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Neuroimaging findings from childhood, early adulthood, and the Norwegian Mother and Child Cohort Study

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Thesis for the Degree of
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Hjerneutvikling, konnektivitet og kognisjon etter for tidlig fødsel med svært lav fødselsvekt

For tidlig fødsel (<37 uker gestasjon) og svært lav fødselsvekt (VLBW, fødselsvekt ≤ 1500 gram) medfører økt risiko for tidlig hjerneskade og negative virkninger på kognitive evner og adferd gjennom hele livsløpet. Hjerneavbildning med magnetresonanstomografi (MRI) kan øke vår kunnskap om endringer i hjernestruktur og -funksjon, samt tidsforløpet og hvor i hjernen disse endringene skjer. Dette doktorgradsarbeidet søker å kartlegge vedvarende endringer i hjernens grå og hvite substans ved bruk av strukturell MRI, sett i sammenheng med vansker med visuell-motoriske evner og eksekutivfunksjon, hos for tidlig fødte/VLBW i barndom og tidlig voksen alder.

I den første studien i denne doktorgraden undersøkte vi en kohort unge voksne født mellom 1986 og 1988, enten for tidlig/VLBW (n=47) eller til termin (n=56), ved bruk av strukturell MRI, diffusjonsvektet avbildning og kartlegging av visuell-motoriske evner. Problemer med visuell-motorisk integrasjon hos for tidlig fødte/VLBW unge voksne var knyttet til redusert overflateareal og tykkelse av hjernebarken, i tillegg til redusert fraksjonell anisotropi i den midtre hjernebjelken (corpus callosum) og i intrahemisfæriske nervebaner. Dette kan tyde på endret sammenheng mellom struktur og funksjon i hjernen relatert til for tidlig fødsel/VLBW, og at disse endringene vedvarer inn i voksen alder.

I den andre studien undersøkte vi eksekutivfunksjon og hjernestruktur på to ulike tidspunkt (ved cirka 8 og 9,5 år) i en gruppe for tidlig fødte/VLBW barn (n=41) og en gruppe friske deltakere i Den norske mor og barn-undersøkelsen (n=128), født mellom 2001 og 2007. Ved første tidspunkt fant vi ikke signifikante gruppeforskjeller i diffusjonsparametere i 18 undersøkte nervebaner. Longitudinell analyse viste derimot redusert overflateareal og avvikende tykkelse i hjernebarken, samt reduserte volumer av subkortikale hjernestrukturer hos den for tidlig fødte/VLBW gruppa, og at disse endringene vedvarte over tid. Vi fant ingen holdepunkter for at hjernen utvikler seg annerledes i for tidlig fødte/VLBW barn enn i kontrollgruppen mellom de to tidspunktene. Eksekutivfunksjon viste ikke noe interaksjon med hjernestruktur, mens IQ-skårer var lavere i den for tidlig fødte/VLBW gruppa og var forbundet med overflateareal i enkelte regioner av hjernebarken. Den for tidlig fødte /VLBW-gruppa viste ikke tegn på kompensatorisk vekst over tid, hverken i grå eller hvit substans, eller i eksekutiv funksjon.

Dette doktorgradsarbeidet påviser avvik i hjernestruktur og svekkede kognitive ferdigheter hos de for tidlig fødte/VLBW, både i barndom og tidlig voksen alder. Disse resultatene støtter hypotesen om at nevral og kognitiv utvikling hos de for tidlig fødte/VLBW er annerledes – ikke bare forsinket – sammenlignet med terminfødte jevnaldrende. Disse funnene kan forhåpentligvis bidra til en grundigere forståelse av de langsiktige konsekvensene for sentralnervesystemet av for tidlig fødsel med VLBW, og utgjør et grunnlag for videre forskning på tidlige intervensjon som kan forhindre slik avvikende utvikling.

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	Live Eikenes, Gro C. Løhaugen (biveiledere)
Finansieringskilde:	Samarbeidsorganet mellom Helse Midt-Norge og NTNU

Brain development, connectivity, and cognition following preterm birth with very low birthweight

Preterm birth (<37 weeks of gestation) and very low birth weight (VLBW, birth weight ≤ 1500 grams) are linked to risks for early brain injury and negative effects on cognitive skills and behavior throughout life. Neuroimaging with magnetic resonance imaging (MRI) can improve our understanding of the location and timing of changes in brain structure and function. This PhD thesis seeks to further characterize long-term alterations in gray and white matter structures in the brain using structural MRI, as well as difficulties in visual-motor skills and executive function, in the preterm-born/VLBW population in childhood and early adulthood.

For the first long-term follow-up study in this thesis, we investigated group differences in a cohort of young adults born preterm/VLBW (n=47) or at-term (n=56) between 1986 and 1988, using structural MRI, diffusion-weighted imaging, and assessment of visual-motor skills. Worse performance on visual-motor integration tasks in the preterm/VLBW individuals was associated with reduced surface area and thickness in cortical regions, as well as reduced fractional anisotropy in corpus callosum and intrahemispheric white matter tracts. These results suggest altered structure-function relationships in the brain following preterm birth/VLBW that can last into adulthood.

For the second study, we investigated differences in executive function and brain structure at two timepoints (at approximately 8 and 9.5 years of age) in children born preterm/VLBW (n=41) or healthy participants in the Norwegian Mother and Child Cohort Study (n=128), born between 2001 and 2007. At the first timepoint, group differences on diffusion measures in 18 white matter tracts were not significant. Longitudinal analysis, by contrast, showed widespread reduced cortical surface area, altered cortical thickness, and smaller subcortical structures in the preterm/VLBW group, which persisted over time. However, we did not find evidence for divergent brain growth trajectories in preterm/VLBW children. Executive function did not show interactions with brain structure, while IQ scores were lower in the preterm/VLBW group and showed a positive association to surface area in cortical regions. The preterm/VLBW group did not demonstrate “catch up” growth in gray or white matter structures or executive function.

This thesis provides evidence for differences in the preterm/VLBW brain and deficits in cognitive skills, both in childhood and young adulthood. These results lend support to the hypothesis of a neurocognitive developmental trajectory in the preterm-born/VLBW population that is different – rather than merely delayed – from their term-born peers. The findings presented here will hopefully contribute to a more comprehensive understanding of lasting impacts of preterm birth with VLBW, and support further early intervention research.

This thesis has been found worthy of a public defense for the degree PhD in Neuroscience.
The disputas will take place in the MTA Auditorium at the MTFS Building,
Norwegian University of Science & Technology (NTNU),
Wednesday, 23 May 2018, at 12:15pm.

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Thank you to all my friends. I feel incredibly lucky to have shared many special experiences and conversations with each of you. Thank you for listening to me and laughing at my bad jokes. And a special thanks to Kiki.

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Kam Sripada

Trondheim, Norway

Submitted 23 January 2018

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NeuroImage. 2015 Apr 1;109:493-504. Open access.

II Limited microstructural and connectivity deficits despite subcortical volume reductions in school-aged children born preterm with very low birth weight. Sølsnes AE*, Sripada K*, Yendiki A, Bjuland KJ, Østgård HF, Aanes S, Grunewaldt KH, Løhaugen GC, Eikenes L, Håberg AK, Rimol LM, Skranes J.
NeuroImage. 2016 Apr 15;130:24-34. Open access. *Shared first authorship

III Long-term effects on brain development of preterm birth with very low birth weight at early school age. Sripada K, Bjuland KJ, Sølsnes AE, Håberg AK, Grunewaldt KH, Løhaugen GC, Rimol LM, Skranes J.
Submitted to *NeuroImage*, 28 Nov 2017. Resubmitted 7 May 2018, under review.

