.

Luhmann, H.J., Kilb, W., Hanganu-Opatz, I., 2009. Subplate cells: Amplifiers of neuronal activity in the developing cerebral cortex. *Front Neuroanat* 3, 19.

Luu, T.M., Ment, L., Allan, W., et al., 2011a. Executive and memory function in adolescents born very preterm. *Pediatrics* 127, e639-e646.

Luu, T.M., Vohr, B.R., Allan, W., et al., 2011b. Evidence for catch-up in cognition and receptive vocabulary among adolescents born very preterm. *Pediatrics* 128, 313-322.

MacBean, V., Drysdale, S.B., Zivanovic, S., et al., 2019. Participant retention in follow-up studies of prematurely born children. *BMC Public Health* 19, 1233.

MacCallum, R.C., Zhang, S., Preacher, K.J., et al., 2002. On the practice of dichotomization of quantitative variables. *Psychol Methods* 7, 19.

Machado-Rivas, F., Afacan, O., Khan, S., et al., 2021. Tractography of the cerebellar peduncles in second-and third-trimester fetuses. *AJNR Am J Neuroradiol* 42, 194-200.

Maiya, P., Nagashree, S., Shaik, M.S., 2001. Role of score for neonatal acute physiology (snap) in predicting neonatal mortality. *Indian J Pediatr* 68, 829-834.

Makropoulos, A., Aljabar, P., Wright, R., et al., 2016. Regional growth and atlasing of the developing human brain. *Neuroimage* 125, 456-478.

Mangin, K.S., Horwood, L.J., Woodward, L.J., 2017. Cognitive development trajectories of very preterm and typically developing children. *Child Dev* 88, 282-298.

Manly, T., 2002. Tea-ch: The test of everyday attention for children. Harcourt Assessment.

Månsson, J., Stjernqvist, K., Bäckström, M., 2014. Behavioral outcomes at corrected age 2.5 years in children born extremely preterm. *J Dev Behav Pediatr* 35, 435-442.

Manuck, T.A., 2017. Racial and ethnic differences in preterm birth: A complex, multifactorial problem. *Semin Perinatol* 41, 511-518.

Manuck, T.A., Rice, M.M., Bailit, J.L., et al., 2016. Preterm neonatal morbidity and mortality by gestational age: A contemporary cohort. *Am J Obstet Gynecol* 215, 103.e101-103.e114.

Maroziene, L., Grazuleviciene, R., 2002. Maternal exposure to low-level air pollution and pregnancy outcomes: A population-based study. *Environ Health* 1, 6.

Martínez-Nadal, S., Bosch, L., 2021. Cognitive and learning outcomes in late preterm infants at school age: A systematic review. *Int J Environ Res Public Health* 18, 74.

Martins, C.B.S., Cassiano, R.G.M., Linhares, M.B.M., 2021. Negative affectivity moderated by preterm birth predicted toddlers' behavior problems. *Infant Behav Dev* 63, 101544.

Martinussen, R., Tannock, R., 2006. Working memory impairments in children with attention-deficit hyperactivity disorder with and without comorbid language learning disorders. *J Clin Exp Neuropsychol* 28, 1073-1094.

Mathiasen, R., Hansen, B.M., Nybo Anderson, A.M., et al., 2009. Socio-economic achievements of individuals born very preterm at the age of 27 to 29 years: A nationwide cohort study. *Dev Med Child Neurol* 51, 901-908.

Matijasevich, A., Victora, C.G., Lawlor, D.A., et al., 2012. Association of socioeconomic position with maternal pregnancy and infant health outcomes in birth cohort studies from brazil and the uk. *J Epidemiol Community Health* 66, 127-135.

Mauer, N., Borkenau, P., 2007. Temperament and early information processing: Temperament-related attentional bias in emotional stroop tasks. *Pers Individ Dif* 43, 1063-1073.

Mayes, S.D., Calhoun, S.L., Bixler, E.O., et al., 2009. Iq and neuropsychological predictors of academic achievement. *Learn Individ Differ* 19, 238-241.

McConnell, R., Berhane, K., Gilliland, F., et al., 2003. Prospective study of air pollution and bronchitic symptoms in children with asthma. *Am J Respir Crit Care Med* 168, 790-797.

McGoey, K.E., DuPaul, G.J., Haley, E., et al., 2007. Parent and teacher ratings of attention-deficit/hyperactivity disorder in preschool: The adhd rating scale-iv preschool version. *Journal of psychopathology and behavioral assessment* 29, 269-276.

McKinstry, R.C., Miller, J.H., Snyder, A.Z., et al., 2002. A prospective, longitudinal diffusion tensor imaging study of brain injury in newborns. *Neurology* 59, 824-833.

McLoyd, V.C., Jayaratne, T.E., Ceballo, R., et al., 1994. Unemployment and work interruption among african american single mothers: Effects on parenting and adolescent socioemotional functioning. *Child Dev* 65, 562-589.

Menon, V., 2011. Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn Sci* 15, 483-506.

Menon, V., 2013. Developmental pathways to functional brain networks: Emerging principles. *Trends Cogn Sci* 17, 627-640.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: A network model of insula function. *Brain Struct Funct* 214, 655-667.

Ment, L.R., Constable, R.T., 2007. Injury and recovery in the developing brain: Evidence from functional mri studies of prematurely born children. *Nat Clin Pract Neurol* 3, 558-571.

Merrell, K., 2001. Helping students overcome depression and anxiety: A practical guide. Second edition. Guilford Publications.

Merrell, K., 2008. The guilford practical intervention in the schools series. Helping students overcome depression and anxiety: A practical guide. Guilford Press New York, NY.

Mestre, M.V., Samper, P., Frías, M.D., et al., 2009. Are women more empathetic than men? A longitudinal study in adolescence. *Span J Psychol* 12, 76-83.

Mesulam, M.-M., 2002. The human frontal lobes: Transcending the default mode through contingent encoding, in: Stuss, D.T., & Knight, R. T. (Eds.) (Ed.), Principles of frontal lobe function, vol. 54. Oxford University Press, pp. 8-30.

Miller, S.P., Vigneron, D.B., Henry, R.G., et al., 2002. Serial quantitative diffusion tensor mri of the premature brain: Development in newborns with and without injury. *J Magn Reson Imaging* 16, 621-632.

Mills, K.L., Goddings, A.L., Herting, M.M., et al., 2016. Structural brain development between childhood and adulthood: Convergence across four longitudinal samples. *Neuroimage* 141, 273-281.

Mito, R., Raffelt, D., Dhollander, T., et al., 2018. Fibre-specific white matter reductions in alzheimer's disease and mild cognitive impairment. *Brain* 141, 888-902.

Miyake, A., Friedman, N.P., Emerson, M.J., et al., 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cogn Psychol* 41, 49-100.

Modi, N., Lewis, H., Al-Naqeeb, N., et al., 2001. The effects of repeated antenatal glucocorticoid therapy on the developing brain. *Pediatr Res* 50, 581-585.

Moeskops, P., Benders, M.J., Pearlman, P.C., et al., 2013. Assessment of quantitative cortical biomarkers in the developing brain of preterm infants, Medical Imaging 2013: Computer-Aided Diagnosis. International Society for Optics and Photonics, p. 867011.

Montagna, A., Karolis, V., Batalle, D., et al., 2020. Adhd symptoms and their neurodevelopmental correlates in children born very preterm. *PLoS One* 15, e0224343.

Montagna, A., Nosarti, C., 2016. Socio-emotional development following very preterm birth: Pathways to psychopathology. *Front Psychol* 7, 80.

Montirosso, R., Peverelli, M., Frigerio, E., et al., 2010. The development of dynamic facial expression recognition at different intensities in 4- to 18-year-olds. *Soc Dev* 19, 71-92.

Moore, S.A., Zoellner, L.A., Mollenholt, N., 2008. Are expressive suppression and cognitive reappraisal associated with stress-related symptoms? *Behaviour research and therapy* 46, 993-1000.

Moreno, M.B., Concha, L., González-Santos, L., et al., 2014. Correlation between corpus callosum sub-segmental area and cognitive processes in school-age children. *PLoS One* 9, e104549.

Moriguchi, Y., 2014. The early development of executive function and its relation to social interaction: A brief review. *Front Psychol* 5, 388.

Morken, N.-H., Källen, K., Hagberg, H., et al., 2005. Preterm birth in sweden 1973-2001: Rate, subgroups, and effect of changing patterns in multiple births, maternal age, and smoking. *Acta Obstet Gynecol Scand* 84, 558-565.

Mossad, S.I., AuCoin-Power, M., Urbain, C., et al., 2016. Thinking about the thoughts of others; temporal and spatial neural activation during false belief reasoning. *Neuroimage* 134, 320-327.

Mossad, S.I., Muscat, C., Pang, E.W., et al., 2020. Emerging atypical connectivity networks for processing angry and fearful faces in very preterm born children. *Hum Brain Mapp* 41, 3794-3806.

Mossad, S.I., Smith, M.L., Pang, E.W., et al., 2017. Neural correlates of "theory of mind" in very preterm born children. *Hum Brain Mapp* 38, 5577-5589.

Mossad, S.I., Vandewouw, M.M., Smith, M.L., et al., 2021. The preterm social brain: Altered functional networks for theory of mind in very preterm children. *Brain Commun* 3, fcaa237.

Muglia, L.J., Katz, M., 2010. The enigma of spontaneous preterm birth. *N Engl J Med* 362, 529-535.

Mulder, H., Pitchford, N.J., Hagger, M.S., et al., 2009. Development of executive function and attention in preterm children: A systematic review. *Dev Neuropsychol* 34, 393-421.

Mullen, K.M., Vohr, B.R., Katz, K.H., et al., 2011. Preterm birth results in alterations in neural connectivity at age 16 years. *Neuroimage* 54, 2563-2570.

Muris, P., 2006. Relation of attention control and school performance in normal children. *Percept Mot Skills* 102, 78-80.

Murner-Lavanchy, I., Ritter, B.C., Spencer-Smith, M.M., et al., 2014. Visuospatial working memory in very preterm and term born children--impact of age and performance. *Dev Cogn Neurosci* 9, 106-116.

Mürner-Lavanchy, I.M., Kelly, C.E., Reidy, N., et al., 2018. White matter microstructure is associated with language in children born very preterm. *Neuroimage Clin* 20, 808-822.

Murphy, B.P., Inder, T.E., Huppi, P.S., et al., 2001. Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pediatrics* 107, 217-221.

Murray, A.L., Scratch, S.E., Thompson, D.K., et al., 2014. Neonatal brain pathology predicts adverse attention and processing speed outcomes in very preterm and/or very low birth weight children. *Neuropsychology* 28, 552-562.

Murray, A.L., Thompson, D.K., Pascoe, L., et al., 2016. White matter abnormalities and impaired attention abilities in children born very preterm. *Neuroimage* 124, 75-84.

Murray, K.T., Kochanska, G., 2002. Effortful control: Factor structure and relation to externalizing and internalizing behaviors. *J Abnorm Child Psychol* 30, 503-514.

Myers, E.H., Hampson, M., Vohr, B., et al., 2010. Functional connectivity to a right hemisphere language center in prematurely born adolescents. *Neuroimage* 51, 1445-1452.

Nagy, A., Kalmár, M., Beke, A.M., et al., 2021. Intelligence and executive function of school-age preterm children in function of birth weight and perinatal complication. *Appl Neuropsychol Child* 6, 1-12.

Narberhaus, A., Segarra, D., Caldu, X., et al., 2008. Corpus callosum and prefrontal functions in adolescents with history of very preterm birth. *Neuropsychologia* 46, 111-116.

Nauta, M.H., Scholing, A., Rapee, R.M., et al., 2004. A parent-report measure of children's anxiety: Psychometric properties and comparison with child-report in a clinic and normal sample. *Behaviour research and therapy* 42, 813-839.

Neil, J.J., Shiran, S.I., McKinstry, R.C., et al., 1998. Normal brain in human newborns: Apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor mr imaging. *Radiology* 209, 57-66.

Newman, E., Thompson, W.K., Bartsch, H., et al., 2016. Anxiety is related to indices of cortical maturation in typically developing children and adolescents. *Brain Struct Funct* 221, 3013-3025.

NICE, N.C.C.f.W.s.a.C.s.H., 2015. Preterm labour and birth.

Nijman, J., Gunkel, J., De Vries, L.S., et al., 2013. Reduced occipital fractional anisotropy on cerebral diffusion tensor imaging in preterm infants with postnatally acquired cytomegalovirus infection. *Neonatology* 104, 143-150.

Normann, E., Lacaze-Masmonteil, T., Eaton, F., et al., 2009. A novel mouse model of ureaplasma-induced perinatal inflammation: Effects on lung and brain injury. *Pediatr Res* 65, 430-436.

Nosarti, C., Al Asady, M.H., Frangou, S., et al., 2002. Adolescents who were born very preterm have decreased brain volumes. *Brain* 125, 1616-1623.

Nosarti, C., Allin, M.P., Frangou, S., et al., 2005. Hyperactivity in adolescents born very preterm is associated with decreased caudate volume. *Biol Psychiatry* 57, 661-666.

Nosarti, C., Giouroukou, E., Healy, E., et al., 2008. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain* 131, 205-217.

Nosarti, C., Nam, K.W., Walshe, M., et al., 2014. Preterm birth and structural brain alterations in early adulthood. *Neuroimage Clin* 6, 180-191.

Nosarti, C., Rubia, K., Smith, A.B., et al., 2006. Altered functional neuroanatomy of response inhibition in adolescent males who were born very preterm. *Dev Med Child Neurol* 48, 265-271.

Nosarti, C., Rushe, T.M., Woodruff, P.W., et al., 2004. Corpus callosum size and very preterm birth: Relationship to neuropsychological outcome. *Brain* 127, 2080-2089.

O'Donnell, L.J., Westin, C.F., 2011. An introduction to diffusion tensor image analysis. *Neurosurg Clin N Am* 22, 185-196, viii.

O'Meagher, S., Kemp, N., Norris, K., et al., 2017. Risk factors for executive function difficulties in preschool and early school‐age preterm children. *Acta Paediatr* 106, 1468-1473.

Ogawa, S., Tank, D.W., Menon, R., et al., 1992. Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci U S A* 89, 5951-5955.

Olausson, P.O., Cnattingius, S., Haglund, B., 1999. Teenage pregnancies and risk of late fetal death and infant mortality. *Br J Obstet Gynaecol* 106, 116-121.

Olausson, P.O., Lichtenstein, P., Cnattingius, S., 2000. Aetiology of teenage childbearing: Reasons for familial effects. *Twin Res* 3, 23-27.

Olson, I.R., Plotzker, A., Ezzyat, Y., 2007. The enigmatic temporal pole: A review of findings on social and emotional processing. *Brain* 130, 1718-1731.

Omizzolo, C., Scratch, S.E., Stargatt, R., et al., 2014. Neonatal brain abnormalities and memory and learning outcomes at 7 years in children born very preterm. *Memory* 22, 605-615.

Onderdonk, A.B., Hecht, J.L., McElrath, T.F., et al., 2008. Colonization of second-trimester placenta parenchyma. *Am J Obstet Gynecol* 199, 52.e51-52.e10.

ONS, O.f.N.S., 2016. Ethnic group, national identity and religion, measuring equality: A guide for the collection and classification of ethnic group, national identity and religion data in the uk.

ONS, O.f.N.S., 2020. Births in england and wales 2019: Live births, stillbirths and the intensity of childbearing, measured by the total fertility rate.

Oosterlaan, J., Sergeant, J.A., 1998. Response inhibition and response re-engagement in attention-deficit/hyperactivity disorder, disruptive, anxious and normal children. *Behavioural brain research* 94, 33-43.

Ormel, J., Bastiaansen, A., Riese, H., et al., 2013. The biological and psychological basis of neuroticism: Current status and future directions. *Neuroscience and biobehavioral reviews* 37, 59-72.

Ornstein, M., Ohlsson, A., Edmonds, J., et al., 1991. Neonatal follow-up of very low birthweight/extremely low birthweight infants to school age: A critical overview. *Acta Paediatr* 80, 741-748.

Pagliaccio, D., Luby, J.L., Bogdan, R., et al., 2015. Amygdala functional connectivity, hpa axis genetic variation, and life stress in children and relations to anxiety and emotion regulation. *J Abnorm Psychol* 124, 817-833.

Pannek, K., Fripp, J., George, J.M., et al., 2018. Fixel-based analysis reveals alterations is brain microstructure and macrostructure of preterm-born infants at term equivalent age. *Neuroimage Clin* 18, 51-59.

Pannek, K., George, J.M., Boyd, R.N., et al., 2020. Brain microstructure and morphology of very preterm-born infants at term equivalent age: Associations with motor and cognitive outcomes at 1 and 2 years. *Neuroimage* 221, 117163.

Pannek, K., Hatzigeorgiou, X., Colditz, P.B., et al., 2013. Assessment of structural connectivity in the preterm brain at term equivalent age using diffusion mri and t2 relaxometry: A network-based analysis. *PLoS One* 8, e68593.

Papini, C., White, T.P., Montagna, A., et al., 2016. Altered resting-state functional connectivity in emotion-processing brain regions in adults who were born very preterm. *Psychol Med* 46, 3025-3039.

Parry, G., Tucker, J., Tarnow-Mordi, W., et al., 2003. Crib ii: An update of the clinical risk index for babies score. *Lancet* 361, 1789-1791.

Partridge, S.C., Mukherjee, P., Henry, R.G., et al., 2004. Diffusion tensor imaging: Serial quantitation of white matter tract maturity in premature newborns. *Neuroimage* 22, 1302-1314.

Paschke, L.M., Dörfel, D., Steimke, R., et al., 2016. Individual differences in self-reported self-control predict successful emotion regulation. *Social cognitive and affective neuroscience* 11, 1193-1204.

Pecheva, D., Tournier, J.D., Pietsch, M., et al., 2019. Fixel-based analysis of the preterm brain: Disentangling bundle-specific white matter microstructural and macrostructural changes in relation to clinical risk factors. *Neuroimage Clin* 23, 101820.

Penn, A.A., Gressens, P., Fleiss, B., et al., 2016. Controversies in preterm brain injury. *Neurobiol Dis* 92, 90-101.

Penzo, M.A., Robert, V., Tucciarone, J., et al., 2015. The paraventricular thalamus controls a central amygdala fear circuit. *Nature* 519, 455-459.

Pérez-Pereira, M., Cruz, R., 2017. A longitudinal study of vocabulary size and composition in low risk preterm children. *First Lang* 38, 72-94.

Pérez-Pereira, M., Fernández, P., Gómez-Taibo, M.L., et al., 2014. Language development of low risk preterm infants up to the age of 30 months. *Early Hum Dev* 90, 649-656.

Pérez-Pereira, M., Martínez-López, Z., Maneiro, L., 2020. Longitudinal relationships between reading abilities, phonological awareness, language abilities and executive functions: Comparison of low risk preterm and full-term children. *Front Psychol* 11, 468-468.

Perge, J.A., Niven, J.E., Mugnaini, E., et al., 2012. Why do axons differ in caliber? *J Neurosci* 32, 626-638.

Pessoa, L., Adolphs, R., 2010. Emotion processing and the amygdala: From a 'low road' to 'many roads' of evaluating biological significance. *Nat Rev Neurosci* 11, 773-783.

Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. *Annu Rev Neurosci* 35, 73-89.

Petersen, S.E., Sporns, O., 2015. Brain networks and cognitive architectures. *Neuron* 88, 207-219.

Peterson, B.S., 2003. Brain imaging studies of the anatomical and functional consequences of preterm birth for human brain development. *Ann N Y Acad Sci* 1008, 219-237.

Peterson, B.S., Anderson, A.W., Ehrenkranz, R., et al., 2003. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. *Pediatrics* 111, 939-948.

Peterson, B.S., Vohr, B., Staib, L.H., et al., 2000. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA* 284, 1939-1947.

Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron* 48, 175-187.

Pickering, S.J., 2001. The development of visuo-spatial working memory. *Memory* 9, 423-432.

Piedvache, A., van Buuren, S., Barros, H., et al., 2021. Strategies for assessing the impact of loss to follow-up on estimates of neurodevelopmental impairment in a very preterm cohort at 2 years of age. *BMC Med Res Methodol* 21, 118.

Pierpaoli, C., Basser, P.J., 1996. Toward a quantitative assessment of diffusion anisotropy. *Magn Reson Med* 36, 893-906.

Pierpaoli, C., Jezzard, P., Basser, P.J., et al., 1996. Diffusion tensor mr imaging of the human brain. *Radiology* 201, 637-648.

Pieterman, K., White, T.J., van den Bosch, G.E., et al., 2018. Cerebellar growth impairment characterizes school-aged children born preterm without perinatal brain lesions. *AJNR Am J Neuroradiol* 39, 956-962.

Pineda, R., Durant, P., Mathur, A., et al., 2017a. Auditory exposure in the neonatal intensive care unit: Room type and other predictors. *J Pediatr* 183, 56-66.e53.

Pineda, R., Guth, R., Herring, A., et al., 2017b. Enhancing sensory experiences for very preterm infants in the nicu: An integrative review. *J Perinatol* 37, 323-332.

Pineda, R.G., Neil, J., Dierker, D., et al., 2014. Alterations in brain structure and neurodevelopmental outcome in preterm infants hospitalized in different neonatal intensive care unit environments. *J Pediatr* 164, 52-60.e52.

Piotrowska, P.J., Stride, C.B., Croft, S.E., et al., 2015. Socioeconomic status and antisocial behaviour among children and adolescents: A systematic review and meta-analysis. *Clin Psychol Rev* 35, 47-55.

Plunkett, J., Muglia, L.J., 2008. Genetic contributions to preterm birth: Implications from epidemiological and genetic association studies. *Ann Med* 40, 167-195.

Pogribna, U., Burson, K., Lasky, R.E., et al., 2014. Role of diffusion tensor imaging as an independent predictor of cognitive and language development in extremely low-birth-weight infants. *AJNR Am J Neuroradiol* 35, 790-796.

Pogribna, U., Yu, X., Burson, K., et al., 2013. Perinatal clinical antecedents of white matter microstructural abnormalities on diffusion tensor imaging in extremely preterm infants. *PloS One* 8, e72974.

Posner, M.I., Rothbart, M.K., Tang, Y., 2013. Developing self-regulation in early childhood. *Trends Neurosci Educ* 2, 107-110.

Potijk, M.R., de Winter, A.F., Bos, A.F., et al., 2012. Higher rates of behavioural and emotional problems at preschool age in children born moderately preterm. *Arch Dis Child* 97, 112-117.

Potijk, M.R., Kerstjens, J.M., Bos, A.F., et al., 2013. Developmental delay in moderately preterm-born children with low socioeconomic status: Risks multiply. *J Pediatr* 163, 1289-1295.

Power, J.D., Barnes, K.A., Snyder, A.Z., et al., 2012. Spurious but systematic correlations in functional connectivity mri networks arise from subject motion. *Neuroimage* 59, 2142-2154.

Preacher, K.J., MacCallum, R.C., 2003. Repairing tom swift's electric factor analysis machine. *Understanding Statistics* 2, 13-43.

Price, J.L., 2003. Comparative aspects of amygdala connectivity. *Ann N Y Acad Sci* 985, 50-58.

Pritchard, V.E., Bora, S., Austin, N.C., et al., 2014. Identifying very preterm children at educational risk using a school readiness framework. *Pediatrics* 134, e825-832.

Provenzi, L., Fumagalli, M., Bernasconi, F., et al., 2017. Very preterm and full‐term infants' response to socio‐emotional stress: The role of postnatal maternal bonding. *Infancy : the official journal of the International Society on Infant Studies* 22, 695-712.

Provenzi, L., Giusti, L., Fumagalli, M., et al., 2016. Pain-related stress in the neonatal intensive care unit and salivary cortisol reactivity to socio-emotional stress in 3-month-old very preterm infants. *Psychoneuroendocrinology* 72, 161-165.

Puthussery, S., Li, L., Tseng, P.-C., et al., 2019. Ethnic variations in risk of preterm birth in an ethnically dense socially disadvantaged area in the uk: A retrospective cross-sectional study. *BMJ open* 9, e023570.

Putnam, S.P., Ellis, L.K., Rothbart, M.K., 2001. The structure of temperament from infancy through adolescence, in: (Eds.), A.E.A.A. (Ed.), Advances in research on temperament, vol. 165. Pabst Science Publishers, Lengerich, Germany, pp. 164-182.

Putnam, S.P., Rothbart, M.K., 2006. Development of short and very short forms of the children's behavior questionnaire. *Journal of personality assessment* 87, 102-112.

Qin, S., Young, C.B., Supekar, K., et al., 2012. Immature integration and segregation of emotion-related brain circuitry in young children. *Proc Natl Acad Sci U S A* 109, 7941-7946.

Quirk, G.J., Likhtik, E., Pelletier, J.G., et al., 2003. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *J Neurosci* 23, 8800-8807.

Rademaker, K.J., Lam, J.N., Van Haastert, I.C., et al., 2004. Larger corpus callosum size with better motor performance in prematurely born children. *Semin Perinatol* 28, 279-287.

Raffelt, D.A., Smith, R.E., Ridgway, G.R., et al., 2015. Connectivity-based fixel enhancement: Whole-brain statistical analysis of diffusion mri measures in the presence of crossing fibres. *Neuroimage* 117, 40-55.

Raffelt, D.A., Tournier, J.D., Smith, R.E., et al., 2017. Investigating white matter fibre density and morphology using fixel-based analysis. *Neuroimage* 144, 58-73.

Raichle, M.E., 2015. The brain's default mode network. *Annu Rev Neurosci* 38, 433-447.

Ramasubbu, R., Konduru, N., Cortese, F., et al., 2014. Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. *Front Psychiatry* 5, 17.

Ramphal, B., Whalen, D.J., Kenley, J.K., et al., 2020. Brain connectivity and socioeconomic status at birth and externalizing symptoms at age 2 years. *Dev Cogn Neurosci* 45, 100811.

Rand, K.M., Austin, N.C., Inder, T.E., et al., 2016. Neonatal infection and later neurodevelopmental risk in the very preterm infant. *J Pediatr* 170, 97-104.

Ranger, M., Chau, C.M., Garg, A., et al., 2013. Neonatal pain-related stress predicts cortical thickness at age 7 years in children born very preterm. *PloS One* 8, e76702.

Ranger, M., Synnes, A.R., Vinall, J., et al., 2014. Internalizing behaviours in school-age children born very preterm are predicted by neonatal pain and morphine exposure. *Eur J Pain* 18, 844-852.

Ranger, M., Zwicker, J.G., Chau, C.M., et al., 2015. Neonatal pain and infection relate to smaller cerebellum in very preterm children at school age. *J Pediatr* 167, 292-298.e291.

Rastogi, P.K., Sreenivas, V., Kumar, N., 2010. Validation of crib ii for prediction of mortality in premature babies. *Indian pediatr* 47, 145-147.

Ratnarajah, N., Rifkin-Graboi, A., Fortier, M.V., et al., 2013. Structural connectivity asymmetry in the neonatal brain. *Neuroimage* 75, 187-194.

Raybaud, C., Ahmad, T., Rastegar, N., et al., 2013. The premature brain: Developmental and lesional anatomy. *Neuroradiology* 55, 23-40.

Redwood, S., Gill, P.S., 2013. Under-representation of minority ethnic groups in research—call for action. British Journal of General Practice, pp. 342-343.

Reidy, N., Morgan, A., Thompson, D.K., et al., 2013. Impaired language abilities and white matter abnormalities in children born very preterm and/or very low birth weight. *J Pediatr* 162, 719-724.

Reiss, A.L., Kesler, S.R., Vohr, B., et al., 2004. Sex differences in cerebral volumes of 8-year-olds born preterm. *J Pediatr* 145, 242-249.

Reiss, J.D., Peterson, L.S., Nesamoney, S.N., et al., 2022. Perinatal infection, inflammation, preterm birth, and brain injury: A review with proposals for future investigations. *Exp Neurol* 351, 113988.

Rempel-Clower, N.L., 2007. Role of orbitofrontal cortex connections in emotion. *Ann N Y Acad Sci* 1121, 72-86.

Reuter, M., Rosas, H.D., Fischl, B., 2010. Highly accurate inverse consistent registration: A robust approach. *Neuroimage* 53, 1181-1196.

Reyes, L.M., Jaekel, J., Kreppner, J., et al., 2020. A comparison of the effects of preterm birth and institutional deprivation on child temperament. *Dev Psychopathol* 32, 1524-1533.

Richardson, D.K., Corcoran, J.D., Escobar, G.J., et al., 2001. Snap-ii and snappe-ii: Simplified newborn illness severity and mortality risk scores. *J Pediatr* 138, 92-100.

Richardson, D.K., Gray, J.E., McCormick, M.C., et al., 1993. Score for neonatal acute physiology: A physiologic severity index for neonatal intensive care. *Pediatrics* 91, 617-623.

Richardson, J.T., Mittelmeier, J., Rienties, B., 2020. The role of gender, social class and ethnicity in participation and academic attainment in uk higher education: An update. *Oxf Rev Educ* 46, 346-362.

Rieffe, C., Ketelaar, L., Wiefferink, C.H., 2010. Assessing empathy in young children: Construction and validation of an empathy questionnaire (emque). *Pers Individ Dif* 49, 362-367.

Ritchie, K., Bora, S., Woodward, L.J., 2015. Social development of children born very preterm: A systematic review. *Dev Med Child Neurol* 57, 899-918.

Ritchie, K., Bora, S., Woodward, L.J., 2018. Peer relationship outcomes of school-age children born very preterm. *J Pediatr* 201, 238-244.

Robins, D.L., Fein, D., Barton, M.L., et al., 2001. The modified checklist for autism in toddlers: An initial study investigating the early detection of autism and pervasive developmental disorders. *J Autism Dev Disord* 31, 131-144.

Robins, R.W., John, O.P., Caspi, A., et al., 1996. Resilient, overcontrolled, and undercontrolled boys: Three replicable personality types. *Journal of personality and social psychology* 70, 157.

Robson, D.A., Allen, M.S., Howard, S.J., 2020. Self-regulation in childhood as a predictor of future outcomes: A meta-analytic review. *Psychological bulletin* 146, 324-354.

Rodger, H., Vizioli, L., Ouyang, X., et al., 2015. Mapping the development of facial expression recognition. *Developmental science* 18, 926-939.

Rogers, C.E., Anderson, P.J., Thompson, D.K., et al., 2012. Regional cerebral development at term relates to school-age social-emotional development in very preterm children. *Journal of the American Academy of Child and Adolescent Psychiatry* 51, 181-191.

Rogers, C.E., Barch, D.M., Sylvester, C.M., et al., 2014. Altered gray matter volume and school age anxiety in children born late preterm. *J Pediatr* 165, 928-935.

Rogers, C.E., Smyser, T., Smyser, C.D., et al., 2016. Regional white matter development in very preterm infants: Perinatal predictors and early developmental outcomes. *Pediatr Res* 79, 87-95.

Rogers, C.E., Sylvester, C.M., Mintz, C., et al., 2017. Neonatal amygdala functional connectivity at rest in healthy and preterm infants and early internalizing symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry* 56, 157-166.

Rohr, C.S., Arora, A., Cho, I.Y.K., et al., 2018. Functional network integration and attention skills in young children. *Dev Cogn Neurosci* 30, 200-211.

Rose, S.A., Feldman, J.F., 1996. Memory and processing speed in preterm children at eleven years: A comparison with full-terms. *Child Dev* 67, 2005-2021.

Rose, S.A., Feldman, J.F., Jankowski, J.J., 2002. Processing speed in the 1st year of life: A longitudinal study of preterm and full-term infants. *Dev Psychol* 38, 895-902.

Rose, S.A., Feldman, J.F., Jankowski, J.J., et al., 2011. The structure of memory in infants and toddlers: An sem study with full-terms and preterms. *Developmental science* 14, 83-91.

Rothbart, M., Derryberry, D., 1981. Development of individual differences in temperament, in: M. E. Lamb, A.L.B.E. (Ed.), Advances in developmental psychology, vol. Vol. 1. Lawrence Erlbaum Associates, Hillsdale, NJ, pp. 37-86.

Rothbart, M.K., Ahadi, S.A., Hershey, K.L., et al., 2001. Investigations of temperament at three to seven years: The children's behavior questionnaire. *Child Dev* 72, 1394-1408.

Rothbart, M.K., Bates, J.E., 1998. Temperament, Handbook of child psychology: Social, emotional, and personality development, vol. 3, 5th ed. John Wiley & Sons, Inc., Hoboken, NJ, US, pp. 105-176.

Rothbart, M.K., Sheese, B.E., Rueda, M.R., et al., 2011. Developing mechanisms of self-regulation in early life. *Emotion review : journal of the International Society for Research on Emotion* 3, 207-213.

Rudasill, K.M., Konold, T.R., 2008. Contributions of children's temperament to teachers' judgments of social competence from kindergarten through second grade. *Early Educ Dev* 19, 643-666.

Rudebeck, P.H., Mitz, A.R., Chacko, R.V., et al., 2013. Effects of amygdala lesions on reward-value coding in orbital and medial prefrontal cortex. *Neuron* 80, 1519-1531.

Rueckert, D., Frangi, A.F., Schnabel, J.A., 2003. Automatic construction of 3-d statistical deformation models of the brain using nonrigid registration. *IEEE Trans Med Imaging* 22, 1014-1025.

Rueckert, D., Sonoda, L.I., Hayes, C., et al., 1999. Nonrigid registration using free-form deformations: Application to breast mr images. *IEEE Trans Med Imaging* 18, 712-721.

Rueda, M.R., Fan, J., McCandliss, B.D., et al., 2004. Development of attentional networks in childhood. *Neuropsychologia* 42, 1029-1040.

Rueda, M.R., Pozuelos, J.P., Cómbita, L.M., 2015. Cognitive neuroscience of attention from brain mechanisms to individual differences in efficiency. *AIMS Neurosci* 2, 183-202.

Ruiz, N., Piskernik, B., Witting, A., et al., 2018. Parent-child attachment in children born preterm and at term: A multigroup analysis. *PLoS One* 13, e0202972.

Rushe, T.M., Rifkin, L., Stewart, A.L., et al., 2001. Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure. *Dev Med Child Neurol* 43, 226-233.

Sa de Almeida, J., Lordier, L., Zollinger, B., et al., 2020. Music enhances structural maturation of emotional processing neural pathways in very preterm infants. *Neuroimage* 207, 116391.

Saavalainen, P., Luoma, L., Bowler, D., et al., 2007. Spatial span in very prematurely born adolescents. *Dev Neuropsychol* 32, 769-785.

Saigal, S., Doyle, L.W., 2008. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 371, 261-269.

Salimi-Khorshidi, G., Douaud, G., Beckmann, C.F., et al., 2014. Automatic denoising of functional mri data: Combining independent component analysis and hierarchical fusion of classifiers. *Neuroimage* 90, 449-468.

Salvan, P., Tournier, J.D., Batalle, D., et al., 2017. Language ability in preterm children is associated with arcuate fasciculi microstructure at term. *Hum Brain Mapp* 38, 3836-3847.

Salzman, C.D., Fusi, S., 2010. Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. *Annu Rev Neurosci* 33, 173-202.

Salzwedel, A.P., Stephens, R.L., Goldman, B.D., et al., 2019. Development of amygdala functional connectivity during infancy and its relationship with 4-year behavioral outcomes. *Biol Psychiatry Cogn Neurosci Neuroimaging* 4, 62-71.

Samuelsson, M., Holsti, A., Adamsson, M., et al., 2017. Behavioral patterns in adolescents born at 23 to 25 weeks of gestation. *Pediatrics* 140, e20170199.