Additional papers

"Beginning with the Smallest Intake": Children's Brain Development and the Role of Neuroscience in Global Environmental Health. Sripada K.
Neuron. 2017 Sep 13;95(6):1242-1245. Open access.

Childhood epilepsy and ADHD comorbidity in an Indian tertiary medical center outpatient population. Choudhary A, Gulati S, Sagar R, Sankhyan N, Sripada K.
Scientific Reports. 2018 Feb 8;8(1):2670.

Abbreviations

AD	Axial diffusivity
ATR	Anterior thalamic radiation
CAB	Cingulum – angular infracallosal bundle
CCG	Cingulum – cingulate gyrus, supracallosal bundle
CST	Corticospinal tract
dMRI	Diffusion-weighted MRI
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
eTIV	Estimated total intracranial volume
FA	Fractional anisotropy
FDR	False discovery rate
FMRIB	Functional MRI of the Brain
FSL	FMRIB software library
ICV	Intracranial volume
ILF	Inferior longitudinal fasciculus
IQ	Intelligence quotient
MD	Mean diffusivity
MoBa	Norwegian Mother and Child Cohort Study
MPRAGE	Magnetization prepared rapid acquisition gradient echo
MRI	Magnetic resonance imaging
NEPSY	Developmental NEuroPSYchological Assessment
NICHD	National Institute of Child Health and Human Development

NICU	Neonatal intensive care unit
RD	Radial diffusivity
SGA	Small for gestational age
SLFP	Superior longitudinal fasciculus – parietal bundle
SLFT	Superior longitudinal fasciculus – temporal bundle
SPM	Statistical Parametric Mapping
TBSS	Tract-Based Spatial Statistics
TRACULA	TRActs Constrained by UnderLying Anatomy
UNC	Uncinate fasciculus
VLBW	Very low birth weight (≤ 1500 grams)
VMI	Visual-Motor Integration
WASI	Wechsler Abbreviated Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children
WMS	Wechsler Memory Scale
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

Introduction

Around the world, approximately 15 million neonates each year are born preterm (< 37 completed weeks of gestation) (Blencowe et al., 2012). Advances in neonatal intensive care over the last three decades, especially the introduction of commercial surfactants and antenatal steroids (Grytten et al., 2017), have dramatically improved survival rates for infants born preterm by reducing the severity of respiratory distress syndrome, intraventricular hemorrhage, and related disorders (Volpe, 2014). Indeed, 80% of children born in high-income countries at just 25 weeks of gestation now survive (Blencowe et al., 2013).

Nevertheless, health and cognitive outcomes for individuals born preterm range widely. Those born preterm and with very low birth weight (VLBW, birth weight ≤ 1500 grams) face higher risks for perinatal brain injury and long-term negative effects on cognitive skills and behavior (Back et al., 2007; Nosarti et al., 2010; Zeitlin et al., 2016). Neuroimaging, especially magnetic resonance imaging (MRI), has become a fundamental tool for understanding the location and timing of changes in brain structure and function – "neuromarkers" – in the preterm/VLBW population (Mathur et al., 2010; Ment et al., 2009; Myers and Ment, 2009; Parikh, 2016; Tao and Neil, 2014). Findings of altered brain structure and cognitive deficits associated with preterm birth have been reported throughout the lifespan:

- ***In utero*** (Thomason et al., 2017)
- **At term-equivalent age** (Brouwer et al., 2017; Smyser et al., 2016)
- **During childhood** (Dodson et al., 2017; Johnson et al., 2009; Rathbone et al., 2011)
- **In adolescence** (Karolis et al., 2017; Martinussen et al., 2009; Skranes et al., 2007)
- **In adulthood** (Kalpakidou et al., 2014; Kroll et al., 2017; Lund et al., 2012)

This article-based PhD thesis seeks to further characterize long-term alterations in gray and white matter structures in the brain using structural MRI analysis, as well as implications for visual-motor skills and executive function in the preterm-born/VLBW population, in childhood and early adulthood.

Neurodevelopment *in utero*

Neurodevelopment *in utero* lays the foundation for brain structure for the rest of life (Rees et al., 2011; Volpe, 2008):

- **Neural proliferation** at the ventricular and subventricular zones (3 to 4 months of gestation)
- **Migration of neurons** – movement from location of genesis to target locations on the cortical plate (peaks between 3 to 5 months of gestation)
- **Organization** – establishment and differentiation of subplate neurons, synaptogenesis, and elimination; glial growth (5 months of gestation to years postnatally)
- **Myelination** of white matter (second trimester to years postnatally)

A major burst of brain development takes place during the second half of fetal life (**Figure 1**), involving growth of gray matter, white matter, synaptogenesis, and dendritic arborization (Lenroot and Giedd, 2006; Semple et al., 2013). The majority of neurons are generated during the second trimester of pregnancy (Stiles, 2008), and between weeks 20 and 40 of gestation, brain weight grows by 90% (Guihardcosta and Larroche, 1990; Kinney, 2006). Intracranial volume has been estimated to increase approximately 1.4% (15 mL) per week between 29 to 41 weeks of gestation (Hüppi et al., 1998). Gyrification, or the folding of the cortex, begins as early as gestational week 8 and continues into the postnatal period (Stiles and Jernigan, 2010), and the number of gyri increases the fastest between weeks 26 and 28 of gestation (Chi et al., 1977; Volpe, 2008).

White matter development begins *in utero* and can last for decades, as glial cells are produced throughout life and myelination follows the development of cognitive networks which take

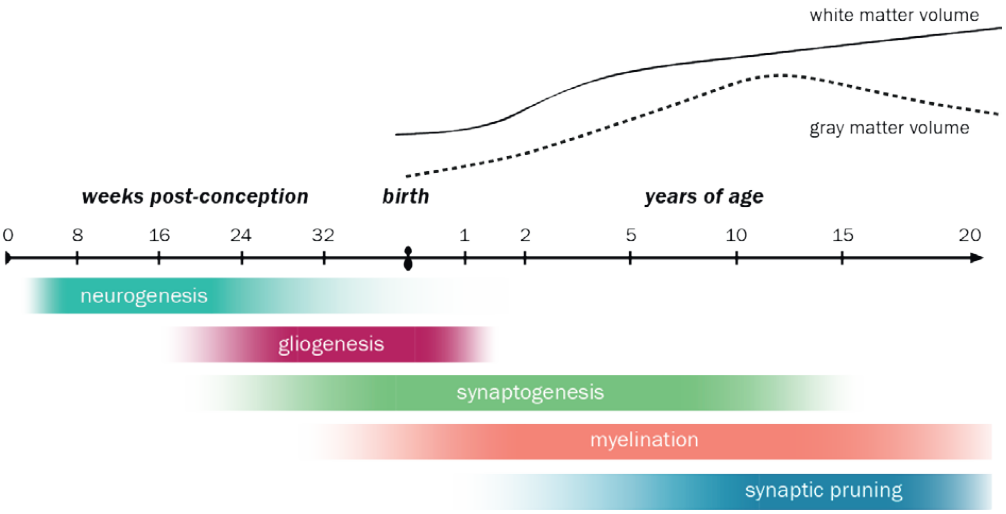

Figure 1. Timeline of key neurodevelopmental processes in humans from pregnancy through adolescence (not to scale), modified from Semple et al. (2013) and originally adapted from Lenroot and Giedd (2006), reproduced here with permission.

form over many years (Stiles, 2008). The thalamocortical and corticothalamic pathways, which are essential for relaying sensory and motor information to the cortex, begin to form in the second trimester and are complete by gestational week 26 (Kostovic and Jovanov-Milosevic, 2006; Stiles and Jernigan, 2010). Myelinated white matter visible on MRI increases five-fold between gestational weeks 35 and 41 (Hüppi et al., 1998).

"Encephalopathy of prematurity"

Preterm birth occurs in the midst of this rapid brain development. The damage to cerebral white matter and neuronal/axonal structures in the preterm-born population, together referred to as "**encephalopathy of prematurity**" (Volpe, 2009; Volpe, 2011), involves hypoxia-ischemia (i.e., diminished blood and oxygen flow to the brain), which can last days or weeks following insult, and systemic infection and inflammation (Aylward, 2014). White matter injury in the preterm brain, especially adjacent to the lateral ventricles, is typically non-cystic and involves diffuse injury to pre-oligodendrocytes (a type of early differentiating glial cell) through a number of cellular mechanisms which are not fully understood (Volpe, 2011). Surviving pre-oligodendrocytes and cells which replace eliminated pre-oligodendrocytes, do

not appear to adequately mature to produce myelin, leading to myelination failure, or hypomyelination. The vulnerable window for pre-oligodendrocytes coincides with the peak period of occurrence of periventricular white matter injury, especially from 24 to 32 weeks of gestation (Volpe, 2011). Inflammation also appears to disrupt oligodendrocyte and axon maturation processes and is related to reduced diameter of myelinated axons in a mouse model of preterm birth (Favrais et al., 2011). Subplate neurons are particularly vulnerable to hypoxia-ischemia (Kanold and Luhmann, 2010; Volpe, 2008). White matter injury is estimated to affect at least 20% of preterm-born/VLBW infants born without intraventricular hemorrhage, and 53% in those with (Takashima et al., 1989; Volpe, 2008).

While the most severe lesions including cystic periventricular leukomalacia have declined following advances in neonatal care, periventricular white matter injury is still common in the preterm-born population (Back et al., 2007). Infants born preterm are vulnerable to a range of complicating intrinsic factors in the neonatal period as well, including an immature immune system and risk for infection, respiratory problems, insufficient nutrition, and complications associated with low blood pressure and cerebral hypoperfusion, which can affect neurological outcomes (Rezaie and Dean, 2002). The long-term impact of prenatal and perinatal insults to the preterm brain is also influenced by recovery and reorganization of neural functions due to external factors in the extrauterine neonatal environment (Aylward, 2014; Viola et al., 2011).

Overall, there is a string of intrinsic and extrinsic factors that exert a strong influence on brain development before preterm birth and in neonatal life. Decreased brain growth, even in the absence of severe brain injury, has been reported among preterm/VLBW infants who live *ex utero* for their "third trimester," compared to fetuses of comparable age, suggesting that their course of brain development leading up to this period is altered (Bouyssi-Kobar et al., 2016). Deviations from a typical perinatal neurodevelopmental trajectory, such as disruption in cell migration, may underlie later impairments in cognition and behavior (Aylward, 2014; Volpe, 2011), which will be discussed in the next section.

Cognitive deficits associated with preterm birth and very low birth weight

Preterm birth has wide-ranging impacts on the individual and society (**Table 1**) and is a risk factor for neurocognitive impairments that can start early and touch many aspects of life (Aarnoudse-Moens et al., 2013; Hack et al., 2005; Lund et al., 2012; Nosarti et al., 2010):

- **Neurosensory impairments** in vision and hearing
- **Deficits in cognitive skills**: poorer working memory, visuospatial ability, and executive function
- **Adverse mental health outcomes**: inattention, emotional difficulties, and socialization problems
- **Difficulties in daily life**: reduced participation in physical activities, language and communication difficulties, learning impairments

Prevalence figures for neurocognitive sequelae following preterm birth and VLBW are higher than in the term-born/typical gestational weight population, though the reported rates vary. Blencowe et al. (2013) estimate that, worldwide, 52% of those born at prior to 28 completed weeks of gestation, 24% of those born at 28 to 31 weeks, and 5% of those born at 32 to 36 weeks of gestation (all birthweights) who survive the neonatal period have some degree of neurodevelopmental impairment. A recent global systematic review found that among newborns weighing 1500 grams or less (all gestational ages), 26.7% had at least one neurological sequela (Mwaniki et al., 2012). Altogether, approximately 25 to 50% of survivors of preterm birth with VLBW exhibit cognitive deficits (Volpe, 2008).

Many of these neurocognitive deficits, especially subtle impairments in sensory-motor function or executive functioning, may not appear as early as severe disabilities following a high-risk delivery, and therefore require long-term follow-up research (Aylward, 2002; Skranes and Løhaugen, 2016). Research has shown a gradient effect for adverse neurocognitive outcomes in children born preterm, with gestational age at delivery demonstrating a dose-dependent relationship with developmental delays (Kerstjens et al., 2012) and need for special education (MacKay et al., 2010).

Table 1. Long-term impacts of preterm birth on survivors, modified from Blencowe et al. (2013) and Mwaniki et al. (2012), and used here with permission.

Long-term outcomes		Examples
Neurodevelopmental/ behavioral effects	Mild disorders of executive functioning	• Specific learning impairments, dyslexia, reduced academic achievement
	Moderate to severe global developmental delay	• Moderate/severe cognitive impairment, mental retardation • Motor impairment • Cerebral palsy
	Psychiatric/behavioral sequelae	• Attention deficit • Increased anxiety and depression
Specific physical effects	Vision and hearing	• Blindness or severe myopia after retinopathy of prematurity • Increased hypermetropia and myopia, strabismus • Hearing impairment
	Chronic lung disease of prematurity	• From reduced exercise tolerance to requirement for oxygen at home • Increased hospital admissions in childhood for lower respiratory tract infections
	Long-term cardiovascular morbidity and non-communicable disease	• Increased blood pressure • Reduced lung function • Increased rates of asthma • Growth failure in infancy, accelerated weight gain in adolescence
Family, economic, and societal effects	Impact on family Impact on health service Intergenerational	• Psychosocial, emotional, and economic effects • Cost of care – acute and chronic • Risk of preterm birth in offspring

A constellation of impairments that includes visual, motor, learning, and psychosocial difficulties are often linked to preterm birth/VLBW and encephalopathy of prematurity (Van Hus et al., 2014; Volpe, 2009). Rose et al. (2011) used structural equation modeling to describe the cascade of downstream effects on worse cognitive performance:

Prematurity
→ Slower processing speed
→ Poorer executive functioning (working memory)
→ Lower achievement in math and reading

The cognitive skills addressed by this thesis will each be briefly introduced here.

Visual-motor function

Visual-motor function integrates several sensory and movement systems: visual perception, visual-motor integration, hand-eye coordination, and fine motor speed and control (Aylward, 2014).

Visual and motor dysfunction in individuals born preterm/VLBW is well-documented, ranging from cerebral palsy and retinopathy of prematurity to subtle visual-motor impairments (de Kieviet et al., 2009; Vicari et al., 2004). In some cases, preterm/VLBW children show gains of motor skills over time (Janssen et al., 2016) but, in general, continue to underperform their term-born peers, even when they do not have a history of visual impairment (Butcher et al., 2012; Oudgenoeg-Paz et al., 2017; Petkovic et al., 2016). Emerging evidence indicates that early motor dysfunction and later cognitive impairments in this population may have a shared neurobiological basis (Oudgenoeg-Paz et al., 2017). Because of its importance for hand-eye coordination, precision, speed, and planning, visual-motor integration has implications for classroom and job performance in later years.