San José Cáceres, A., Keren, N., Booth, R., et al., 2014. Assessing theory of mind nonverbally in those with intellectual disability and asd: The p enny h iding g ame. *Autism Research* 7, 608-616.

Sandman, C.A., Glynn, L., Schetter, C.D., et al., 2006. Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (crh): Priming the placental clock. *Peptides* 27, 1457-1463.

Sarsour, K., Sheridan, M., Jutte, D., et al., 2011. Family socioeconomic status and child executive functions: The roles of language, home environment, and single parenthood. *J Int Neuropsychol Soc* 17, 120-132.

Sato, J., Vandewouw, M.M., Bando, N., et al., 2021. Early nutrition and white matter microstructure in children born very low birth weight. *Brain Commun* 3, fcab066.

Sato, M., Nishimaki, S., Yokota, S., et al., 2011. Severity of chorioamnionitis and neonatal outcome. *J Obstet Gynaecol Res* 37, 1313-1319.

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., et al., 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage* 64, 240-256.

Savitz, D.A., Terry, J.W., Jr., Dole, N., et al., 2002. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. *Am J Obstet Gynecol* 187, 1660-1666.

Schafer, R.J., Lacadie, C., Vohr, B., et al., 2009. Alterations in functional connectivity for language in prematurely born adolescents. *Brain* 132, 661-670.

Scheinost, D., Kwon, S.H., Lacadie, C., et al., 2016a. Prenatal stress alters amygdala functional connectivity in preterm neonates. *Neuroimage Clin* 12, 381-388.

Scheinost, D., Kwon, S.H., Shen, X., et al., 2016b. Preterm birth alters neonatal, functional rich club organization. *Brain Struct Funct* 221, 3211-3222.

Schieve, L.A., Tian, L.H., Rankin, K., et al., 2016. Population impact of preterm birth and low birth weight on developmental disabilities in us children. *Ann Epidemiol* 26, 267-274.

Schmidt, L.A., Miskovic, V., Boyle, M.H., et al., 2008. Shyness and timidity in young adults who were born at extremely low birth weight. *Pediatrics* 122, e181-187.

Schmithorst, V.J., Wilke, M., Dardzinski, B.J., et al., 2002. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: A cross-sectional diffusion-tensor mr imaging study. *Radiology* 222, 212-218.

Schneider, J., Fumeaux, C.J.F., Duerden, E.G., et al., 2018. Nutrient intake in the first two weeks of life and brain growth in preterm neonates. *Pediatrics* 141.

Schultz, R.T., Grelotti, D.J., Klin, A., et al., 2003. The role of the fusiform face area in social cognition: Implications for the pathobiology of autism. *Philos Trans R Soc Lond B Biol Sci* 358, 415-427.

Serag, A., Aljabar, P., Ball, G., et al., 2012. Construction of a consistent high-definition spatio-temporal atlas of the developing brain using adaptive kernel regression. *Neuroimage* 59, 2255-2265.

Shah, D.K., Doyle, L.W., Anderson, P.J., et al., 2008. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr* 153, 170-175.e171.

Shaw, P., Kabani, N.J., Lerch, J.P., et al., 2008. Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci* 28, 3586-3594.

Sherman, L.E., Rudie, J.D., Pfeifer, J.H., et al., 2014. Development of the default mode and central executive networks across early adolescence: A longitudinal study. *Dev Cogn Neurosci* 10, 148-159.

Shi, F., Yap, P.T., Wu, G., et al., 2011. Infant brain atlases from neonates to 1- and 2-year-olds. *PLoS One* 6, e18746.

Shim, S.Y., Jeong, H.J., Son, D.W., et al., 2012. Altered microstructure of white matter except the corpus callosum is independent of prematurity. *Neonatology* 102, 309-315.

Shrim, A., Ates, S., Mallozzi, A., et al., 2011. Is young maternal age really a risk factor for adverse pregnancy outcome in a canadian tertiary referral hospital? *J Pediatr Adolesc Gynecol* 24, 218-222.

Silveira, F., Shafer, K., Dufur, M.J., et al., 2021. Ethnicity and parental discipline practices: A cross‐national comparison. *J Marriage Fam* 83, 644-666.

Silvers, J.A., Insel, C., Powers, A., et al., 2017. Vlpfc–vmpfc–amygdala interactions underlie age-related differences in cognitive regulation of emotion. *Cereb Cortex* 27, 3502-3514.

Simcock, G., McLoughlin, L.T., De Regt, T., et al., 2020. Associations between facial emotion recognition and mental health in early adolescence. *Int J Environ Res Public Health* 17, 330.

Simmons, W.K., Reddish, M., Bellgowan, P.S.F., et al., 2010. The selectivity and functional connectivity of the anterior temporal lobes. *Cereb Cortex* 20, 813-825.

Simonds, J., Rothbart, M.K., 2004. The temperament in middle childhood questionnaire (tmcq): A computerized self-report instrument for ages 7–10, Poster Sess Present Occas Temperament Conf Athens, GA.

Skranes, J., Vangberg, T.R., Kulseng, S., et al., 2007. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain* 130, 654-666.

Slater, R., Cantarella, A., Gallella, S., et al., 2006. Cortical pain responses in human infants. *J Neurosci* 26, 3662-3666.

Smiley, P.A., Dweck, C.S., 1994. Individual differences in achievement goals among young children. *Child Dev* 65, 1723-1743.

Smith, A.P.R., Stephan, K.E., Rugg, M.D., et al., 2006. Task and content modulate amygdala-hippocampal connectivity in emotional retrieval. *Neuron* 49, 631-638.

Smith, G.C., Gutovich, J., Smyser, C., et al., 2011. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol* 70, 541-549.

Smith, L.K., Draper, E.S., Manktelow, B.N., et al., 2007. Socioeconomic inequalities in very preterm birth rates. *Arch Dis Child Fetal Neonatal Ed* 92, F11-14.

Smith, R.E., Tournier, J.D., Calamante, F., et al., 2013. Sift: Spherical-deconvolution informed filtering of tractograms. *Neuroimage* 67, 298-312.

Smith, S.M., 2002. Fast robust automated brain extraction. *Hum Brain Mapp* 17, 143-155.

Smith, S.M., Fox, P.T., Miller, K.L., et al., 2009. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A* 106, 13040-13045.

Smith, S.M., Jenkinson, M., Woolrich, M.W., et al., 2004. Advances in functional and structural mr image analysis and implementation as fsl. *Neuroimage* 23 Suppl 1, S208-219.

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 44, 83-98.

Smith-Donald, R., Raver, C.C., Hayes, T., et al., 2007. Preliminary construct and concurrent validity of the preschool self-regulation assessment (psra) for field-based research. *Early Child Res Q* 22, 173-187.

Smyser, C.D., Inder, T.E., Shimony, J.S., et al., 2010. Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex* 20, 2852-2862.

Smyser, C.D., Snyder, A.Z., Shimony, J.S., et al., 2016. Resting-state network complexity and magnitude are reduced in prematurely born infants. *Cereb Cortex* 26, 322-333.

Snook, L., Paulson, L.-A., Roy, D., et al., 2005. Diffusion tensor imaging of neurodevelopment in children and young adults. *Neuroimage* 26, 1164-1173.

Soares, J.M., Magalhães, R., Moreira, P.S., et al., 2016. A hitchhiker's guide to functional magnetic resonance imaging. *Front Neurosci* 10, 515.

Sølsnes, A.E., Grunewaldt, K.H., Bjuland, K.J., et al., 2015. Cortical morphometry and iq in vlbw children without cerebral palsy born in 2003-2007. *Neuroimage Clin* 8, 193-201.

Sølsnes, A.E., Sripada, K., Yendiki, A., et al., 2016. Limited microstructural and connectivity deficits despite subcortical volume reductions in school-aged children born preterm with very low birth weight. *Neuroimage* 130, 24-34.

Somerville, L.H., Jones, R.M., Ruberry, E.J., et al., 2013. The medial prefrontal cortex and the emergence of self-conscious emotion in adolescence. *Psychol Sci* 24, 1554-1562.

Song, S.-K., Sun, S.-W., Ju, W.-K., et al., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 20, 1714-1722.

Song, S.-K., Sun, S.-W., Ramsbottom, M.J., et al., 2002a. Dysmyelination revealed through mri as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17, 1429-1436.

Song, S.K., Sun, S.W., Ramsbottom, M.J., et al., 2002b. Dysmyelination revealed through mri as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17, 1429-1436.

Song, S.K., Yoshino, J., Le, T.Q., et al., 2005. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage* 26, 132-140.

Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., et al., 1977. State and trait anxiety inventory for adults. Mind Garden, Redwood City, CA.

Spinrad, T.L., Eisenberg, N., Harris, E., et al., 2004. The relation of children's everyday nonsocial peer play behavior to their emotionality, regulation, and social functioning. *Dev Psychol* 40, 67-80.

Spittle, A.J., Thompson, D.K., Olsen, J.E., et al., 2021. Predictors of long-term neurodevelopmental outcomes of children born extremely preterm. *Semin Perinatol*, 151482.

Spittle, A.J., Treyvaud, K., Doyle, L.W., et al., 2009. Early emergence of behavior and social-emotional problems in very preterm infants. *Journal of the American Academy of Child and Adolescent Psychiatry* 48, 909-918.

Srinivasan, L., Dutta, R., Counsell, S.J., et al., 2007. Quantification of deep gray matter in preterm infants at term-equivalent age using manual volumetry of 3-tesla magnetic resonance images. *Pediatrics* 119, 759-765.

Stålnacke, J., Lundequist, A., Böhm, B., et al., 2019. A longitudinal model of executive function development from birth through adolescence in children born very or extremely preterm. *Child Neuropsychol* 25, 318-335.

Stein, Z., Susser, M., 2000. The risks of having children in later life: Social advantage may make up for biological disadvantage. *BMJ* 320, 1681-1682.

Steinhorn, R., McPherson, C., Anderson, P.J., et al., 2015. Neonatal morphine exposure in very preterm infants-cerebral development and outcomes. *J Pediatr* 166, 1200-1207.e1204.

Sternberg, R.J., 2000. Handbook of intelligence. Cambridge University Press.

Stevenson, R.A., Segers, M., Ferber, S., et al., 2014. The impact of multisensory integration deficits on speech perception in children with autism spectrum disorders. *Front Psychol* 5, 379.

Stewart, A.L., Rifkin, L., Amess, P.N., et al., 1999. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. *Lancet* 353, 1653-1657.

Supekar, K., Musen, M., Menon, V., 2009. Development of large-scale functional brain networks in children. *PLoS biology* 7, e1000157-e1000157.

Supekar, K., Uddin, L.Q., Prater, K., et al., 2010. Development of functional and structural connectivity within the default mode network in young children. *Neuroimage* 52, 290-301.

Suprano, I., Kocevar, G., Stamile, C., et al., 2020. White matter microarchitecture and structural network integrity correlate with children intelligence quotient. *Scientific reports* 10, 20722.

Suzuki, Y., Matsuzawa, H., Kwee, I.L., et al., 2003. Absolute eigenvalue diffusion tensor analysis for human brain maturation. *NMR Biomed* 16, 257-260.

Sylvester, C.M., Smyser, C.D., Smyser, T., et al., 2018a. Cortical functional connectivity evident after birth and behavioral inhibition at age 2. *Am J Psychiatry* 175, 180-187.

Sylvester, C.M., Whalen, D.J., Belden, A.C., et al., 2018b. Shyness and trajectories of functional network connectivity over early adolescence. *Child Dev* 89, 734-745.

Takahashi, M., Ono, J., Harada, K., et al., 2000. Diffusional anisotropy in cranial nerves with maturation: Quantitative evaluation with diffusion mr imaging in rats. *Radiology* 216, 881-885.

Tam, E.W.Y., Chau, V., Ferriero, D.M., et al., 2011. Preterm cerebellar growth impairment after postnatal exposure to glucocorticoids. *Sci Transl Med* 3, 105ra105-105ra105.

Tang, Y.-Y., Tang, Y., Tang, R., et al., 2017. Brief mental training reorganizes large-scale brain networks. *Front Syst Neurosci* 11, 6.

Tarnow-Mordi, W., Ogston, S., Wilkinson, A.R., et al., 1990. Predicting death from initial disease severity in very low birthweight infants: A method for comparing the performance of neonatal units. *BMJ* 300, 1611-1614.

Taylor, H.G., Clark, C.A., 2016. Executive function in children born preterm: Risk factors and implications for outcome, Semin Perinatol. Elsevier, pp. 520-529.

Taylor, H.G., Margevicius, S., Schluchter, M., et al., 2015. Persisting behavior problems in extremely low birth weight adolescents. *J Dev Behav Pediatr* 36, 178-187.

Taylor, H.G., Minich, N.M., Klein, N., et al., 2004. Longitudinal outcomes of very low birth weight: Neuropsychological findings. *J Int Neuropsychol Soc* 10, 149-163.

Taylor, M.J., Donner, E.J., Pang, E.W., 2012. Fmri and meg in the study of typical and atypical cognitive development. *Neurophysiol Clin* 42, 19-25.

Team, R.C., 2013. R: A language and environment for statistical computing.

Teixeira, R., Queiroga, A.C., Freitas, A.I., et al., 2021. Completeness of retention data and determinants of attrition in birth cohorts of very preterm infants: A systematic review. *Front Pediatr* 9, 30.

Theunissen, M.H.C., de Wolff, M.S., Reijneveld, S.A., 2019. The strengths and difficulties questionnaire self-report: A valid instrument for the identification of emotional and behavioral problems. *Acad Pediatr* 19, 471-476.

Theurel, A., Witt, A., Malsert, J., et al., 2016. The integration of visual context information in facial emotion recognition in 5- to 15-year-olds. *J Exp Child Psychol* 150, 252-271.

Thomas, L.A., De Bellis, M.D., Graham, R., et al., 2007. Development of emotional facial recognition in late childhood and adolescence. *Developmental science* 10, 547-558.

Thomason, M.E., Dassanayake, M.T., Shen, S., et al., 2013. Cross-hemispheric functional connectivity in the human fetal brain. *Sci Transl Med* 5, 173ra124.

Thomason, M.E., Grove, L.E., Lozon, T.A., Jr., et al., 2015. Age-related increases in long-range connectivity in fetal functional neural connectivity networks in utero. *Dev Cogn Neurosci* 11, 96-104.

Thompson, D., Yuan-Mou Yang, J., Chen, J., et al., 2021. Brain white matter development over the first 13 years in very preterm and typically developing children based on the t1-w/t2-w ratio. *Neurology*, [Epub ahead of print].

Thompson, D.K., Chen, J., Beare, R., et al., 2016. Structural connectivity relates to perinatal factors and functional impairment at 7years in children born very preterm. *Neuroimage* 134, 328-337.

Thompson, D.K., Inder, T.E., Faggian, N., et al., 2011. Characterization of the corpus callosum in very preterm and full-term infants utilizing mri. *Neuroimage* 55, 479-490.

Thompson, D.K., Inder, T.E., Faggian, N., et al., 2012. Corpus callosum alterations in very preterm infants: Perinatal correlates and 2 year neurodevelopmental outcomes. *Neuroimage* 59, 3571-3581.

Thompson, D.K., Kelly, C.E., Chen, J., et al., 2019. Characterisation of brain volume and microstructure at term-equivalent age in infants born across the gestational age spectrum. *Neuroimage Clin* 21, 101630.

Thompson, D.K., Loh, W.Y., Connelly, A., et al., 2020. Basal ganglia and thalamic tract connectivity in very preterm and full-term children; associations with 7-year neurodevelopment. *Pediatr Res* 87, 48-56.

Thompson, D.K., Omizzolo, C., Adamson, C., et al., 2014. Longitudinal growth and morphology of the hippocampus through childhood: Impact of prematurity and implications for memory and learning. *Hum Brain Mapp* 35, 4129-4139.

Thompson, J.M., Irgens, L.M., Rasmussen, S., et al., 2006. Secular trends in socio-economic status and the implications for preterm birth. *Paediatr Perinat Epidemiol* 20, 182-187.

Thompson, R.A., 1994. Emotion regulation: A theme in search of definition. *Monogr Soc Res Child Dev* 59, 25-52.

Thompson, S.A., Patterson, K., Hodges, J.R., 2003. Left/right asymmetry of atrophy in semantic dementia: Behavioral–cognitive implications. *Neurology* 61, 1196-1203.

Tokariev, M., Vuontela, V., Lönnberg, P., et al., 2019. Altered working memory-related brain responses and white matter microstructure in extremely preterm-born children at school age. *Brain Cogn* 136, 103615.

Toledano, M.B., Smith, R.B., Fecht, D., et al., 2018. Traffic-related air and noise pollution, preterm birth and stillbirth in london, ISEE Conference Abstracts.

Torrioli, M.G., Frisone, M.F., Bonvini, L., et al., 2000. Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities. *Brain Dev* 22, 163-168.

Toulmin, H., Beckmann, C.F., O'Muircheartaigh, J., et al., 2015. Specialization and integration of functional thalamocortical connectivity in the human infant. *Proc Natl Acad Sci U S A* 112, 6485-6490.

Toulmin, H., O'Muircheartaigh, J., Counsell, S.J., et al., 2021. Functional thalamocortical connectivity at term equivalent age and outcome at 2 years in infants born preterm. *Cortex; a journal devoted to the study of the nervous system and behavior* 135, 17-29.

Tournier, J.-D., Mori, S., Leemans, A., 2011. Diffusion tensor imaging and beyond. *Magn Reson Med* 65, 1532.

Tournier, J.D., Calamante, F., Connelly, A., 2007. Robust determination of the fibre orientation distribution in diffusion mri: Non-negativity constrained super-resolved spherical deconvolution. *Neuroimage* 35, 1459-1472.