Executive function

While its definition varies, executive function is often thought to encompass working memory, cognitive control, and inhibitory control/reward processing (Barkley, 2012; Farah et al., 2006) – in other words, an individual's ability to regulate their own thinking and

behavior. Executive function is therefore important for language development, reading, planning, social interactions, and learning new skills (Aylward, 2014; Barkley, 2012; Stevens et al., 2009).

The preterm behavioral phenotype has been described as anxious and inattentive, rather than hyperactive or disruptive, which may also mean that their cognitive difficulties may not be as readily visible in a classroom setting (Johnson and Marlow, 2017; Olsen et al., 2017). A meta-analysis by Mulder et al. (2009) indicated that executive function and attention are generally reported to be weaker in children born preterm, though patterns for specific executive function components varies. Deficits in executive function have consequences for general cognitive functioning. As preterm-born children enter school age, they have been reported to have increased distractibility, worse inhibitory control, and poorer executive function skills that may contribute to poorer social competence (Alduncin et al., 2014; Loe et al., 2012). Poorer executive function in preterm children at school age appears to remain even after controlling for lower IQ scores (Aarnoudse-Moens et al., 2009; Bohm et al., 2004). A recent study among adults born preterm between 1979 and 1984 found both worse executive function persisting into adulthood and a stronger positive association between executive function and “real-life” educational and employment achievement compared to term-born peers (Kroll et al., 2017). Deficits in executive function in late adolescence have also been linked to smaller cortical surface area in regions involved in higher order cognition (Østgård et al., 2016).

IQ

Intelligence quotient, or IQ, typically measures baseline levels of functioning in several cognitive domains and, while an imperfect measure of general intelligence, reflects cognitive function relative to the median level of performance in an age-matched sample (Devinsky and D'Esposito, 2004). IQ assessments give low specificity for areas of strength or weakness compared to other neuropsychological tools but may be clinically meaningful for identifying individuals with special needs, such as for educational or psychiatric services (Aylward, 2002). Research suggests that IQ is primarily influenced by genetic and sociodemographic/environmental factors, although the extent to which IQ can be influenced by other factors – such as medical conditions in early life – remains an open question.

The preterm/VLBW population is reported to have lower IQ than the term-born population (Cserjesi et al., 2012; Van Hus et al., 2014), averaging approximately 11.94 points lower, based on a systematic review of 37 estimates (Kerr-Wilson et al., 2012). A recent meta-analysis of long-term outcomes following preterm birth that encompassed 64,601 children reported that gestational age at birth accounted for 38 to 48% of the observed IQ variance (Allotey et al., 2017).

MRI of the preterm/VLBW brain

Visualizing the inner workings of the living human brain is a challenge for researchers and clinicians. To identify the neurobiological sequelae of preterm birth/VLBW and understand the neural underpinnings of the long-term cognitive effects seen in this population, neuroimaging is a powerful tool. Structural MRI, which was used in this PhD project, as well as functional imaging, have shed light on brain regions that appear sensitive to pre- and perinatal insults and the cognitive deficits related to brain structural alterations. Neuroimaging of the cortex, subcortical structures (such as hippocampus and thalamus), and white matter tracts provides distinct and complementary physiological data to help unravel complex structure-function relationships as they develop over the life course. This thesis combines structural neuroimaging of cortex, subcortical structures, and white matter, which will each be introduced here in light of their potential for understanding the preterm brain.

White matter

Diffusion-weighted MRI is sensitive to water diffusion in the brain and is influenced by the content of hydrogen nuclei in tissue, packing of parallel axons, axonal thickness, and myelination, which develop with age (Counsell et al., 2014). Diffusion-weighted MRI can estimate the direction and amount of diffusion of water molecules and is therefore useful for modeling white matter fiber directions and connectivity (Johansen-Berg and Behrens, 2014). Fractional anisotropy (FA) indicates the fraction of water movement through an area of brain tissue in the predominant direction, with 0 being isotropic and 1 being in a single direction (Beaulieu, 2014). Diffusivity is the measure of water movement, parallel (axial) or perpendicular (radial) to the principal direction of diffusion, or their combined mean diffusivity (MD).

Altered diffusivity measures like FA and MD are commonly reported in the preterm-born population, though no single pattern can describe the variation across all tracts (Dodson et al., 2017; Travis et al., 2015). Shortly after birth, elevated cortical FA following ischemia has been linked to disturbances in dendritic arborization of cortical neurons and reduced dendritic spine density (Ball et al., 2013; Dean et al., 2013). By young adulthood, our cohort born preterm/VLBW in the 1980s showed bilateral reduced FA in corticospinal tract, posterior thalamic radiation/optical radiation, and long-range association tracts, likely due to myelin disturbances (Eikenes et al., 2011).

However, more recent cohorts born preterm/VLBW have shown fewer abnormalities in white matter on neuroimaging (Batalle et al., 2017; Feldman et al., 2012). The degree of white matter deviations from the measures typical in the term-born population appear related to complications in the neonatal period and the degree of prematurity (Ball et al., 2010; Favrais et al., 2014; Feldman et al., 2012; Gagliardi et al., 2009; Malavolti et al., 2017). Because widespread white matter injury is a common characteristic in the preterm/VLBW brain, diffusion-weighted MRI is a valuable tool for identifying biomarkers related to neurodevelopmental impairments (van Kooij et al., 2012).

Subcortical structures

Subcortical structures – such as the amygdala, caudate nucleus, globus pallidus, hippocampus, putamen, and thalamus – play an important role in cognition through modulating interactions between stimulus-based and higher-order control systems, and are key to efficient learning and adaptation in the context of novel information (Koziol and Budding, 2009).

Boardman et al. (2010) describes a "**common neonatal image phenotype**" among children born preterm, consisting of diffuse white matter injury and tissue loss in the thalamus, globus pallidus, corona radiata, posterior periventricular white matter, and centrum semiovale. Injury to gray matter in the preterm/VLBW population often comes in tandem with diffuse periventricular white matter injury (Pierson et al., 2007), although the mechanisms behind their shared etiologies are not fully understood (Volpe, 2008).

The thalamus, which plays a role in sensory and motor signaling (Brumbaugh et al., 2016), and the hippocampus, which is central to learning and memory (Scoville and Milner, 1957), are typically smaller in the preterm/VLBW population (Volpe, 2008). Furthermore, connectivity between subcortical gray matter and cortex (e.g., thalamocortical circuitry) is believed to be disrupted (Counsell et al., 2014; Salvan et al., 2014). A recent resting-state functional connectivity study (Scheinost et al., 2016) showed significantly reduced connectivity between the amygdala and thalamus, hypothalamus, brainstem, and insula in neonates born very preterm (< 32 weeks gestation and 500 to 1500 grams) and an amplifying effect of maternal depression or anxiety on amygdala connectivity. Structural abnormalities in subcortical gray and white matter have been linked to worse neurodevelopmental outcomes, an indication of the functional consequences of disruptions in thalamus, basal ganglia, and white matter development (Boardman et al., 2010).

Cortex

Deviations in the trajectories of cortical development can manifest in a spectrum of neurocognitive impairments that can last a lifetime (Kesler et al., 2008; Nosarti et al., 2008; Peterson et al., 2000). MRI over the last two decades has with increasing sophistication identified the regions and functional sequelae of cortical abnormalities in the preterm/VLBW brain (Inder et al., 1999), thought to emerge from the cascading effects on neural migration to and development of the cortex beginning *in utero*.