Tournier, J.D., Calamante, F., Gadian, D.G., et al., 2004. Direct estimation of the fiber orientation density function from diffusion-weighted mri data using spherical deconvolution. *Neuroimage* 23, 1176-1185.

Tournier, J.D., Smith, R., Raffelt, D., et al., 2019. Mrtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *Neuroimage* 202, 116137.

Travis, K.E., Adams, J.N., Ben-Shachar, M., et al., 2015. Decreased and increased anisotropy along major cerebral white matter tracts in preterm children and adolescents. *PLoS One* 10, e0142860.

Travis, K.E., Ben-Shachar, M., Myall, N.J., et al., 2016. Variations in the neurobiology of reading in children and adolescents born full term and preterm. *Neuroimage Clin* 11, 555-565.

Travis, K.E., Castro, M.R.H., Berman, S., et al., 2019. More than myelin: Probing white matter differences in prematurity with quantitative t1 and diffusion mri. *Neuroimage Clin* 22, 101756.

Treloar, S.A., Macones, G.A., Mitchell, L.E., et al., 2000. Genetic influences on premature parturition in an australian twin sample. *Twin Res* 3, 80-82.

Treyvaud, K., Ure, A., Doyle, L.W., et al., 2013. Psychiatric outcomes at age seven for very preterm children: Rates and predictors. *J Child Psychol Psychiatry* 54, 772-779.

Troller-Renfree, S.V., Buzzell, G.A., Bowers, M.E., et al., 2019. Development of inhibitory control during childhood and its relations to early temperament and later social anxiety: Unique insights provided by latent growth modeling and signal detection theory. *J Child Psychol Psychiatry* 60, 622-629.

Tu, T.W., Williams, R.A., Lescher, J.D., et al., 2016. Radiological–pathological correlation of diffusion tensor and magnetization transfer imaging in a closed head traumatic brain injury model. *Ann Neurol* 79, 907-920.

Tustison, N.J., Avants, B.B., Cook, P.A., et al., 2010. N4itk: Improved n3 bias correction. *IEEE Trans Med Imaging* 29, 1310-1320.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., et al., 2002. Automated anatomical labeling of activations in spm using a macroscopic anatomical parcellation of the mni mri single-subject brain. *Neuroimage* 15, 273-289.

Uddin, L.Q., Supekar, K.S., Ryali, S., et al., 2011. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *J Neurosci* 31, 18578-18589.

Ullman, H., Spencer-Smith, M., Thompson, D.K., et al., 2015. Neonatal mri is associated with future cognition and academic achievement in preterm children. *Brain* 138, 3251-3262.

Unger, A., Alm, K.H., Collins, J.A., et al., 2016. Variation in white matter connectivity predicts the ability to remember faces and discriminate their emotions. *J Int Neuropsychol Soc* 22, 180-190.

Unsworth, N., Engle, R.W., 2007. The nature of individual differences in working memory capacity: Active maintenance in primary memory and controlled search from secondary memory. *Psychol Rev* 114, 104.

Urbain, C., Sato, J., Hammill, C., et al., 2019. Converging function, structure, and behavioural features of emotion regulation in very preterm children. *Hum Brain Mapp* 40, 3385-3397.

Vaccaro, S.M., Tofighi, D., Moss, N., et al., 2021. The association of infant temperament and maternal sensitivity in preterm and full-term infants. *Infant Ment Health J* 42, 374-385.

van de Weijer-Bergsma, E., Wijnroks, L., Jongmans, M.J., 2008. Attention development in infants and preschool children born preterm: A review. *Infant Behav Dev* 31, 333-351.

Van Den Broek, N., Ntonya, C., Kayira, E., et al., 2005. Preterm birth in rural malawi: High incidence in ultrasound-dated population. *Hum Reprod* 20, 3235-3237.

Van Dijk, K.R., Sabuncu, M.R., Buckner, R.L., 2012. The influence of head motion on intrinsic functional connectivity mri. *Neuroimage* 59, 431-438.

van Kooij, B.J., de Vries, L.S., Ball, G., et al., 2012. Neonatal tract-based spatial statistics findings and outcome in preterm infants. *AJNR Am J Neuroradiol* 33, 188-194.

van Os, J., Kenis, G., Rutten, B.P., 2010. The environment and schizophrenia. *Nature* 468, 203-212.

van Pul, C., van Kooij, B.J., de Vries, L.S., et al., 2012a. Quantitative fiber tracking in the corpus callosum and internal capsule reveals microstructural abnormalities in preterm infants at term-equivalent age. *AJNR Am J Neuroradiol* 33, 678-684.

van Pul, C., van Kooij, B.J.M., de Vries, L.S., et al., 2012b. Quantitative fiber tracking in the corpus callosum and internal capsule reveals microstructural abnormalities in preterm infants at term-equivalent age. *AJNR Am J Neuroradiol* 33, 678-684.

Van Steenwinckel, J., Schang, A.-L., Sigaut, S., et al., 2014. Brain damage of the preterm infant: New insights into the role of inflammation. *Biochem Soc Trans* 42, 557-563.

Veraart, J., Fieremans, E., Novikov, D.S., 2016. Diffusion mri noise mapping using random matrix theory. *Magn Reson Med* 76, 1582-1593.

Vieira, M.E., Linhares, M.B., 2011. Developmental outcomes and quality of life in children born preterm at preschool- and school-age. *J Pediatr* 87, 281-291.

Vinall, J., Grunau, R.E., 2014. Impact of repeated procedural pain-related stress in infants born very preterm. *Pediatr Res* 75, 584-587.

Vohr, B., 2014. Speech and language outcomes of very preterm infants. *Semin Fetal Neonatal Med* 19, 78-83.

Voigt, B., Brandl, A., Pietz, J., et al., 2013. Negative reactivity in toddlers born prematurely: Indirect and moderated pathways considering self-regulation, neonatal distress and parenting stress. *Infant Behav Dev* 36, 124-138.

Vollmer, B., Lundequist, A., Martensson, G., et al., 2017. Correlation between white matter microstructure and executive functions suggests early developmental influence on long fibre tracts in preterm born adolescents. *PLoS One* 12, e0178893.

Vollmer, B., Stålnacke, J., 2019. Young adult motor, sensory, and cognitive outcomes and longitudinal development after very and extremely preterm birth. *Neuropediatrics* 50, 219-227.

Volpe, J.J., 2001. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res* 50, 553-562.

Volpe, J.J., 2009a. Brain injury in premature infants: A complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 8, 110-124.

Volpe, J.J., 2009b. Cerebellum of the premature infant: Rapidly developing, vulnerable, clinically important. *J Child Neurol* 24, 1085-1104.

von Allmen, D.Y., Wurmitzer, K., Klaver, P., 2014. Hippocampal and posterior parietal contributions to developmental increases in visual short-term memory capacity. *Cortex; a journal devoted to the study of the nervous system and behavior* 59, 95-102.

Von Der Heide, R.J., Skipper, L.M., Klobusicky, E., et al., 2013. Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain* 136, 1692-1707.

von Eye, A., Bergman, L.R., 2003. Research strategies in developmental psychopathology: Dimensional identity and the person-oriented approach. *Dev Psychopathol* 15, 553-580.

Vongas, J.G., Al Hajj, R., 2015. The evolution of empathy and women's precarious leadership appointments. *Front Psychol* 6, 1751.

Wagner, R.K., Torgesen, J.K., Rashotte, C.A., et al., 1999. Comprehensive test of phonological processing: Ctopp. Pro-ed Austin, TX.

Wakschlag, L.S., Leventhal, B.L., Briggs-Gowan, M.J., et al., 2005. Defining the “disruptive” in preschool behavior: What diagnostic observation can teach us. *Clin Child Fam Psychol Rev* 8, 183-201.

Wang, S., Fan, G., Xu, K., et al., 2013. Potential of diffusion tensor mr imaging in the assessment of cognitive impairments in children with periventricular leukomalacia born preterm. *European journal of radiology* 82, 158-164.

Wang, X., Hagberg, H., Nie, C., et al., 2007. Dual role of intrauterine immune challenge on neonatal and adult brain vulnerability to hypoxia-ischemia. *J Neuropathol Exp Neurol* 66, 552-561.

Watson, A.C., Nixon, C.L., Wilson, A., et al., 1999. Social interaction skills and theory of mind in young children. *Dev Psychol* 35, 386-391.

Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: The panas scales. *Journal of personality and social psychology* 54, 1063-1070.

Wechsler, D., 2003. Wechsler intelligence scale for children–fourth edition (wisc-iv). The Psychological Corporation, San Antonio, TX.

Wechsler, D., 2012. Wechsler preschool and primary scale of intelligence—fourth edition. The Psychological Corporation San Antonio, TX.

Wechsler, D., 2014. Wechsler intelligence scale for children-fifth edition. Pearson, Bloomington, MN.

Weissberg, R., Goren, P., Domitrovich, C., et al., 2013. Casel guide effective social and emotional learning programs: Preschool and elementary school edition. CASEL, Chicago, IL:.

Wendler, D., Kington, R., Madans, J., et al., 2006. Are racial and ethnic minorities less willing to participate in health research? *PLoS Med* 3, e19.

Werry, J.S., Quay, H.C., 1971. The prevalence of behavior symptoms in younger elementary school children. *The American journal of orthopsychiatry* 41, 136-143.

Westergaard, N., Gehring, U., Slama, R., et al., 2017. Ambient air pollution and low birth weight - are some women more vulnerable than others? *Environ Int* 104, 146-154.

Wheelock, M.D., Austin, N.C., Bora, S., et al., 2018. Altered functional network connectivity relates to motor development in children born very preterm. *Neuroimage* 183, 574-583.

Wheelock, M.D., Lean, R.E., Bora, S., et al., 2021. Functional connectivity network disruption underlies domain-specific impairments in attention for children born very preterm. *Cereb Cortex* 31, 1383-1394.

WHO, 1977. Who: Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. *Acta Obstet Gynecol Scand* 56, 247-253.

Wickremasinghe, A.C., Rogers, E.E., Johnson, B.C., et al., 2013. Children born prematurely have atypical sensory profiles. *J Perinatol* 33, 631-635.

Widen, S.C., Russell, J.A., 2013. Children's recognition of disgust in others. *Psychological bulletin* 139, 271-299.

Wilke, M., Hauser, T.K., Krägeloh-Mann, I., et al., 2014. Specific impairment of functional connectivity between language regions in former early preterms. *Hum Brain Mapp* 35, 3372-3384.

Williamson, K.E., Jakobson, L.S., 2014. Social attribution skills of children born preterm at very low birth weight. *Dev Psychopathol* 26, 889-900.

Wilson-Ching, M., Molloy, C.S., Anderson, V.A., et al., 2013. Attention difficulties in a contemporary geographic cohort of adolescents born extremely preterm/extremely low birth weight. *J Int Neuropsychol Soc* 19, 1097-1108.

Witham, M.D., Anderson, E., Carroll, C.B., et al., 2020. Ensuring that covid-19 research is inclusive: Guidance from the nihr include project. *BMJ open* 10, e043634.

Wocadlo, C., Rieger, I., 2007. Phonology, rapid naming and academic achievement in very preterm children at eight years of age. *Early Hum Dev* 83, 367-377.

Wolf, M.J., Koldewijn, K., Beelen, A., et al., 2002. Neurobehavioral and developmental profile of very low birthweight preterm infants in early infancy. *Acta Paediatr* 91, 930-938.

Wolke, D., 2019. Is social inequality in cognitive outcomes increased by preterm birth–related complications? *JAMA Netw Open* 2, e192902-e192902.

Wolke, D., Baumann, N., Strauss, V., et al., 2015. Bullying of preterm children and emotional problems at school age: Cross-culturally invariant effects. *J Pediatr* 166, 1417-1422.

Wolke, D., Samara, M., Bracewell, M., et al., 2008. Specific language difficulties and school achievement in children born at 25 weeks of gestation or less. *J Pediatr* 152, 256-262.

Wong, H.S., Edwards, P., 2013. Nature or nurture: A systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. *Matern Child Health J* 17, 1689-1700.

Woodward, L.J., Bora, S., Clark, C.A., et al., 2014. Very preterm birth: Maternal experiences of the neonatal intensive care environment. *J Perinatol* 34, 555-561.

Woodward, L.J., Clark, C.A., Bora, S., et al., 2012. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. *PLoS One* 7, e51879.

Woodward, L.J., Clark, C.A., Pritchard, V.E., et al., 2011. Neonatal white matter abnormalities predict global executive function impairment in children born very preterm. *Dev Neuropsychol* 36, 22-41.

Woodward, L.J., Moor, S., Hood, K.M., et al., 2009. Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years. *Arch Dis Child Fetal Neonatal Ed* 94, F339-344.

Woolrich, M.W., Ripley, B.D., Brady, M., et al., 2001. Temporal autocorrelation in univariate linear modeling of fmri data. *Neuroimage* 14, 1370-1386.

Wright, R., Kyriakopoulou, V., Ledig, C., et al., 2014. Automatic quantification of normal cortical folding patterns from fetal brain mri. *Neuroimage* 91, 21-32.

Yaple, Z., Arsalidou, M., 2018. N-back working memory task: Meta-analysis of normative fmri studies with children. *Child Dev* 89, 2010-2022.

Yates, R., Treyvaud, K., Doyle, L.W., et al., 2020. Rates and stability of mental health disorders in children born very preterm at 7 and 13 years. *Pediatrics* 145, e20192699.

Yates, T., Ostrosky, M.M., Cheatham, G.A., et al., 2008. Research synthesis on screening and assessing social-emotional competence. Center on the Social and Emotional Foundations for Early Learning, pp. 1-19.

Ye, A.X., AuCoin-Power, M., Taylor, M.J., et al., 2016. Disconnected neuromagnetic networks in children born very preterm: Disconnected meg networks in preterm children. *Neuroimage Clin* 11, 376-384.

Ylijoki, M., Ekholm, E., Haataja, L., et al., 2012. Is chorioamnionitis harmful for the brain of preterm infants? A clinical overview. *Acta Obstet Gynecol Scand* 91, 403-419.

York, T.P., Eaves, L.J., Neale, M.C., et al., 2014. The contribution of genetic and environmental factors to the duration of pregnancy. *Am J Obstet Gynecol* 210, 398-405.

Young, J.M., Morgan, B.R., Whyte, H.E.A., et al., 2017. Longitudinal study of white matter development and outcomes in children born very preterm. *Cereb Cortex* 27, 4094-4105.

Young, J.M., Powell, T.L., Morgan, B.R., et al., 2015. Deep grey matter growth predicts neurodevelopmental outcomes in very preterm children. *Neuroimage* 111, 360-368.

Young, J.M., Vandewouw, M.M., Morgan, B.R., et al., 2018. Altered white matter development in children born very preterm. *Brain Struct Funct* 223, 2129-2141.

Young, J.M., Vandewouw, M.M., Mossad, S.I., et al., 2019. White matter microstructural differences identified using multi-shell diffusion imaging in six-year-old children born very preterm. *Neuroimage Clin* 23, 101855.

Yung, A., Poon, G., Qiu, D.Q., et al., 2007. White matter volume and anisotropy in preterm children: A pilot study of neurocognitive correlates. *Pediatr Res* 61, 732-736.

Zahn, R., Moll, J., Krueger, F., et al., 2007. Social concepts are represented in the superior anterior temporal cortex. *Proc Natl Acad Sci U S A* 104, 6430-6435.

Zahn-Waxler, C., Radke-Yarrow, M., Wagner, E., et al., 1992. Development of concern for others. *Dev Psychol* 28, 126-136.

Zardo, M.S., Procianoy, R.S., 2003. Comparison between different mortality risk scores in a neonatal intensive care unit. *Rev Saude Publica* 37, 591-596.

Zare, M., Narayan, M., Lasway, A., et al., 2018. Influence of adverse childhood experiences on anxiety and depression in children aged 6 to 11 years. *Pediatr Nurs* 44, 267-274.

Zelazo, P.D., 2006. The dimensional change card sort (dccs): A method of assessing executive function in children. *Nat Protoc* 1, 297-301.

Zeng, L.-L., Shen, H., Liu, L., et al., 2012. Identifying major depression using whole-brain functional connectivity: A multivariate pattern analysis. *Brain* 135, 1498-1507.

Zentner, M., Shiner, R.L., 2012. Fifty years of progress in temperament research: A synthesis of major themes, findings, and challenges and a look forward. The Guilford Press.

Zhang, H., Schneider, T., Wheeler-Kingshott, C.A., et al., 2012. Noddi: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage* 61, 1000-1016.

Zhang, H., Shen, D., Lin, W., 2019. Resting-state functional mri studies on infant brains: A decade of gap-filling efforts. *Neuroimage* 185, 664-684.

Zhao, T., Mishra, V., Jeon, T., et al., 2019. Structural network maturation of the preterm human brain. *Neuroimage* 185, 699-710.

Zimine, S., Lazeyras, F., Henry, F., et al., 2002. Study of brain development by diffusion tensor imaging: Evidence of altered brain development in newborn babies with intrauterine growth restriction, Proc Intl Soc Mag Reson Med.

Zubiaurre-Elorza, L., Soria-Pastor, S., Junqué, C., et al., 2012a. Thalamic changes in a preterm sample with periventricular leukomalacia: Correlation with white-matter integrity and cognitive outcome at school age. *Pediatr Res* 71, 354-360.

Zubiaurre-Elorza, L., Soria-Pastor, S., Junque, C., et al., 2012b. Cortical thickness and behavior abnormalities in children born preterm. *PLoS One* 7, e42148.

Zvara, B.J., Keim, S.A., Boone, K.M., et al., 2019. Associations between parenting behavior and executive function among preschool-aged children born very preterm. *Early Child Res Q* 48, 317-324.

Zwicker, J.G., Grunau, R.E., Adams, E., et al., 2013. Score for neonatal acute physiology–ii and neonatal pain predict corticospinal tract development in premature newborns. *Pediatric neurology* 48, 123-129. e121.

Appendix A

This section is presented as a published journal article and is an exact copy of the following publication.