Whether cortical development in the preterm brain is “delayed” or “different” is a matter of active research, as some studies have demonstrated similar brain growth curves for preterm/VLBW and term-born children and adolescents (Bjuland et al., 2014; de Kieviet et al., 2012; Giedd et al., 1999; Rimol et al., 2016), while others find evidence for divergent trajectories to a limited extent (Murner-Lavanchy et al., 2014). Birthweight has been reported to influence cortical surface area and to a lesser extent cortical thickness, along with cognitive outcomes, even small shifts in which can have significant consequences at the population level (Raznahan et al., 2012). This thesis examines trajectories of cortical surface area, thickness, and subcortical growth in childhood, morphometric group differences in early adulthood, and relationships between cortical morphometry and performance on neuropsychological assessments at both ages.

Aims

Paper 1

First, this study aimed to evaluate visual-motor abilities for visual perception, fine motor tasks, and copying figures, in young adults born with VLBW compared to term-born peers. Second, we related visual-motor abilities in the VLBW group to morphometric and DTI findings. Our hypothesis was that the VLBW adults would achieve lower scores than controls on these visual-motor tests and demonstrate corresponding gray and white matter alterations.

Paper 2

This study aimed to quantify group differences in subcortical volumes and white matter properties in preterm-born/VLBW children and peers participating in the Norwegian Mother and Child Cohort Study (MoBa). We implemented novel analysis tools in TRACULA to examine cortical thickness in white matter tract endpoint projection regions and pointwise diffusion values along each tract. We also investigated relationships between neuroimaging findings and full-scale IQ scores and perinatal risk factors.

Paper 3

Following up to paper 2, this longitudinal study used linear mixed effects models to investigate cortical and subcortical growth trajectories in preterm-born/VLBW children and peers participating in the MoBa study over approximately 16 months in middle childhood. We also assessed executive functions – visual attention, motor inhibition, and spatial span – and examined potential differential relationships to brain morphometric development and perinatal risk factors.

Methods

Definitions

Preterm birth is defined as live birth before 37 weeks of pregnancy are completed (World Health Organization, 2017). In this thesis, **very low birth weight** is defined as birth weight ≤ 1500 grams.

Study design

Paper 1

This study includes term-born control participants who are part of an ongoing multi-center hospital-based, prospective birth cohort follow-up study named the NICHD Study of Successive Small-for-Gestational-Age Births (Bakketeig et al., 1993). Neuroimaging and cognitive data collection for paper 1 was carried out between January 2007 and December 2008.

Papers 2 and 3

This was a longitudinal study of children in the Trondheim area, who were either born preterm with VLBW or participating in the MoBa study, and assessed using neuroimaging and neuropsychological testing at two timepoints approximately 16 months apart. Data collection was carried out between January 2012 and June 2014. For paper 2, only one timepoint was used for each participant. For paper 3, 120 participants (VLBW n=30) had two successful MRI scans, and 49 (VLBW n=11) with only one successful scan were also included.

Study populations

Paper 1 (**Figure 2**)

Preterm-born VLBW group born in 1980s

A total of 121 VLBW infants were admitted to the neonatal intensive care unit (NICU) at the University Hospital in Trondheim, Norway, between 1986 and 1988. Of these, 33 died and nine had moved before follow-up. One child with Down's syndrome and two children with severe cerebral palsy were excluded from follow-up due to inability to perform the tests. Of the remaining 76, 54 participated in follow-up evaluation at age 20, and 47, including three individuals with mild bilateral spastic cerebral palsy, had successful cognitive assessments and MRI acquisitions at 18 to 22 years of age. Twelve of the VLBW participants were twins.

Term-born group born in 1980s

Term-born participants were born to mothers living in the Trondheim area who were recruited before week 20 of pregnancy, between January 1986 and March 1988. Participants in this thesis come from the 10% random sample of mothers who were included for follow-up during pregnancy and recruited via sealed envelope method. Inclusion criteria for this study were singleton pregnancies, para 1 or 2, mothers of Caucasian origin, speakers of a Scandinavian language, and birthweight $\geq 10^{th}$ percentile for gestational age, for a total of n=122 eligible for inclusion. At age 18 to 22, 10 had moved and two were excluded due to congenital malformations. Of the remaining 110, 81 participated at the follow-up, and 66 were examined with MRI. Seven DTI scans were excluded due to image artifacts, leaving 59 with successful DTI scans. Three of these did not have visual-motor assessment or had a poor morphometric MRI, leaving 56 who were successfully evaluated with cognitive testing, morphometric MR, and DTI.

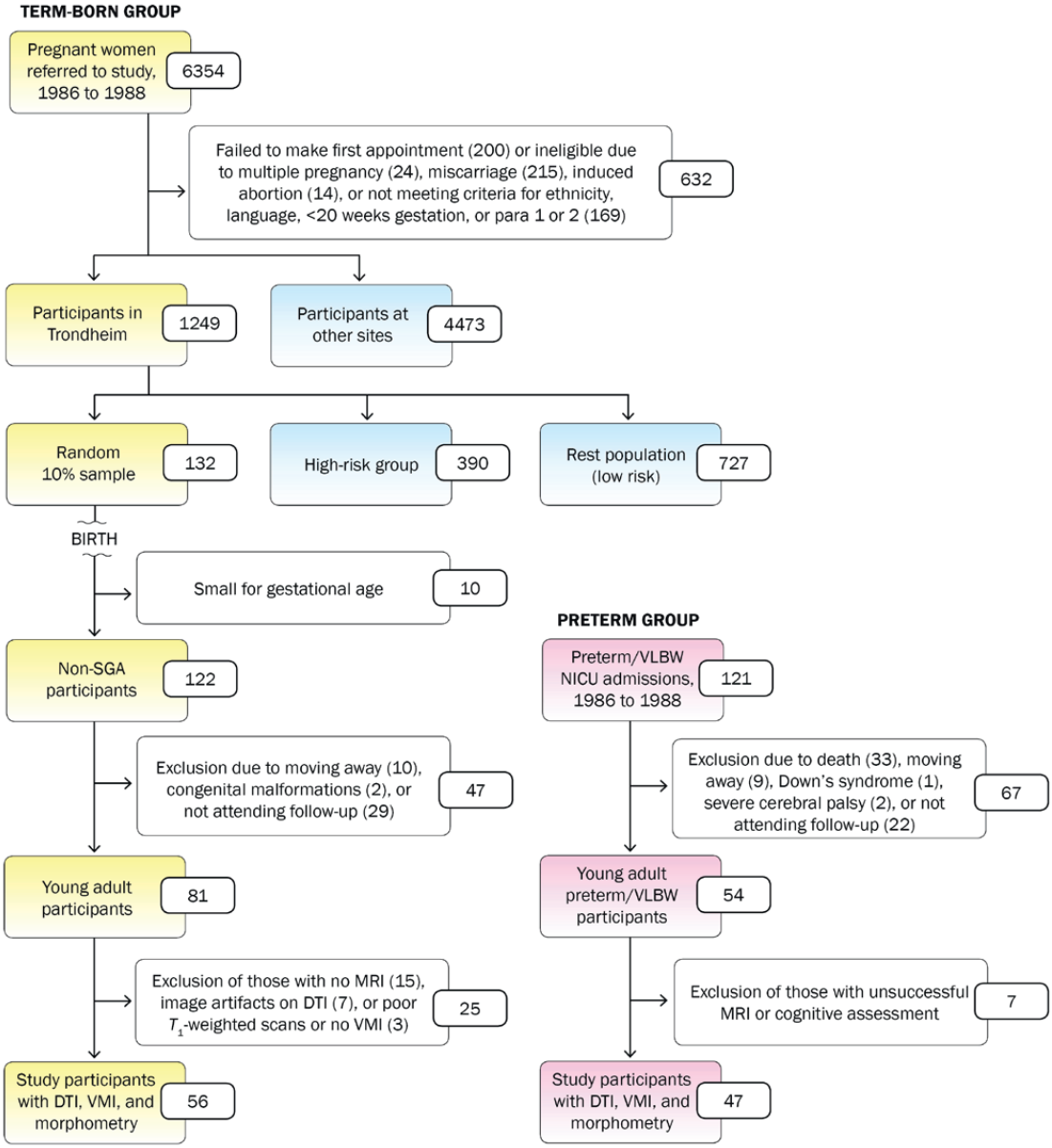

Figure 2. Flowchart of participant inclusion, paper 1.