Kanel, D., Counsell, S.J., Nosarti, C., 2021. Advances in functional and diffusion neuroimaging research into the long-term consequences of very preterm birth. *J Perinatol* 41, 689-706.

Word count: 4,631

Journal of Perinatology (2021) 41:689–706
https://doi.org/10.1038/s41372-020-00865-y

REVIEW ARTICLE

Advances in functional and diffusion neuroimaging research into the long-term consequences of very preterm birth

Dana Kanel[1,2] · Serena J. Counsell[1] · Chiara Nosarti[1,2]

Received: 13 May 2020 / Revised: 21 September 2020 / Accepted: 12 October 2020 / Published online: 24 October 2020

Abstract
Very preterm birth (<32 weeks of gestation) has been associated with lifelong difficulties in a variety of neurocognitive functions. Magnetic resonance imaging (MRI) combined with advanced analytical approaches have been employed in order to increase our understanding of the neurodevelopmental problems that many very preterm born individuals face as they grow up. In this review, we will focus on two novel imaging techniques that have explored relationships between specific brain mechanisms and behavioural outcomes. These are functional MRI, which maps regional, time-varying changes in brain metabolism and diffusion-weighted MRI, which measures the displacement of water molecules in tissue and provides quantitative information about tissue microstructure. Identifying the neurobiological underpinning of the long-term sequelae associated with very preterm birth could inform the development and implementation of preventative interventions (before any cognitive problem emerges) and could facilitate the identification of behavioural targets for improving the life course outcomes of very preterm individuals.

Introduction

The period between 24 and 40 weeks of gestation represents a critical phase of human brain development, during which thalamocortical afferents reach the cortical plate. Cerebral connections are then formed via processes that include synaptic formation, dendritic differentiation, layering of cortical neurons and glial proliferation, which are crucial for typical brain development and function [1, 2]. This dynamic stage of development coincides with the time very preterm babies are born (<32 weeks of gestation), when their immature nervous system is vulnerable to injury and altered growth [3].

Magnetic resonance imaging (MRI) is a non-invasive in-vivo technique that has been used in the past decades to study brain morphology, tissue structure and neural activity following very preterm birth from infancy to adult life. Widespread alterations in cortical mass, surface area and microstructure [4–6] and appreciable differences in structural and functional whole brain connectivity [7–10] have been described in individuals who were born very preterm compared to term born controls. Such developmental alterations have been repeatedly linked with later neurocognitive function [7, 11–14]. The impaired cognitive abilities that have been associated with very preterm birth encompass executive function [15, 16], attention [17], working memory and processing speed [18]. Such impairments have been found to impact real-life functions, including lower academic achievement [19], diminished adult wealth [20], and employment prospects [21]. Cognitive abilities have been further studied as developmental precursors of psychopathology [22]. Compared to term-born peers, very preterm individuals are more likely to experience difficulties in socio-emotional development [23], and to receive a psychiatric diagnosis in early adulthood [24, 25].

These findings highlight the dynamic interaction between both basic and high order cognitive and affective functions, as for instance, the ability to learn to efficiently deal with emotions requires a skilful coordination of multiple cognitive, perceptual and motor processes [26]. Such functions are believed to be subserved by dynamic interactions

✉ Chiara Nosarti
chiara.nosarti@kcl.ac.uk

[1] Centre for the Developing Brain, Department of Perinatal Imaging and Health, School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK

[2] Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Fig. 1 Graphic representation of a verbal fluency paradigm. During this task, participants are asked to overtly generate a word starting with a letter visually presented to them. This phase is regarded as the "experimental" condition. Each letter is presented a fixed number of times within each block. During the 'baseline' condition, participants are visually presented with the word "rest" and are instructed to read "rest" aloud.

between brain networks, none of which is specifically 'behavioural' or 'cognitive' [27], thus neurodevelopmental alterations in distributed networks associated with very preterm birth may underlie both psychiatric and cognitive sequelae.

In this literature review we will be predominantly focussing on our own work, as well as including the contribution of other groups who have explored the associations between specific brain mechanisms and long-term behavioural outcomes in very preterm individuals. We will center the review on two imaging techniques that are increasing our understanding of the neurodevelopmental problems that many very preterm born individuals face as they grow up. These are functional MRI (fMRI), which maps regional, time-varying changes in brain metabolism that correspond to either rest or mental operations and diffusion-weighted MRI (dMRI), which measures the displacement of water molecules in tissue over time and provides quantitative information about tissue microstructure. We will include both studies of very preterm and of low birth weight individuals, as there is often overlap between these events: the majority of babies who are born preterm are also born with a low birth weight [28].

Functional MRI

Neuronal activity is accompanied by an increase in blood flow to the local blood vessels and by an increased demand for oxygen, which is delivered to neurons by haemoglobin in capillary red blood cells. An increase in blood flow results in a change in the ratio of oxygenated to deoxygenated haemoglobin which is measured by the blood oxygenation level dependent (BOLD) signal used in fMRI. As oxy-haemoglobin is diamagnetic, i.e., weakly repulsed from magnetic fields, and deoxy-haemoglobin is paramagnetic, i.e., attracted to externally applied magnetic fields, a change in their ratio leads to a susceptibility difference between the blood and its surrounding tissue. Therefore, changes in oxygenation in the blood are measured as the signal changes. The term 'hemodynamic response' to a specific stimulus reflects the changes in blood flow that accompany the time course of the BOLD signal change, which is delayed from the onset of neural activity by a few seconds. The haemodynamic response is thought to be tightly spatially coupled to electrodynamics which gives the BOLD signal an excellent spatial resolution [29].

During fMRI, several images of the brain are acquired over a period of time, and the fluctuations of BOLD signal are recorded. fMRI can be collected while participants are completing a task in the scanner (i.e., task-based fMRI), while they are viewing a crosshair on the screen or lay still with their eyes closed (i.e., resting-state fMRI). In typical task-based fMRI, the BOLD signal is recorded throughout an entire task, and then subdivided at the analysis stage into different conditions, usually "on" (experimental) and "off" (baseline) trials. By revealing the differential haemodynamic responses associated with each condition, this comparative approach produces results detailing brain regions believed to be implicated in the various mental operations required to complete the task [30].

fMRI limitations include poor temporal resolution due to the latency and longevity of the haemodynamic response. Other functional neuroimaging techniques, such as MagnetoEncephaloGraphy (MEG), derive signals from the dendrites of neurons during synaptic transmission, and are able to capture the dynamics of evoked responses with high temporal resolution [31]. Therefore, integration of MEG and fMRI may offer optimal characterisation of functional brain physiology [32].

An example of a task vs. baseline comparison is shown in Fig. 1, which schematically summarises a well-validated phonemic verbal fluency paradigm we have used in our work [33, 34].

Task-based fMRI studies have highlighted significant differences in regional haemodynamic responses between very preterm adults compared to term-born controls when challenged with a variety of cognitive tasks and often in the absence of observed between group-differences in task performance. This suggests an altered recruitment of brain

regions that are typically involved in specific cognitive operations, but also the presence of compensatory neural processes, whereby very preterm individuals rely on different neural pathways from those observed in controls in order to adequately perform a given task [35, 36]. In this paper, we will summarise the results of fMRI studies that have investigated participants' neural activation associated with learning and memory, executive function and emotion processing.

In order to evaluate learning and memory abilities following very preterm birth in adult life, we have previously used paired associates learning tasks, where participants are requested to encode and recall or recognise specific visual or verbal stimuli [37–39] and will describe one in detail. Brittain et al. [38] compared learning-related changes in haemodynamic response between very preterm adults and controls, conducting a linear trend analysis across four learning/recognition blocks, which probed the investigation of patterns of functional adaptation in relation to visual learning strategies. Results of this study showed that at the behavioural level, the two groups displayed similar learning effects, i.e., they correctly remembered more visual pairs in the fourth compared to the first block of presented images. However, fMRI results showed that the way in which learning took place was different between the groups. During encoding, very preterm adults showed progressively decreasing haemodynamic responses in the hippocampal gyrus and thalamus, while controls displayed an opposite activation pattern, i.e., progressively increasing haemodynamic responses. The thalamus is part of an "extended-hippocampal system" which supports episodic memory and recollective-based recognition [40]. Conversely, very preterm adults showed progressively increasing activation, compared to controls' progressively decreasing activation, in the right superior frontal gyrus, another key episodic memory region that typically displays decreasing activation with repeated stimuli presentations [41]. A failure of suppression of regional brain activity to repeated stimuli has been associated with poorer learning of new information [42]. Taken together, these results suggest a suboptimal engagement of brain areas subserving key memory functions, which may be studied in relation to very preterm children's academic difficulties [18].

Previous fMRI studies investigated executive functions in very preterm adults and controls using verbal fluency and response inhibition tasks. During performance of a phonological verbal fluency task and with increasing cognitive-load, very preterm individuals displayed hyper-activation in cortical (frontal, temporal and parietal) and subcortical (caudate nucleus, insula, and thalamus) regions compared with controls [34, 43]. Similarly, during a task that exercised motor planning, initiation and execution, between-group differences were observed in regions spanning the cerebellum and the temporal lobe, with very preterm participants showing increased BOLD signal [44].

A study by Daamen et al. (2015) focused on executive attention using flanker stimuli (i.e., processing of incongruent vs. congruent arrows) and did not find between-group differences in haemodynamic response Gestational age was negatively associated with BOLD signal in the dorsal anterior cingulate cortex [45], which is implicated in monitoring aspects of cognitive control [46]. In another study, Daamen et al. (2014) used fMRI during a working memory task with different cognitive loads and found significant deactivation, or enhanced BOLD signal suppression, in the precuneus and parahippocampal regions in very preterm adults compared to controls [47]. This pattern of deactivation was associated with a slowing of response latencies, which could help account for impaired processing speed in this sample [18].

More recently, fMRI has been used to study the rich dynamics of brain function 'at rest' and this is referred to as resting-state fMRI (rs-fMRI). Rs-fMRI measures the spontaneous, low frequency fluctuations in the BOLD signal to characterise synchronous activations in large-scale spatially distinct regions, in order to determine dissociable resting-state networks (RSN) that intrinsically work together during rest [48]. The functional relevance of these RSNs can be deduced from their spatial congruence with networks of regions that display synchronous activation in association with specific cognitive tasks [49], or inter-regional structural connectivity [50]. Rs-fMRI is concerned with the "functional connectivity" of different brain regions, rather than the sole activation of distinct regions that are implicated in performing a specific task (i.e., task-based fMRI). Among the benefits of rs-fMRI over task-based fMRI is that it can be used even in those individuals who are unable to perform an in-scanner task, due to age (e.g., infants) or clinical status (e.g., who may be unable to produce a motor response) [51].

In terms of analytical approaches used in rs-fMRI, Independent Component Analysis is a data-driven method that defines RSNs by subdividing the rs-fMRI sequences into spatial components that have similar temporal patterns. Alternatively, seed-based methods define a region of interest, or "seed region," and then study how the time series of the BOLD signal in such "seed region" is correlated with the time series of all other voxels in the brain, producing correlation coefficients that define levels of connectivity between the "seed region" and the rest of the brain.

Of the more commonly studied RSNs is the default mode network (DMN), which includes the medial prefrontal, posterior cingulate, parietal, and lateral temporal cortices, as well as the hippocampus. The DMN shows decreased activation during specific goal-directed behaviours, but is actively implicated in internal or introspective thoughts, or

"mind-wandering" [52]. Some studies have described functional connectivity patterns resembling the emerging DMN in very preterm infants [53], whereas others have not [54]. We previously reported dysconnectivity between the DMN and two other key neurocognitive brain networks in very preterm adults compared to full-term controls [55], namely the salience network, whose activity is driven by cognitive and emotional salience, and the central executive network, which is activated by tasks involving attention, working memory and response selection [56]. These results suggest lower coordination between the DMN and networks responsible for task-appropriate attentional focus, which could be further investigated in relation to the well-documented increase in attentional problems in preterm samples [15, 17].

Research in very preterm individuals has further shown altered functional connectivity in relation to various behavioural outcomes, including intelligence [57, 58], visual attention [59], and language abilities [60]. Functional connectivity has also been studied to probe emotional information processing, in order to better understand the biological underpinnings of the socio-emotional difficulties often experienced by preterm born individuals. Previous literature proposes the amygdala as a central node modulating various neural networks important for social cognition, including the ability to recognise facial expressions, which is a crucial skill for successful interpersonal interactions [61]. Papini et al. (2016) used rs-fMRI to study functional amygdalar connectivity in very preterm and control adults [62]. Results showed hypo-connectivity in the very preterm group between the amygdala and the posterior cingulate cortex and precuneus, two core regions of the DMN that are implicated in emotional processing [63]. Furthermore, the ability to recognise angry facial expressions was associated with connectivity between the left amygdala and posterior cingulate cortex in control but not very preterm individuals. These findings suggest a potential mechanism associated with emotion recognition impairments in the very preterm group, possibly resulting from inadequate amygdalar modulation, with implications for social cognition, especially in situations that require the attribution of mental states to others [64]. These results are supported by other studies that show associations between altered amygdala-posterior cingulate cortex functional connectivity in very preterm adolescents and diminished social functioning [65].

A summary of all fMRI studies reviewed here is given in Table 1. Figure 2 graphically shows examples of selected brain regions frequently identified as displaying haemodynamic responses that are both altered in preterm individuals compared to controls and associated with behavioural outcomes.

Taken together, results of most investigations show altered hemodynamic responses in preterm individuals compared to controls, both during on-line task completion and at rest. A potential explanation for such findings involves neural plasticity, which refers to the brain's ability to adapt to environmental changes and to reorganise and recover from injury [66], via two main structural processes that can be regenerative or compensatory [67]. The developing brain is characterised by an early postnatal burst of synaptogenesis, followed by an environment-driven elimination (or "pruning") of selective synapses [68]. This process continues throughout childhood and facilitates remodelling of neurosynaptic maps [69], while organisation of neural networks is less functionally crystallized than later in adulthood [70]. Such flexibility may be an advantage for the reorganization of functions in the preterm brain, although as shown by some of the fMRI studies reviewed here, functional remapping, as reflected by altered haemodynamic response patterns, may be both adaptive and maladaptive [33, 35, 62].

Diffusion MRI

dMRI characterizes the direction-dependent diffusion of water molecules in the brain and is contingent on the organisation and density of axonal fibres. The most commonly used dMRI analysis approach is diffusion tensor imaging (DTI). The diffusion tensor model measures microstructural characteristics of white matter by approximating the directional profile of water diffusion in each voxel as a 3-D Gaussian distribution [71, 72]. Measures derived from DTI include fractional anisotropy (FA), mean diffusivity (MD), axial (AD) and radial diffusivity (RD). High FA values are observed in voxels containing fibres that are aligned, including regions such as the corpus callosum. Low FA values are observed in voxels containing fibres that are not closely aligned or voxels containing fibres of differing directions. Isotropic diffusion (where there is no directional dependence of water molecular motion) is observed in cerebrospinal fluid spaces and in grey matter. MD is a measure of the average diffusion within a voxel; AD reflects diffusion parallel to the principal axis of diffusion (considered to be along the axis of a white matter tract) and RD reflects diffusion perpendicular to primary direction of diffusion.

The diffusion tensor model has limitations [73], in particular, it is able to model only one fibre population per imaging voxel and does not work well where voxels contain multiple crossing fibres [74]. This is a significant constraint, as the occurrence of such complex fibre structures in a voxel containing white matter is common (60–90%) [75]. In addition, although FA is highly sensitive to microstructural

Table 1 Summary of fMRI studies in very preterm adolescent and adult samples.