Papers 2 and 3 (**Figure 3**)

Preterm-born VLBW group born in 2000s

Preterm-born VLBW participants born between 2003 and 2007 were included based on admittance to the Neonatal Intensive Care Unit at St. Olav University Hospital in Trondheim, Norway and being 4 to 11 years of age at time of recruitment. Exclusion criteria were severe cerebral palsy (unable to complete neuropsychological testing and MRI), severe sensory impairments, and/or MRI contraindications. A total of 63 children were invited, and 55 meeting inclusion criteria agreed to participate. Six of the preterm participants were twins. Different researchers conducted MRI quality control for paper 2 and paper 3 and thus determined which subjects could be included based on image quality; I collaborated on this for the TRACULA portion of paper 2 and all of paper 3. Moreover, several participants with high-quality scans only at the second timepoint were included in paper 3. For these reasons, sample size of the preterm/VLBW group differs between paper 2 (n=37) and paper 3 (n=41).

Term-born group born in 2000s

Term-born control participants from the Trondheim area born between 2001 and 2007 were recruited from the national MoBa study, coordinated by the Norwegian Institute of Public Health (Magnus et al., 2016; Magnus et al., 2006). Inclusion criteria for term-born participants were 4 to 11 years of age, participating in the MoBa study, not a twin, the oldest sibling if multiple children were born in the same year, and having responded to the MoBa follow-up questionnaire at age 3. Exclusion criteria were current psychiatric treatment, use of psychoactive drugs known to affect central nervous system functioning, birth weight below 2500 grams, and/or MRI contraindications. Invitation letters were sent to 643 MoBa participants, of whom 203 responded, and 143 met for assessment. Two MoBa participants who were born at 36 weeks of gestation were included in the volumetric portion of paper 2 (and not the TRACULA portion) but were removed in paper 3. Different researchers conducted MRI quality control for paper 2 and paper 3 and thus determined which subjects could be included based on image quality; I collaborated on this for the TRACULA portion of paper 2 and all of paper 3. Moreover, several participants with high-quality scans only at the second timepoint were included in paper 3. For these reasons, sample size of the MoBa group differs between paper 2 (n=103) and paper 3 (n=128).

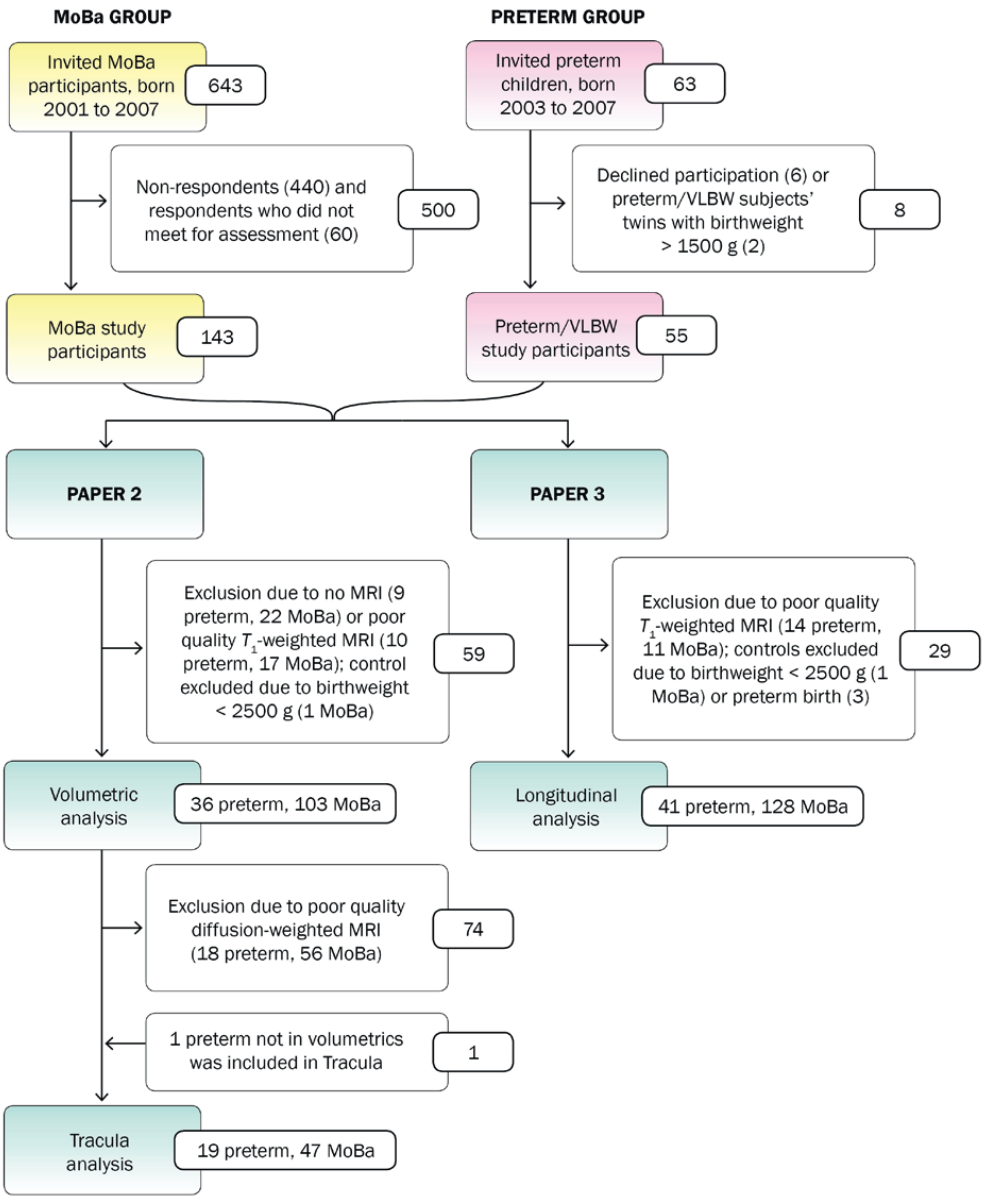

Figure 3. Flowchart of participant inclusion, papers 2 and 3.

Non-participation

For the cohorts born in the 1980s, participants and non-participants did not show significant differences at birth in terms of birthweight, gestational age, maternal age, or education. For the cohorts born in the 2000s, some of those invited reported lack of motivation or time as reasons for not participating. Some participants underwent cognitive assessment but declined to participate in neuroimaging.

Cognitive assessments

IQ (papers 2 and 3)

Age-appropriate IQ assessments were administered for the study, and full-scale IQ Index scores were used for analysis. In the VLBW group, children ≥ 6 years were assessed with Wechsler Intelligence Scale for Children, fourth edition (WISC- IV) (Wechsler, 2003). VLBW children < 6 years of age were assessed with the complete version of the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III) (Wechsler, 2002). Term-born children ≥ 6.5 years of age were assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and those < 6.5 years of age completed a short form of the WPPSI-III (Wechsler, 2002), including the vocabulary, similarities, block design, and matrices subtests. Since most participants were tested twice, scores from their first cognitive assessment were used here to avoid practice effects, except in cases where the first timepoint scores were not valid or not available.