Ref	Cases (*n*)	Controls (*n*)	Type	Task	Mean age (y)	Results
Schafer et al. 2009 [36]	22 PT (660–1250 g BW)	26 FT	fMRI task-based	Online: semantic association task	12	Online task performance: PT = FT BOLD signal: PT = FT Functional connectivity: PT only: between TG and SMA FT only: between IFG and R MTG Behaviour-function association: PT = FT: accuracy and L MTG activation PT only: accuracy and L IFG activation FT only: accuracy and L SMA activation
Narberhaus et al. 2009 [37]	21 PT (<33 weeks GA)	22 FT	fMRI task-based	Online: ViPA	20	Online task performance: PT = FT BOLD signal: Encoding: PT > FT: L CAU, R cuneus and L SPL PT < FT: R IFG Recognition: PT > FT: R CB and ACC
Brittain et al. 2014 [38]	24 PT (<33 weeks GA)	22 FT	fMRI task-based	Online: ViPA	20	Online task performance: PT = FT BOLD signal: Linear trend differences between groups (both PT > and < FT) Encoding: CB, ACC, midbrain/substantia nigra, MTG (including PHG), IFG and SFG Recognition: claustrum and posterior cerebellum
Lawrence et al. 2010 [39]	22 PT (<33 weeks GA)	22 FT	fMRI task-based	Online: VePA	20	Online task performance: PT = FT BOLD signal: Encoding: PT > FT: L PHG and PrG Recall: PT > FT: PrG
Nosarti et al. 2009 [43]	28 PT (<33 weeks GA)	26 FT	fMRI task-based	Online: VFT ('easy' and 'hard' trials)	20	Online task performance: PT = FT BOLD signal: 'Easy': PT < FT: ACC, R CAU and L IFG 'Hard': PT < FT: L MFG PT > FT: ACC
Kalpakidou et al. 2014 [34]	13 PT (<33 weeks GA) PVH + VD; 17 PT UPVH; 13 normal PT	17 FT	fMRI task-based	Online: VFT ('easy' and 'hard' trials)	22	Online task performance: PVH + VD = UPVH = normal PT = FT BOLD signal: all PT > FT: FG, TG, PL, CAU, insula and thalamus
		None			22	

Table 1 (continued)

Ref	Cases (*n*)	Controls (*n*)	Type	Task	Mean age (y)	Results
same as previous (2 tasks presented)	10 PT (<33 weeks GA) PVH + VD; 8 PT UPVH;		fMRI task-based	Online: n-back task with varying cognitive load		Online task performance: PVH + VD < UPVH BOLD signal: PVH + VD < UPVH: FG
Lawrence et al. 2014 [44]	20 PT (<33 weeks GA)	20 FT	fMRI task-based	Online: Cued motor task	20	Online task performance: PT = FT BOLD signal: PT > FT: R CB, LiG, PHG and TG
Daamen et al. 2015 [45]	86 PT (<32 weeks GA and/or <1500 g BW)	100 FT	fMRI task-based	Online: ANT	27	Online task performance: PT < FT BOLD signal: PT = FT Behaviour-function association: PT only: GA and dorsal ACC and occipital cortex (–)
Daamen et al. 2014 [47]	73 PT (<32 weeks GA and/or <1500 g BW)	73 FT	fMRI task-based	Online: n-back task with varying cognitive load	27	Online task performance: PT = FT BOLD signal: PT = FT Functional connectivity: PT < FT: posterior DMN, R ventral PC and R PHG
White et al. 2014 [55]	29 PT (<33 weeks' GA)	23 FT	rs-fMRI	Offline: HSCT	28	Offline task performance: PT < FT Functional connectivity: Within-network: PT = FT Between-network: PT < FT (DMN and salience network)
Shang et al. 2019 [57]	94 PT (<32 weeks GA and/or <1500 g BW)	92 FT	rs-fMRI	Offline: WASI	26	Offline task performance: PT < FT ALFF: PT > FT: thalamus, PrG, PoG and PL PT < FT: STG
Baumlet al. 2017 [58]	72 PT (previously seen at 8 yrs) (<37 weeks GA)	71 FT (prev. seen at 8 yrs)	rs-fMRI	Offline: Child: maths test and K-ABC Adult: WASI	8; 26	Offline child task performance: PT > FT Offline adult task performance: PT > FT Behaviour-function association: Childhood maths scores and adult fronto-parietal FC is different for PT and FT; PT only: association (+) between maths scores and R fronto-parietal network, association (-) between maths scores and L fronto-parietal network; this pattern is reversed in FT PT = FT: association between adults' right fronto-parietal FC and IQ
Finke et al. 2015 [59]	33 PT (<37 weeks GA)	32 FT	rs-fMRI	Offline: vSTM	26	Offline task performance: vSTM: PT < FT Processing speed and attentional weighting: PT = FT Functional connectivity: Both PT > FT and PT < FT in LiG (visual networks) and SPL (attention networks) Behaviour-function association:

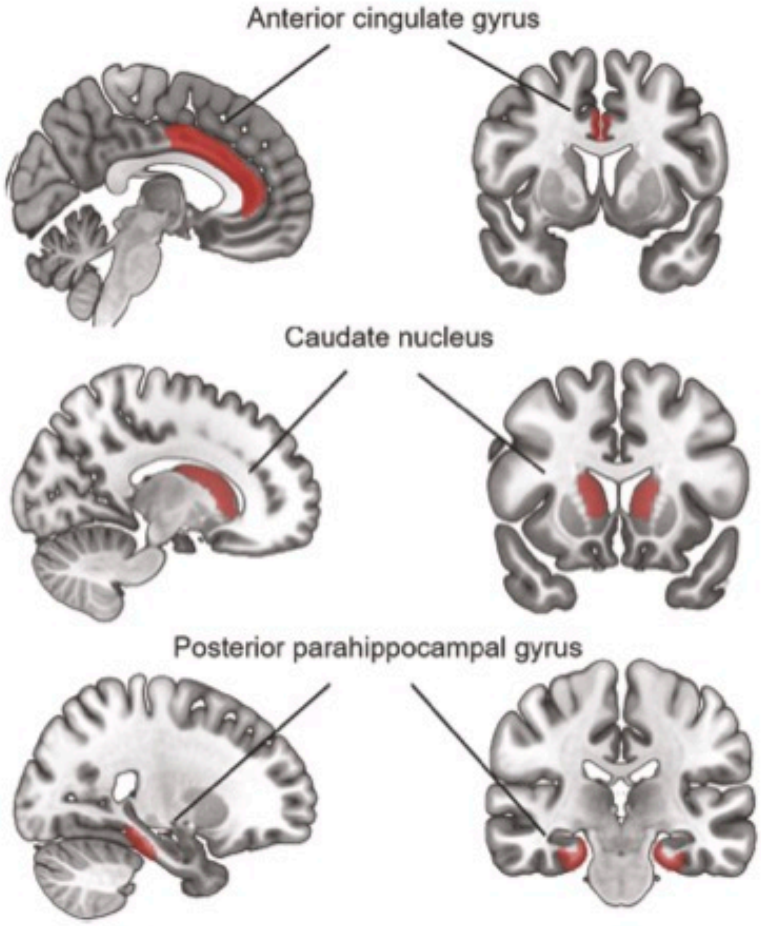


Fig. 2 Examples of selected brain regions frequently identified as displaying haemodynamic responses that are both altered in preterm individuals compared to controls and associated with behavioural outcomes. Created using MRIcroGL [122] and the Harvard-Oxford cortical and subcortical structural atlases [123].

alterations, its specificity is low. Thus, the interpretation of FA values as a quantitative measure of white matter microstructure is problematic. Recently developed methods are better suited to resolve multiple fibre crossings in a voxel. An example of such an approach is constrained spherical deconvolution (CSD), which provides a direct estimate of fibre orientations within a voxel [76, 77]. CSD has been found to yield the least fibre orientation error and greatest detection rate of fibres for complex crossing regions on diffusion weighted images, when compared to other reconstruction methods [78] (see Fig. 3). Furthermore, the absolute amplitude of each lobe of the fibre orientation distribution can be used as a measure to characterise the diffusion properties along each fibre orientation, termed hindrance modulated orientation anisotropy [79].

Diffusion tractography is a dMRI modelling technique that provides a three-dimensional representation of white matter fibre bundles. There are two common approaches, deterministic and probabilistic tractography [80]. Deterministic or streamline tractography produces one reconstructed trajectory per seed point by connecting a set of voxels based on their estimated fibre orientation (i.e., direction of maximum diffusivity for the tensor model). It typically uses anatomical knowledge originating from post-mortem studies and necessitates a priori hypotheses about the course of the fibre tract. An example of dissected tracts using deterministic tractography and regions of interest that were manually drawn based on anatomical features in native space is shown in Fig. 4 [33].

Probabilistic tractography produces multiple solutions in order to account for the presence of some uncertainty in the

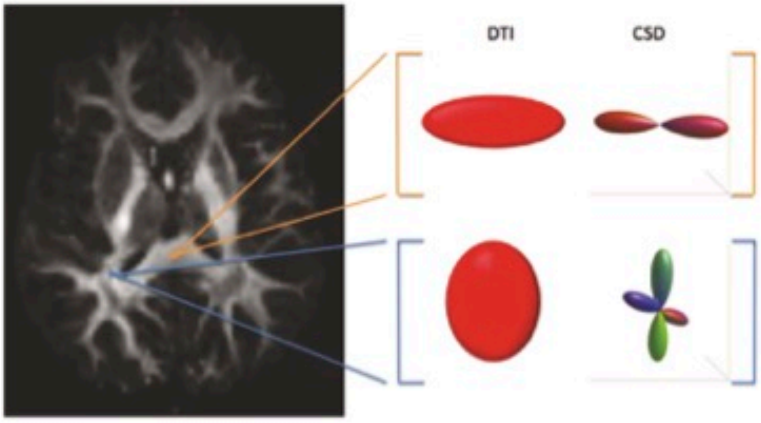


Fig. 3 Schematic overview of different reconstruction methods. The left panel displays an axial brain slice. The location of two voxels is shown in blue and orange. The right panel displays diffusion signal for the orange (top) and blue (bottom) sites as 3-D surfaces. DTI = diffusion tensor model, CSD = constrained spherical deconvolution model (colours indicate direction of diffusion). In a voxel where there are crossing fibres, the tensor model does not differentiate orientations, while the CSD model indicates multiple probable directions.

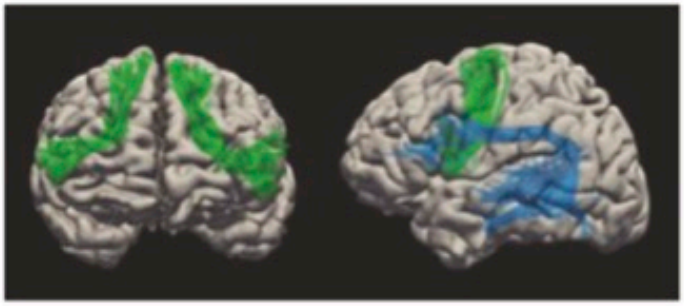


Fig. 4 Deterministic tractography example. The arcuate fasciculus, which connects caudal temporal cortex and inferior frontal lobe, is shown in blue; the frontal aslant tract, which connects the lateral inferior frontal gyrus and the pre-supplementary and supplementary motor areas of the medial superior frontal gyrus, is shown in green.

fibre orientation [81, 82]. Instead of reconstructing a single trajectory per seed point, it generates multiple streamline samples from a given seed point. The probability distribution of possible orientations is estimated at each voxel, and connections are traced several times using slightly different orientations based on their likelihood (Fig. 5). Quantitative results from tractography analyses can then be compared between individuals, or groups of individuals, by quantifying their size (e.g., number of streamlines) and/or tract-specific properties, including tensor measures and hindrance modulated orientation anisotropy.

Widespread white matter microstructural alterations have been extensively reported in very preterm individuals compared to controls from birth to adult life [9, 83, 84]. These alterations may be implicated in the neurodevelopmental sequelae associated with very preterm birth, with findings highlighting correlations between microstructural properties of specific white matter tracts and a variety of cognitive outcomes. The majority of studies investigating specific white matter tracts and cognitive outcomes have been conducted in cohorts of children [85–89].

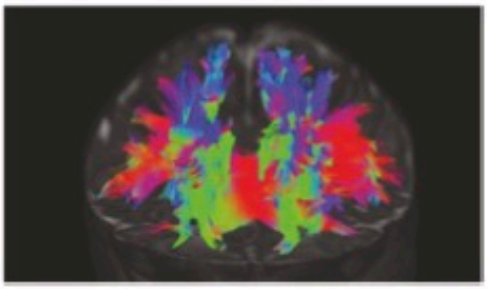


Fig. 5 Whole-brain probabilistic tractography of an infant's brain [Figure courtesy of Dafnis Batalle]. The colour-coding reflects the fibre orientation (red: left–right, green: dorsal–ventral, blue: cranial–caudal.

In preterm adolescents, lower IQ, working memory, cognitive flexibility and language scores were associated with reduced FA in major white matter association tracts, including the uncinate fasciculus [90–92]. Similarly, in preterm adults, lower FA values in several major white

Table 2 Key characteristics of the human connectome.

Measure	Definition
Node degree	Number of connections linking node to rest of network.
Path length	Minimum number of edges that need to be crossed to move between pairs of nodes.
Clustering	Neighbours of a node tend to form connections, leading to the formation of triangles of interconnected nodes, i.e., clustering. Together, short path length and high clustering produce "small worldness".
Modularity	Number of modules, or subnetworks, that are comprised in the connectome. High modularity suggests sparse connections between nodes in different modules and dense connections between nodes within modules.
Hubs	Nodes with a high degree (large number of connections linking node to rest of network), or high centrality (number of shortest paths between all other node pairs in the network that pass through a node). Nodes with high centrality are crucial for efficient communication.
Rich-club	High-degree nodes belonging to different modules that are more highly interconnected with each-other than low-degree nodes belonging to separate modules.

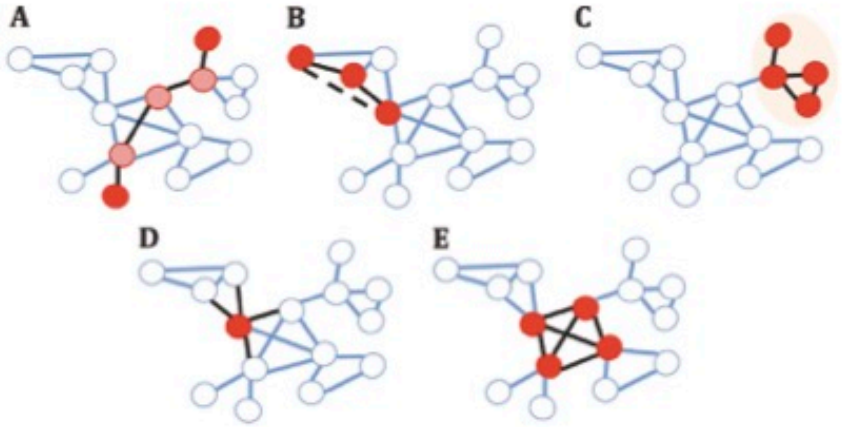


Fig. 6 Illustration of key characteristics of the human connectome. (**a**) Path length; (**b**) Clustering; (**c**) Modularity; (**d**) Hubs; (**e**) Rich-club.

matter tracts, including the corpus callosum and superior longitudinal fasciculus, were associated with lower IQ and poorer memory function [83, 93, 94].

Our previous work used tractography to delineate memory-related tracts and to study their association with memory abilities in very preterm and term-born adults [95]. At the anatomical level, smaller volumes in the dorsal cingulum (connecting medial frontal and parietal lobes), ventral cingulum (connecting medial parietal and temporal lobes) and fornix (connecting hippocampus, mamillary bodies, and septal region) were observed in very preterm individuals compared to controls. The greatest alterations were seen in those very preterm individuals who experienced severe perinatal brain injury (PBI) in the form of intraventricular haemorrhage and ventricular dilatation, qualitatively evaluated from neonatal ultrasound. Smaller fornix and cingulum volumes were associated with more memory errors and lower IQ scores, suggesting that selective structural connectivity alterations could at least partly explain the memory difficulties that have been associated with very preterm birth.

Recent theoretical frameworks have shifted the focus of attention from single regions to a comprehensive mapping of the inter-connections throughout the whole brain. Using graph theory, researchers have modelled the network topology of white matter, or the "connectome" [96]. Graph theory represents a branch of mathematics that allows the quantification of networks, their elements, and the connections between them. When applied to the study of brain connectivity, graph theory offers insight into the structure and function of neural networks through various characteristics, some of which are described in Table 2 and Fig. 6. Networks are defined as a set of nodes and the connectivity (or "edges") between them [97]. The brain's

network efficiency, or how well it is able to integrate information between multiple regions, is related to cognitive performance [98–100].

Several studies have investigated whole brain connectivity following very preterm birth. The presence of a "rich-club", which is believed to enable efficient network communication, was described in preterm neonates well before the typical time of birth, by 30 weeks' gestation [101]. However, during the third trimester of gestation, there is a rapid increase of hub and rich-club connections, together with the proliferation of short-range and within-module connections [102]. Therefore, extra-uterine stressors during this time are likely to influence their development.

Previous work investigating the connectome in school-age children who were born extremely preterm (EP, <28 weeks' gestation) and with a history of intrauterine growth restriction (IUGR) showed a reduced averaged network node strength when compared with those born moderately preterm with normal growth [103]. Furthermore, both extreme prematurity and IUGR were associated with alterations in network structure, despite very similar levels of modularity. This suggests that although brain networks are organised differently after neonatal adverse events, a tight modular structure is preserved in order to maintain rich-club and small-world characteristics.

We investigated modularity and rich-club in very preterm adults and controls [104]. The analysis of real networks showed that rich-club indices were either significantly greater in the very preterm group at an uncorrected level or numerically higher for a range of rich-club degrees. This suggests that rich-club connections were prioritised in the very preterm brain, as they were assigned disproportionally greater connection weights. There were no significant between-group differences in modularity. In order to establish the impact of individual elements on the whole network architecture, we then used a simulated lesion approach and deleted components, one at a time, from the connectivity matrix (i.e., nodes and edges). We found that "lesioning" striatal-cortical connections produced greater alterations in global connectivity in the very preterm group compared to controls, reflecting their altered role in supporting a global exchange of information throughout the brain. Furthermore, network alterations had functional implications; they correlated with measures of information flow and rule learning.

A summary of dMRI studies reviewed here is shown in Table 3. Examples of selected white matter tracts frequently identified to have altered microstructure in preterm individuals compared to controls which are also associated with behavioural outcomes are shown in Fig. 7.

Combining imaging modalities

The collection of multiple MRI modalities in a single subject has increased in popularity in recent years [33, 35, 105]. Multimodal imaging has the potential to increase our current understanding of the neurodevelopmental alterations underlying the long-term sequelae of very preterm birth, as it integrates structural and functional features associated with specific outcomes that may not be captured by only one modality at a time. For instance, a multimodal imaging approach has been used in other neurodevelopmental disorders, such as attention deficit hyperactivity disorder, revealing multimodal components that share the same across-subject variation, and thus displaying co-occurring and mechanistically related anatomical and functional alterations [106].

To date only a few studies in very preterm samples have combined multiple imaging modalities, with the majority of these focussing on child cohorts [11, 107, 108]. We previously used fMRI-informed tractography to probe verbal paired associate learning [109]. This involved choosing brain regions that exhibited significantly different haemodynamic responses during paired associate learning between the very preterm and the control group as seed regions for tractography. Manually traced tracts encompassed the anterior cingulate gyrus, caudate nucleus and thalamus/parahippocampal gyrus. At the structural level, reduced FA was particularly noted in the hippocampal fornix, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. These results led us to speculate that the differential patterns of brain activation during a learning task observed in the very preterm group could reflect possible adaptive plastic processes in the presence of altered microstructural characteristics of memory-related white matter tracts.

In another study, we investigated the neuroanatomy of working memory in very preterm individuals subdivided according to the presence or absence of PBI [35]. Whilst no between-group differences in working memory performance were observed, adults who suffered PBI compared with controls showed reduced haemodynamic responses in a fronto-parietal-cerebellar network, typically associated with working memory. They further displayed relative increased responses in bilateral perisylvian cortex. At the structural level, dorsal cingulum volume was smaller in the PBI compared to the other two groups, and smaller volume correlated with increased perisylvian cortex activation, which in turn correlated with better task performance. These results were interpreted as suggesting that the underutilisation of traditional working memory resources in the PBI group may be accompanied by upregulation of activity in the perisylvian cortex in order to support task performance.

Table 3 Summary of dMRI studies in very preterm adolescent and adult samples.

Ref	Cases (*n*)	Controls (*n*)	Type	Offline Task	Mean age (y)	Results
Allin et al. 2011 [83]	80 PT (<33 weeks' GA)	41 FT	Whole-brain analysis	WASI, CVLT	19	Task performance: PT < FT FA: PT < FT: CC, SLF and L superior CR PT > FT: IFOF, anterior CR, UF and SLF Behaviour-structure association: PT only: WASI and CVLT and FA in PT < FT clusters (+)
Skranes et al. 2007 [90]	34 PT (<1500 g BW)	47 FT	Whole-brain analysis	WISC, VMI, M-ABC, GP, ASSQ, CGAS, ADHD IV	15	Task performance: PT < FT FA: PT < FT: IC, EC, CC, SLF, MSF and ILF Behaviour-structure association: PT only: WISC and FA in L EC, ILF, IFOF and L MSF (+) VMI and FA in EC, L IC, L IFOF and L ILF (+) M-ABC and FA in EC, CC, ILF, IFOF, R SF and L MSF (+) GP and FA in IC, EC, R SF and L MSF (+) ASSQ and FA in L EC and L SF (-) CGAS and FA in L IC, L EC, L ILF, L IFOF, SF and L MSF (+) ADHD (inattention) and FA in L EC, R SF, L MSF (−)
Mullen et al. 2011 [91]	44 PT (600–1250 g BW)	41 FT	Whole-brain analysis	PPVT, CTOPP	16	Task performance: PT < FT FA: PT < FT: UF, EC, CC (splenium) and WM serving IFG Behaviour-structure association: PT only: PPVT scores and FA in UF (+) CTOPP scores and FA in AF (+)
Vollmer et al. 2017 [92]	71 PT (<36 weeks GA and <1501 g BW)	63 FT	Whole-brain analysis	WISC, D-KEFS	15	Task performance: PT < FT FA: PT < FT: ILF, EC, IFOF, UF, R IC, L F and L occipital WM Behaviour-structure association: PT only: WISC and FA in L UF, IFOF, SLF, L IC, L CST, anterior TR (+) PT only: D-KEFS and FA in UF, IFOF, ILF, SLF, L IC, CST, anterior TR, R EC and forceps minor (+)
Jurcoane et al. 2016 [93]	56 PT (<32 weeks GA and/or <1500 g BW)	53 FT	Whole-brain analysis and tractography of CST	/	26	FA (tractography): PT = FT: whole CST PT > FT: CST at the level of the CR FA (TBSS): PT < FT: centrum semiovale and brain stem regions of CST Diffusivity (tractography and TBSS): PT > FT: whole CST, CR and regions of capsula interna and brain stem
Eikenes et al. 2011 [94]	49 PT (<36 weeks GA and <1500 g BW)	59 FT	Whole-brain analysis	WASI	20	Task performance: PT < FT FA: PT < FT: CP, CST, CPT, CR, UF, SLF, IFOF, ILF, anterior TR,

Table 3 (continued)

Ref	Cases (*n*)	Controls (*n*)	Type	Offline Task	Mean age (y)	Results
						thalamus, CC, EC, F, C and stria terminalis PT > FT: R SLF Diffusivity (MD): PT > FT: same as FA PT < FT, and additionally IC and superior TR Clinical-structure association: PT only: Clinical variables and FA (+) and MD (-) in CR, SLF, IFOF, ILF, C, TR, CC, forceps major, IC, F, UF, CST, CTP, EC and thalamus Behaviour-structure association: PT only: WASI and FA in several major WM tracts (+) WASI and MD in genu, CC, UF, IFOF, ILF and SLF (−)
Caldinelli et al. 2017 [95]	84 PT (<32 weeks GA): 64 with no or low PBI, 20 PT-PBI	48 FT	Tractography of C and F	WASI, CVLT, WMS-R	19	Task performance: PT < FT: WASI, CVLT (PE), WMS-R WM volume: PT-PBI < FT: dorsal C, ventral C and F PT with no or low PBI < FT: ventral C and F HMOA: All PT < FT: F Behaviour-structure association: PT only: WASI and ventral C volume (+) PE and F and dorsal C volume (−) WMS-R and ventral C volume (+)
Karolis et al. 2016 [104]	51 (<33 weeks GA)	60 FT	Whole-brain tractography and graph-theory analysis	WASI, TMT, COWAT, HSCT, CANTAB	29	Task performance: PT < FT: WASI, TMT, HSCT, CANTAB Structural connectivity: Rich-club index: PT > FT Virtually 'lesioning' striatal-cortical connections produced greater alterations in global connectivity in PT compared to FT Behaviour-structure association: Degree of network alterations correlated with measures of information flow and rule learning (verbal IQ, HSCT, CANTAB)

Please note that when laterality is not stated, results refer to bilateral findings. Performance results refer to behavioural assessments.

AD axial diffusivity, *AF* arcuate fasciculus, *ASSQ* Autism Spectrum Screening Questionnaire, *ADHD* Attention Deficit/Hyperactivity Disorder Rating Scale IV, *BG* basal ganglia, *BW* birth weight, *C* cingulum, *CC* corpus callosum, *CR* corona radiata, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *CGAS* Children's Global Assessment Scale, *COWAT* Controlled Oral Word Association Test, *CP* cerebellar peduncle, *CPT* corticopontine tract, *CST* corticospinal tract, *CTOPP* Comprehensive Test of Phonological Processing, *CVLT* California Verbal Learning Test, *D-KEFS* Delis-Kaplan Executive Function Systems, *EC* external capsule, *EF* executive functions, *F* fornix, *FA* fractional anisotropy, *FT* full-term group, *GA* gestational age, *GM* grey matter, *GP* Grooved Pegboard test, *HMOA* hindrance-modulated orientational anisotropy, *HSCT* Hayling Sentence Completion Test, *IC* internal capsule, *IFG* inferior frontal gyri, *IFOF* inferior fronto-occipital fasciculus, *ILF* inferior longitudinal fasciculus, *L* left, *M-ABC* Movement Assessment Battery for Children, *MD* mean diffusivity, *MSF* middle superior fasciculus, *PBI* perinatal brain injury, *PE* perseveration errors, *PPVT* Peabody Picture Vocabulary Test, *PT* preterm group, *R* right, *RD* radial diffusivity, *SLF* superior longitudinal fasciculus, *TMT* Trail Making Test; *TR* thalamic radiation, *UF* uncinate fasciculus, *VMI* (developmental test of) Visual-Motor Integration, *WASI* Wechsler Abbreviated Scale of Intelligence, *WISC* Wechsler Intelligence Scale for Children (WISC); *WM* white matter, *WMS-R* Wechsler Memory Scale-Revised, *WM* white matter.

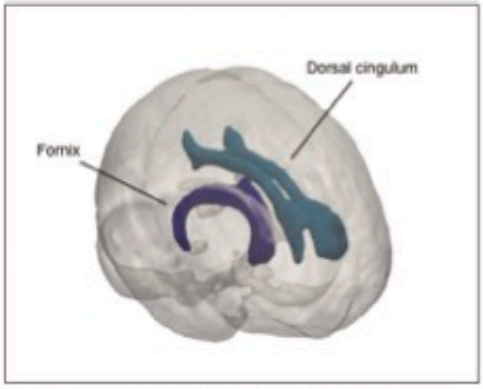


Fig. 7 Examples of selected white matter tracts frequently identified to have altered microstructure in preterm individuals compared to controls which are also associated with behavioural outcomes. Created using ParaView and the JHU White-Matter Tractography Atlas.

Using a similar study design we further investigated the neuroanatomy of visual recognition [105], a function that is crucial for learning and adapting appropriately to the environment, and that has been described as impaired in preterm individuals [110]. In addition to poorer performance on an in-scanner recognition memory task, preterm adults compared to controls exhibited a complex pattern of altered haemodynamic responses, showing both increased and decreased BOLD signal and smaller memory-related white matter tracts, with microstructural alterations clearly pronounced in the fornix, which is implicated in episodic recognition [111]. BOLD signal increase in bilateral lateral occipital cortex observed in the preterm group was associated with worse task performance, and with poorer fornix microstructural integrity. These findings are inconsistent with our previous fMRI study of working memory described above, which showed that BOLD signal increase in perisylvian cortex was associated with functional adaptation [35] and suggest that altered patterns of activation may be both compensatory and maladaptive [112].

In an overlapping cohort of very preterm participants and controls we used both fMRI and spherical deconvolution tractography to assess the neuroanatomy of verbal fluency [33]. Decreased haemodynamic response suppression was observed in very preterm adults in several brain regions during completion of both easy and hard letter trials. Furthermore, in all participants regardless of group, decreased brain activity suppression in the right sensorimotor cortex was associated with worse performance on the most cognitively demanding condition of the task. In controls only, increased left-laterality in the arcuate fasciculus, which is a white matter tract centrally implicated in language, was associated with increased right hemispheric haemodynamic response suppression. In the preterm group only, altered white matter microstructure in the bilateral frontal aslant tract, which is involved in speech fluency, was related to weaker haemodynamic response suppression during the hard letter trials. Taken together, these findings suggest that verbal fluency is affected by altered functional lateralization in adults who were born very preterm.

A summary of combined dMRI and fMRI studies is shown in Table 4.

Conclusions and future directions

Advanced neuroimaging has considerably increased our understanding of the brain alterations associated with very preterm birth that underlie neurocognitive outcomes throughout the life span and could lead to the formulation of new aetiopathological frameworks [113]. Here, we discussed recent findings that employ advanced non-invasive MRI techniques to highlight relationships between specific brain mechanisms and behavioural outcomes.

In recent years, novel diffusion-weighted imaging techniques have been used to study brain development in very preterm neonates and children [114–118], but are yet to be explored in adults. These include neurite orientation dispersion and density imaging (NODDI), which provides a more specific marker of brain tissue microstructure than traditional DTI. NODDI identifies both the branching complexity of dendrites, i.e. "dendritic density", in addition to the orientation dispersion index which quantifies the bending and fanning of axons, which allows the distinction between voxels containing multiple crossing fibres and those with dispersed fibres that belong to only a single dominant orientation [119]. Furthermore, fixel-based analysis is another novel diffusion imaging analysis method that uses CSD to compute "fixels," or individual fibre orientations distributions within a voxel, allowing the identification of multiple crossing fibres [120].

Longitudinal studies beginning soon after birth can help reveal early biomarkers of emerging cognitive difficulties. Using machine learning and non-subjective clustering of imaging and clinical data, Ball et al. (2017) defined novel imaging features associated with antenatal and postnatal adversity, which predict adverse outcomes [11]. Such predictions can be very precise, discriminating between different white matter tracts and their involvement in supporting behavioural outcomes. For example, the diffusion characteristics of the arcuate fasciculus but not the superior longitudinal fasciculus at birth predicted language function at 2 years [13] and information about topology of structural brain networks predicted cognitive, motor and developmental outcomes, again at 2 years [121].

Table 4 Summary of combined dMRI and fMRI studies in very preterm adolescent and adult samples.

Ref	Cases (*n*)	Controls (*n*)	Type	Task	Mean age (y)	Results
Salvan et al. 2014 [109]	21 PT (<33 weeks GA)	10 FT	Task-based fMRI, fMRI-informed tractography	Online: VePA	20	Task performance: FT = PT BOLD signal: Encoding: PT> FT: R ACC, superior FG, CAU Recall: PT< FT: L PHG, HC and thalamus FA: PT< FT: F, ILF and IFOF
Froudist-Walsh et al. 2015 [35]	fMRI: 20 PT-PBI, 21 PT without PBI dMRI: 39 PT-PBI, 36 PT without PBI	fMRI: 46 FT dMRI: 80 FT	Task-based fMRI, Tractography of C	Online: n-back task with varying cognitive load	30	Task performance: PT-PBI = PT without PBI = FT BOLD signal: PT-PBI< FT: fronto-parietal regions PT-PBI> FT: PSC WM volume and HMOA: PT-PBI< FT and PT-PBI <PT without PBI: dorsal C Function-structure association: PT-PBI only: PSC activation and dorsal C volume (−) Behaviour-function association: PT-PBI only: task performance and PSC activation (+)
Tseng et al. 2017 [105]	49 PT (<33 weeks GA)	50 FT	Task-based fMRI, Tractography of F and C	Online: VER	30	Task performance: PT <FT BOLD signal: PT< FT: middle FG and posterior C/precuneus PT> FT: L inferior FG and LOC WM volume and HMOA: PT< FT (volume): F and C PT< FT (HMOA): F Behaviour-function association: Both groups: Task performance and LOC activation Function-structure association: PT only: LOC activation and F HMOA
Tseng et al. 2019 [33]	64 PT (<32 weeks GA)	36 FT	Task-based fMRI, Tractography of AF and FAT	Online: VFT ('easy' and 'hard' trials)	31	Task performance: Easy trials: PT = FT Hard trials: PT <FT BOLD signal suppression: PT< FT: STG, insula, thalamus, R SMC Behaviour-function association: Hard trials score and R SMC BOLD signal suppression (+)

Such information could be used to inform the creation and implementation of targeted neurobehaviourally-informed preventative interventions (before any cognitive problem emerges) and could facilitate the identification of behavioural targets for improving the life course outcomes of very preterm individuals.

Compliance with ethical standards

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

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Kostovic I, Jovanov-Milosevic N. The development of cerebral connections during the first 20–45 weeks' gestation. Semin Fetal Neonatal Med. 2006;11:415–22.
2. Kostović I, Judaš M. The development of the subplate and thalamocortical connections in the human foetal brain. Acta Paediatr. 2010;99:1119–27.
3. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8:110–24.
4. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics. 2005;115:286–94.
5. Ball G, Srinivasan L, Aljabar P, Counsell SJ, Durighel G, Hajnal JV, et al. Development of cortical microstructure in the preterm human brain. Proc Natl Acad Sci USA. 2013;110:9541–6.
6. Engelhardt E, Inder TE, Alexopoulos D, Dierker DL, Hill J, Van Essen D, et al. Regional impairments of cortical folding in premature infants. Ann Neurol. 2015;77:154–62.
7. Ball G, Pazderova L, Chew A, Tusor N, Merchant N, Arichi T, et al. Thalamocortical connectivity predicts cognition in children born preterm. Cereb Cortex. 2015;25:4310–8.
8. Fischi-Gomez E, Vasung L, Meskaldji DE, Lazeyras F, Borradori-Tolsa C, Hagmann P, et al. Structural brain connectivity in school-age preterm infants provides evidence for impaired networks relevant for higher order cognitive skills and social cognition. Cereb Cortex. 2014;25:2793–805.
9. Batalle D, Hughes EJ, Zhang H, Tournier JD, Tusor N, Aljabar P, et al. Early development of structural networks and the impact of prematurity on brain connectivity. Neuroimage. 2017;149:379–92.
10. Tokariev A, Stjerna S, Lano A, Metsäranta M, Palva JM, Vanhatalo S. Preterm birth changes networks of newborn cortical activity. Cereb Cortex. 2018;29:814–26.
11. Ball G, Aljabar P, Nongena P, Kennea N, Gonzalez-Cinca N, Falconer S, et al. Multimodal image analysis of clinical influences on preterm brain development. Ann Neurol. 2017;82:233–46.
12. Rogers CE, Lean RE, Wheelock MD, Smyser CD. Aberrant structural and functional connectivity and neurodevelopmental impairment in preterm children. J Neurodev Disord. 2018;10:38.
13. Salvan P, Tournier JD, Batalle D, Falconer S, Chew A, Kennea N, et al. Language ability in preterm children is associated with arcuate fasciculi microstructure at term. Hum Brain Mapp. 2017;38:3836–47.
14. Loh WY, Anderson PJ, Cheong JLY, Spittle AJ, Chen J, Lee KJ, et al. Neonatal basal ganglia and thalamic volumes: very preterm birth and 7-year neurodevelopmental outcomes. Pediatr Res. 2017;82:970–8.
15. Nosarti C, Giouroukou E, Micali N, Rifkin L, Morris RG, Murray RM. Impaired executive functioning in young adults born very preterm. J Int Neuropsychol Soc. 2007;13:571–81.
16. Burnett AC, Scratch SE, Anderson PJ. Executive function outcome in preterm adolescents. Early Hum Dev. 2013;89:215–20.
17. Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D. Attention problems in very preterm children from childhood to adulthood: the Bavarian Longitudinal Study. J Child Psychol Psychiatry. 2016;57:132–40.
18. Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. BJOG. 2018;125:16–25.
19. Mulder H, Pitchford NJ, Marlow N. Processing speed and working memory underlie academic attainment in very preterm children. Arch Dis Child Fetal Neonatal Ed. 2010;95:F267–272.
20. Jaekel J, Baumann N, Bartmann P, Wolke D. General cognitive but not mathematic abilities predict very preterm and healthy term born adults' wealth. PLoS ONE. 2019;14:e0212789.
21. Kroll J, Karolis V, Brittain PJ, Tseng CJ, Froudist-Walsh S, Murray RM, et al. Real-life impact of executive function impairments in adults who were born very preterm. J Int Neuropsychol Soc. 2017;23:381–9.
22. van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. Arch Gen Psychiatry. 1997;54:625–31.
23. Montagna A, Nosarti C. Socio-emotional development following very preterm birth: pathways to psychopathology. Front Psychol. 2016;7:80.
24. Lund LK, Vik T, Skranes J, Brubakk AM, Indredavik MS. Psychiatric morbidity in two low birth weight groups assessed by diagnostic interview in young adulthood. Acta Paediatr. 2011;100:598–604.
25. Nosarti C, Murray RM, Reichenberg A, Cnattingius S, Lambe MP, Yin L, et al. Preterm birth and psychiatric disorders in young adult life. Arch Gen Psychiatry. 2012;69:610–7.
26. Happé F, Frith U. Annual research review: towards a developmental neuroscience of atypical social cognition. J Child Psychol Psychiatry. 2014;55:553–77.
27. Pessoa L. On the relationship between emotion and cognition. Nat Rev Neurosci. 2008;9:148–58.
28. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health. 2019;7:e849–e860.
29. Logothetis NK. The underpinnings of the BOLD functional magnetic resonance imaging signal. J Neurosci. 2003;23:3963–71.
30. Soares JM, Magalhaes R, Moreira PS, Sousa A, Ganz E, Sampaio A, et al. A hitchhiker's guide to functional magnetic resonance imaging. Front Neurosci. 2016;10:515.
31. Glover GH. Overview of functional magnetic resonance imaging. Neurosurg Clin N Am. 2011;22:133–vii.
32. Taylor MJ, Donner EJ, Pang EW. fMRI and MEG in the study of typical and atypical cognitive development. Neurophysiol Clin. 2012;42:19–25.
33. Tseng C-EJ, Froudist-Walsh S, Kroll J, Karolis V, Brittain PJ, Palamin N, et al. Verbal fluency Is affected by altered brain lateralization in adults who were born very preterm. eNeuro. 2019;6:0274–0218.