Visual-motor integration (paper 1)

Visual-motor integration was assessed with the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) and supplemental tests of visual perception and motor coordination (Beery, 2004). VMI is a widely used standardized test that requires both motor and perceptual skills. In the copying test, the participant is instructed to copy 30 geometric designs in increasing order of difficulty without a time limit; scores are based on accuracy and quality standards. The visual perception supplementary test requires the participant to match visual shapes within a 3-minute time limit; total number of correctly matched designs is the raw score. The motor coordination supplemental test requires the participant to trace the designs with a pencil without leaving the double-lined paths, within 5 minutes. Thirty points is the maximum raw score for each of the three tests.

Executive function (paper 3)

NEPSY Visual Attention

The Visual Attention subtest from the Developmental NEuroPSYchological Assessment, Norwegian version (NEPSY) (Korkman M, 2002), assesses a child's ability to focus selectively on and maintain attention to visual targets by searching a page for specific images (cats and faces, respectively) and ignore distractors in a timed scenario. The total score is the sum of face and cat test subscores, with a high score reflecting better visual attention.

NEPSY Statue

The NEPSY Statue subtest is designed to assess motor control and inhibition by asking the child to maintain a body position for 75 seconds and ignore distracting sounds that they are not informed about before the test starts. Points are awarded per 5-second interval: two points for full response inhibition, one point for one inappropriate response, and zero points for more than one inappropriate response (Hermansen et al., 2016). A high score reflects better response inhibition.

Spatial Span

The Spatial Span subtest of the Wechsler Memory Scale, third edition (WMS-III) (Wechsler, 1997) is designed to evaluate visual working memory. The examiner points to blue blocks on a white board and asks the participant to point to the blocks in the same order, with increasing difficulty. Later, the participant is instructed to point in reverse order, also with increasing difficulty. For this study, we used the total outcome score of correctly replicated items.

Structural MRI

In this thesis, we used neuroimaging to study the characteristics and development of brain anatomy. We analyzed structural MRI data of both gray and white matter, as described in this section. MRI equipment and acquisition parameters are detailed in the methods section of each publication.

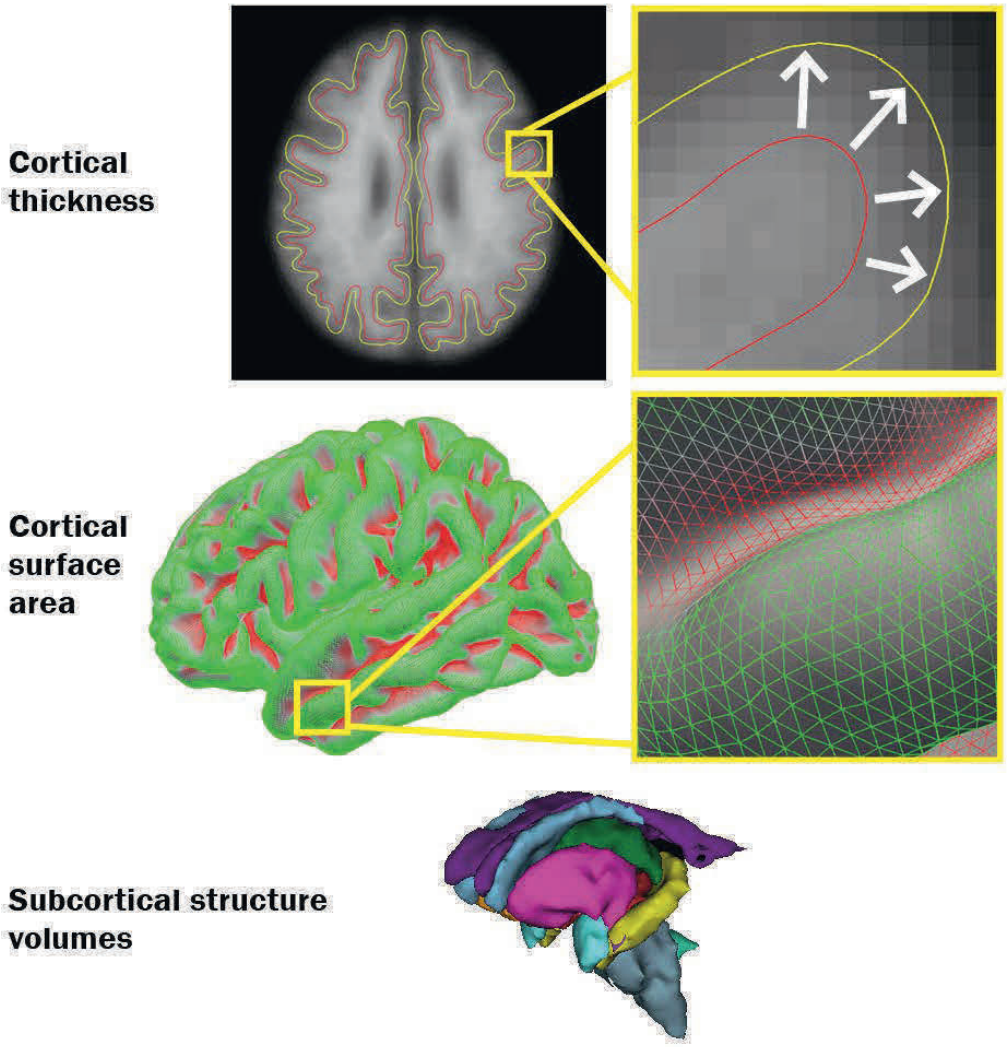

Figure 4. Illustration of the three types of morphometry analyses included in this thesis: cortical thickness, cortical surface area, and subcortical structure volumes. Thickness of the cortex (top row) is measured in millimeters between the boundary of gray and white matter (red curve) and the outer pial surface (yellow curve). Surface area of the cortex (middle row) is measured in square millimeters by creating a triangulated mesh between vertices on the surface, displayed here with red mesh indicating a sulcus and green indicating a gyrus. Volume of each subcortical structure (e.g., hippocampus, thalamus) is calculated in terms of cubic millimeters (bottom row).

Morphometric MRI

Measuring an object's shape and size is also referred to as *morphometry*. For this thesis, we focused on three measurements: cortical thickness, cortical surface area, and volume of subcortical structures, as illustrated in **Figure 4**.

FreeSurfer

Cortical reconstruction and subcortical volumetric segmentation were performed with the freely available FreeSurfer image analysis suite (Dale and Sereno, 1993), version 5.1.0 (paper 1) and 5.3.0 (papers 2 and 3) (http://surfer.nmr.mgh.harvard.edu). Cortical thickness and surface area were estimated as described by Fischl and Dale (2000) and Winkler et al. (2017). The cortical surface for each individual was automatically parcellated using defined gyri and sulci as landmarks, and the surface was divided into 34 anatomical regions for each brain hemisphere defined in FreeSurfer (**Figure 5**) (Fischl et al., 2004b; Desikan et al., 2006). Analysis of subcortical brain structures (papers 2 and 3) was based on the automated segmentation and labeling procedure in FreeSurfer (Fischl et al., 2002; Fischl et al., 2004a). Subcortical structures of principal interest in this thesis were amygdala, caudate nucleus, corpus callosum, globus pallidus, hippocampus, nucleus accumbens, putamen, and thalamus. Longitudinal analysis (paper 3) used FreeSurfer's longitudinal stream for robust image registration (Reuter et al., 2010) and analysis within and across subjects and across timepoints (Reuter et al., 2012).