34. Kalpakidou AK, Allin MP, Walshe M, Giampietro V, McGuire PK, Rifkin L, et al. Functional neuroanatomy of executive function after neonatal brain injury in adults who were born very preterm. PLoS ONE. 2014;9:e113975.
35. Froudist-Walsh S, Karolis V, Caldinelli C, Brittain PJ, Kroll J, Rodriguez-Toscano E, et al. Very early brain damage leads to remodeling of the working memory system in adulthood: a combined fMRI/tractography study. J Neurosci. 2015;35:15787–99.
36. Schafer RJ, Lacadie C, Vohr B, Kesler SR, Katz KH, Schneider KC, et al. Alterations in functional connectivity for language in prematurely born adolescents. Brain. 2009;132:661–70.
37. Narberhaus A, Lawrence E, Allin MP, Walshe M, McGuire P, Rifkin L, et al. Neural substrates of visual paired associates in young adults with a history of very preterm birth: alterations in fronto-parieto-occipital networks and caudate nucleus. Neuroimage. 2009;47:1884–93.
38. Brittain PJ, Froudist Walsh S, Nam KW, Giampietro V, Karolis V, Murray RM, et al. Neural compensation in adulthood following very preterm birth demonstrated during a visual paired associates learning task. Neuroimage Clin. 2014;6:54–63.
39. Lawrence EJ, McGuire PK, Allin M, Walshe M, Giampietro V, Murray RM, et al. The very preterm brain in young adulthood: the neural correlates of verbal paired associate learning. J Pediatr. 2010;156:889–95.
40. Aggleton JP. Multiple anatomical systems embedded within the primate medial temporal lobe: implications for hippocampal function. Neurosci Biobehav Rev. 2012;36:1579–96.
41. Neuner I, Stocker T, Kellermann T, Kircher T, Zilles K, Schneider F, et al. Wechsler Memory Scale Revised Edition: neural correlates of the visual paired associates subtest adapted for fMRI. Brain Res. 2007;1177:66–78.
42. Daselaar SM, Prince SE, Cabeza R. When less means more: deactivations during encoding that predict subsequent memory. Neuroimage. 2004;23:921–7.
43. Nosarti C, Shergill SS, Allin MP, Walshe M, Rifkin L, Murray RM, et al. Neural substrates of letter fluency processing in young adults who were born very preterm: alterations in frontal and striatal regions. Neuroimage. 2009;47:1904–13.
44. Lawrence EJ, Froudist-Walsh S, Neilan R, Nam KW, Giampietro V, McGuire P, et al. Motor fMRI and cortical grey matter volume in adults born very preterm. Dev Cogn Neurosci. 2014;10C:1–9.
45. Daamen M, Bäuml JG, Scheef L, Meng C, Jurcoane A, Jaekel J, et al. Neural correlates of executive attention in adults born very preterm. Neuroimage Clin. 2015;9:581–91.
46. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. Psychol Rev. 2001;108:624–52.
47. Daamen M, Bauml JG, Scheef L, Sorg C, Busch B, Baumann N, et al. Working memory in preterm-born adults: Load-dependent compensatory activity of the posterior default mode network. Hum Brain Mapp. 2015;36:1121–37.
48. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. AJNR Am J Neuroradiol. 2013;34:1866–72.
49. Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC. Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp. 2002;15:247–62.
50. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex. 2009;19:72–78.
51. Lang S, Duncan N, Northoff G. Resting-state functional magnetic resonance imaging: review of neurosurgical applications. Neurosurgery. 2014;74:453–65.
52. Raichle ME. The brain's default mode network. Annu Rev Neurosci. 2015;38:433–47.
53. Doria V, Beckmann CF, Arichi T, Merchant N, Groppo M, Turkheimer FE, et al. Emergence of resting state networks in the preterm human brain. Proc Natl Acad Sci USA. 2010;107:20015–20.
54. Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, et al. Longitudinal analysis of neural network development in preterm infants. Cereb Cortex. 2010;20:2852–62.
55. White TP, Symington I, Castellanos NP, Brittain PJ, Froudist Walsh S, Nam KW, et al. Dysconnectivity of neurocognitive networks at rest in very-preterm born adults. Neuroimage Clin. 2014;4:352–65.
56. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 2002;3:201–15.
57. Shang J, Fisher P, Bäuml JG, Daamen M, Baumann N, Zimmer C, et al. A machine learning investigation of volumetric and functional MRI abnormalities in adults born preterm. Hum Brain Mapp. 2019;40:4239–52.
58. Bäuml JG, Meng C, Daamen M, Baumann N, Busch B, Bartmann P, et al. The association of children's mathematic abilities with both adults' cognitive abilities and intrinsic fronto-parietal networks is altered in preterm-born individuals. Brain Struct Funct. 2017;222:799–812.
59. Finke K, Neitzel J, Bäuml JG, Redel P, Müller HJ, Meng C, et al. Visual attention in preterm born adults: Specifically impaired attentional sub-mechanisms that link with altered intrinsic brain networks in a compensation-like mode. Neuroimage. 2015;107:95–106.
60. Constable RT, Vohr BR, Scheinost D, Benjamin JR, Fulbright RK, Lacadie C, et al. A left cerebellar pathway mediates language in prematurely-born young adults. Neuroimage. 2013;64:371–8.
61. Bickart KC, Dickerson BC, Barrett LF. The amygdala as a hub in brain networks that support social life. Neuropsychologia. 2014;63:235–48.
62. Papini C, White TP, Montagna A, Brittain PJ, Froudist-Walsh S, Kroll J, et al. Altered resting-state functional connectivity in emotion-processing brain regions in adults who were born very preterm. Psychol Med. 2016;46:1–15.
63. Ho TC, Connolly CG, Henje Blom E, LeWinn KZ, Strigo IA, Paulus MP, et al. Emotion-dependent functional connectivity of the default mode network in adolescent depression. Biol Psychiatry. 2015;78:635–46.
64. Saxe R, Powell LJ. It's the thought that counts: specific brain regions for one component of theory of mind. Psychol Sci. 2006;17:692–9.
65. Johns CB, Lacadie C, Vohr B, Ment LR, Scheinost D. Amygdala functional connectivity is associated with social impairments in preterm born young adults. Neuroimage Clin. 2019;21:101626.
66. Johnston MV. Clinical disorders of brain plasticity. Brain Dev. 2004;26:73–80.
67. Ana K. Early brain injury and plasticity: reorganization and functional recovery. Transl Neurosci. 2011;2:33–42.
68. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 1997;387:167–78.
69. Duffau H New insights into functional mapping in cerebral tumor surgery. New York, United States; Nova Science Publishers, Inc; 2009.
70. Kennard MA. Age and other factors in motor recovery from precentral lesions in monkeys. Am J Physiol-Leg Content. 1936;115:138–46.
71. Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. J Magn Reson B. 1994;103:247–54.
72. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J. 1994;66:259–67.

73. Jones DK, Knosche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. Neuroimage. 2013;73:239–54.
74. Tournier JD. Diffusion MRI in the brain – Theory and concepts. Prog Nucl Magn Reson Spectrosc. 2019;112–3:1–16.
75. Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Hum Brain Mapp. 2013;34:2747–66.
76. Tournier JD, Calamante F, Gadian DG, Connelly A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. Neuroimage. 2004;23:1176–85.
77. Tournier JD, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. Neuroimage. 2007;35:1459–72.
78. Wilkins B, Lee N, Gajawelli N, Law M, Lepore N. Fiber estimation and tractography in diffusion MRI: development of simulated brain images and comparison of multi-fiber analysis methods at clinical b-values. Neuroimage. 2015; 109:341–56.
79. Dell'Acqua F, Simmons A, Williams SC, Catani M. Can spherical deconvolution provide more information than fiber orientations? Hindrance modulated orientational anisotropy, a true-tract specific index to characterize white matter diffusion. Hum Brain Mapp. 2013;34:2464–83.
80. Dell'Acqua F, Catani M. Structural human brain networks: hot topics in diffusion tractography. Curr Opin Neurol. 2012;25:375–83.
81. Smith RE, Tournier JD, Calamante F, Connelly A. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. Neuroimage. 2012;62:1924–38.
82. Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? Neuroimage. 2007;34:144–55.
83. Allin MP, Kontis D, Walshe M, Wyatt J, Barker GJ, Kanaan RA, et al. White matter and cognition in adults who were born preterm. PLoS ONE. 2011;6:e24525.
84. Ball G, Boardman JP, Aljabar P, Pandit A, Arichi T, Merchant N, et al. The influence of preterm birth on the developing thalamocortical connectome. Cortex. 2013;49:1711–21.
85. Travis KE, Adams JN, Ben-Shachar M, Feldman HM. Decreased and increased anisotropy along major cerebral white matter tracts in preterm children and adolescents. PLoS ONE. 2015;10: e0142860.
86. Murray AL, Thompson DK, Pascoe L, Leemans A, Inder TE, Doyle LW, et al. White matter abnormalities and impaired attention abilities in children born very preterm. Neuroimage. 2016;124:75–84.
87. Mürner-Lavanchy IM, Kelly CE, Reidy N, Doyle LW, Lee KJ, Inder T, et al. White matter microstructure is associated with language in children born very preterm. Neuroimage Clin. 2018;20:808–22.
88. Dodson CK, Travis KE, Borchers LR, Marchman VA, Ben-Shachar M, Feldman HM. White matter properties associated with pre-reading skills in 6-year-old children born preterm and at term. Dev Med Child Neurol. 2018;60:695–702.
89. Young JM, Vandewouw MM, Morgan BR, Smith ML, Sled JG, Taylor MJ. Altered white matter development in children born very preterm. Brain Struct Funct. 2018;223:2129–41.
90. Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KA, Martinussen M, et al. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain. 2007;130:654–66.
91. Mullen KM, Vohr BR, Katz KH, Schneider KC, Lacadie C, Hampson M, et al. Preterm birth results in alterations in neural connectivity at age 16 years. Neuroimage. 2011;54:2563–70.
92. Vollmer B, Lundequist A, Martensson G, Nagy Z, Lagercrantz H, Smedler AC, et al. Correlation between white matter microstructure and executive functions suggests early developmental influence on long fibre tracts in preterm born adolescents. PLoS ONE. 2017;12:e0178893.
93. Jurcoane A, Duamen M, Scheef L, Bauml JG, Meng C, Wohlschlager AM, et al. White matter alterations of the corticospinal tract in adults born very preterm and/or with very low birth weight. Hum Brain Mapp. 2016;37:289–99.
94. Eikenes L, Lohaugen GC, Brubakk AM, Skranes J, Haberg AK. Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. Neuroimage. 2011;54:1774–85.
95. Caldinelli C, Froudist-Walsh S, Karolis V, Tseng CE, Allin MP, Walshe M, et al. White matter alterations to cingulum and fornix following very preterm birth and their relationship with cognitive functions. Neuroimage. 2017;150:373–82.
96. Fornito A, Bullmore ET. Connectomics: a new paradigm for understanding brain disease. Eur Neuropsychopharmacol. 2015;25:733–48.
97. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 2009;10:186–98.
98. van den Heuvel MP, Stam CJ, Kahn RS, Hulshoff, Pol HE. Efficiency of functional brain networks and intellectual performance. J Neurosci. 2009;29:7619–24.
99. Hilger K, Ekman M, Fiebach CJ, Basten U. Intelligence is associated with the modular structure of intrinsic brain networks. Sci Rep. 2017;7:16088.
100. Bertolero MA, Yeo BTT, Bassett DS, D'Esposito M. A mechanistic model of connector hubs, modularity and cognition. Nat Hum Behav. 2018;2:765–77.
101. Ball G, Aljabar P, Zebari S, Tusor N, Arichi T, Merchant N, et al. Rich-club organization of the newborn human brain. Proc Natl Acad Sci USA. 2014;111:7456–61.
102. Zhao T, Mishra V, Jeon T, Ouyang M, Peng Q, Chalak L, et al. Structural network maturation of the preterm human brain. Neuroimage. 2019;185:699–710.
103. Fischi-Gomez E, Muñoz-Moreno E, Vasung L, Griffa A, Borradori-Tolsa C, Monnier M, et al. Brain network characterization of high-risk preterm-born school-age children. Neuroimage Clin. 2016;11:195–209.
104. Karolis VR, Froudist-Walsh S, Brittain PJ, Kroll J, Ball G, Edwards AD, et al. Reinforcement of the brain's rich-club architecture following early neurodevelopmental disruption caused by very preterm birth. Cereb Cortex. 2016;26:1322–35.
105. Tseng C-EJ, Froudist-Walsh S, Brittain PJ, Karolis V, Caldinelli C, Kroll J, et al. A multimodal imaging study of recognition memory in very preterm born adults. Hum Brain Mapp. 2017;38:644–55.
106. Wu ZM, Llera A, Hoogman M, Cao QJ, Zwiers MP, Bralten J, et al. Linked anatomical and functional brain alterations in children with attention-deficit/hyperactivity disorder. Neuroimage Clin. 2019;23:101851.
107. Solsnes AE, Sripada K, Yendiki A, Bjuland KJ, Ostgard HF, Aanes S, et al. Limited microstructural and connectivity deficits despite subcortical volume reductions in school-aged children born preterm with very low birth weight. Neuroimage. 2016;130:24–34.
108. Urbain C, Sato J, Hammill C, Duerden EG, Taylor MJ. Converging function, structure, and behavioural features of emotion regulation in very preterm children. Hum Brain Mapp. 2019;40:3385–97.

109. Salvan P, Froudist Walsh S, Allin MP, Walshe M, Murray RM, Bhattacharyya S, et al. Road work on memory lane-functional and structural alterations to the learning and memory circuit in adults born very preterm. Neuroimage. 2014;102:152–61.
110. Aanes S, Bjuland KJ, Skranes J, Lohaugen GC. Memory function and hippocampal volumes in preterm born very-low-birthweight (VLBW) young adults. Neuroimage. 2015;105:76–83.
111. Ly M, Adluru N, Destiche DJ, Lu SY, Oh JM, Hoscheidt SM, et al. Fornix microstructure and memory performance is associated with altered neural connectivity during episodic recognition. J Int Neuropsychol Soc. 2016;22:191–204.
112. Turkeltaub PE, Coslett HB, Thomas AL, Faseyitan O, Benson J, Norise C, et al. The right hemisphere is not unitary in its role in aphasia recovery. Cortex. 2012;48:1179–86.
113. Guttmacher AE, Raju TNK. The child is father of the man, and mother of the woman. Pediatrics. 2014;134:e1411–e1412.
114. Kelly CE, Thompson DK, Chen J, Leemans A, Adamson CL, Inder TE, et al. Axon density and axon orientation dispersion in children born preterm. Hum Brain Mapp. 2016; 37:3080–102.
115. Young JM, Vandewouw MM, Mossad SI, Morgan BR, Lee W, Smith ML, et al. White matter microstructural differences identified using multi-shell diffusion imaging in six-year-old children born very preterm. Neuroimage Clin. 2019;23:101855.
116. Pannek K, Fripp J, George JM, Fiori S, Colditz PB, Boyd RN, et al. Fixel-based analysis reveals alterations is brain microstructure and macrostructure of preterm-born infants at term equivalent age. Neuroimage Clin. 2018;18:51–59.
117. Pecheva D, Tournier JD, Pietsch M, Christiaens D, Batalle D, Alexander DC, et al. Fixel-based analysis of the preterm brain: Disentangling bundle-specific white matter microstructural and macrostructural changes in relation to clinical risk factors. Neuroimage Clin. 2019;23:101820.
118. Genc S, Smith RE, Malpas CB, Anderson V, Nicholson JM, Efron D, et al. Development of white matter fibre density and morphology over childhood: a longitudinal fixel-based analysis. Neuroimage. 2018;183:666–76.
119. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage. 2012;61:1000–16.
120. Raffelt DA, Tournier JD, Smith RE, Vaughan DN, Jackson G, Ridgway GR, et al. Investigating white matter fibre density and morphology using fixel-based analysis. Neuroimage. 2017;144:58–73.
121. Kawahara J, Brown CJ, Miller SP, Booth BG, Chau V, Grunau RE, et al. BrainNetCNN: Convolutional neural networks for brain networks; towards predicting neurodevelopment. Neuroimage. 2017;146:1038–49.
122. Li X, Morgan PS, Ashburner J, Smith J, Rorden C. The first step for neuroimaging data analysis: DICOM to NIfTI conversion. J Neurosci Methods. 2016;264:47–56.
123. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31:968–80.