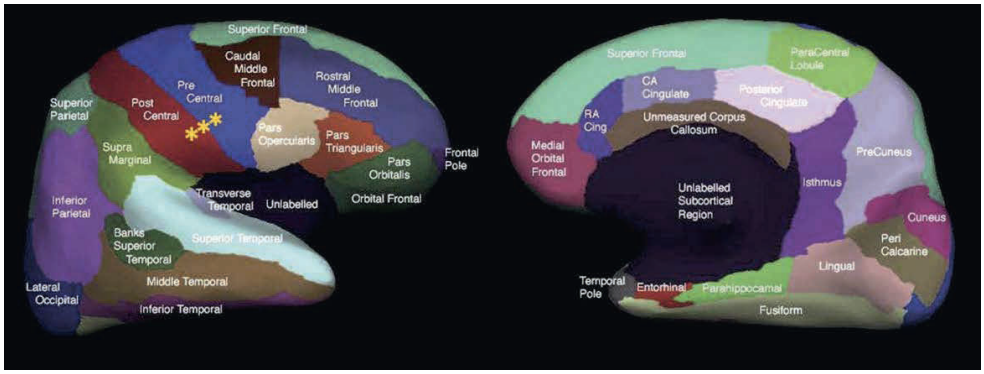

Figure 5. Cortical parcellation map based on the automated labeling system in the Desikan-Kiliany Atlas (Desikan et al., 2006), reproduced here with permission.

Mass univariate analyses were carried out with a model fitted at each of the 163,842 vertices per cerebral hemisphere to evaluate comparisons of interest (e.g., group differences and interaction analyses) to generate effect size and *p*-maps.

Smoothing of MRI data is important and widely used in neuroimaging because it increases signal-to-noise ratio, and it has recently been shown that it is necessary in order to preserve surface area when interpolating from native to atlas space (Winkler et al., 2017). Our research group uses 30mm smoothing to balance the signal-to-noise ratio with stability in the location and extent of brain regions showing statistical significance.

The technical details of the FreeSurfer image processing procedures have been described in prior publications (Dale and Sereno, 1993; Dale et al., 1999; Fischl et al., 1999a; Fischl et al., 1999b; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 2004b; Segonne et al., 2004; Desikan et al., 2006; Han et al., 2006; Jovicich et al., 2006; Destrieux et al., 2010; Reuter et al., 2010; Reuter et al., 2012).

Intracranial volumes

In paper 2, subcortical volumes were controlled for estimated total intracranial volume (eTIV) as computed by FreeSurfer (Buckner et al., 2004). In paper 3, we used a method described by Hansen and Brezova et al. (2015) to measure intracranial volume (ICV). Briefly, ICV was estimated with an automated reverse brain mask method using the “new segment” approach of the SPM8 toolbox (Statistical Parametric Mapping, release 5236, Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm) inside the cranium, including the brain, meninges, and cerebrospinal fluid.

White matter imaging

Paper 1

DTI analysis was performed with the FMRIB software library (FSL, Oxford Centre for Functional MRI of the Brain, Oxford, UK; www.fmrib.ox.ac.uk/fsl). FMRIB’s Diffusion Toolbox was used to fit a diffusion tensor model to the raw diffusion data in each voxel

(Basser and Pierpaoli, 1996) and create voxelwise maps of the eigenvalues (λ_1, λ_2, and λ_3), FA, and MD for both the VLBW and control groups. FSL's Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) was used for voxel-based analysis of the DTI data. Randomise was used to study the relationship between the skeletonized FA, MD, and eigenvalues and scores on the three VMI tests. Anatomical locations were identified using white matter atlases (Hua et al., 2008; Mori, 2005; Oishi, 2011; Wakana et al., 2007).

Paper 2

TRACULA (TRActs Constrained by UnderLying Anatomy), as implemented in FreeSurfer 5.3.0, was used for dMRI analysis and tractography (Yendiki et al., 2011). Briefly, TRACULA applies probabilistic tractography to diffusion data using an anatomical atlas of white matter tracts as well as the subcortical segmentation labels from FreeSurfer (Fischl et al., 2002, 2004a). FA, MD, radial diffusivity (RD), and axial diffusivity (AD) were assessed in the 18 white matter pathways reconstructed by TRACULA bilaterally (**Figure 6**): anterior

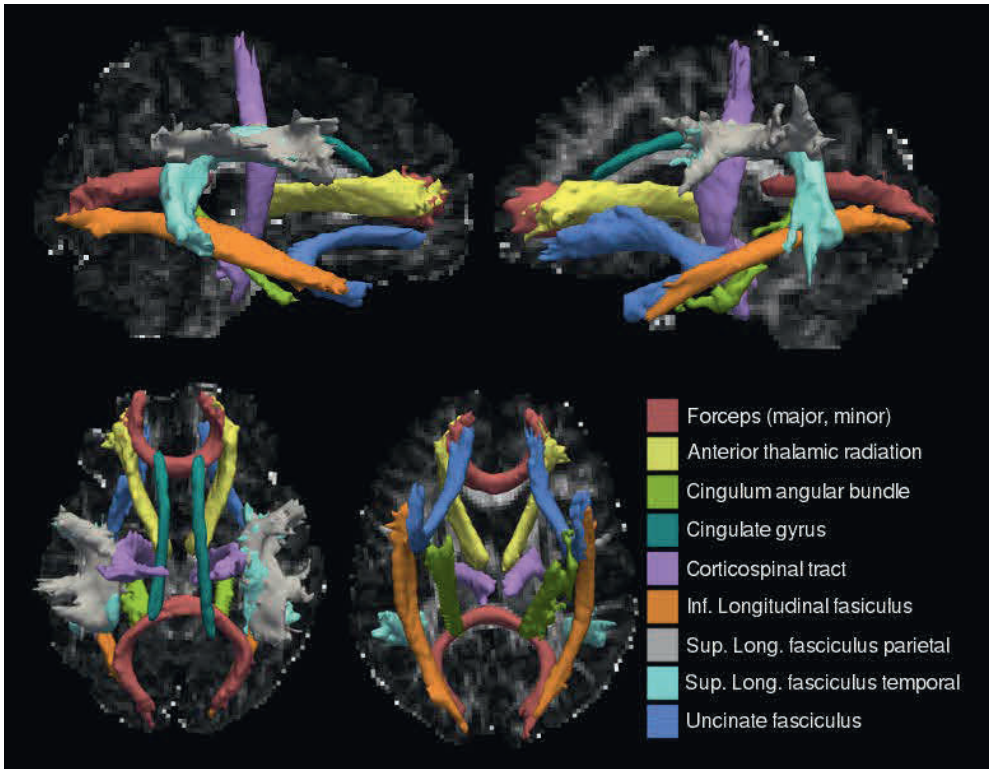

Figure 6. Probabilistic reconstruction of 18 white matter tracts generated by TRACULA, illustrated here in a term-born participant. Figure from Sølsnes and Sripada et al., 2016.

thalamic radiation (ATR), cingulum – angular (infracallosal) bundle (CAB), cingulum – cingulate gyrus, (supracallosal) bundle (CCG), corticospinal tract (CST), corpus callosum forceps major, corpus callosum forceps minor, inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus – parietal bundle (SLFP), superior longitudinal fasciculus – temporal bundle (SLFT, also called arcuate fasciculus), and uncinate fasciculus (UNC).

We conducted tract endpoint cortical thickness analysis by projecting the endpoints of the 18 tracts onto the cortical surface in the participants' native space. Cortical endpoint regions of interest were generated by mapping the probability distribution of each tract's cortical endpoint(s), from its native diffusion-weighted imaging (DWI) space to the space of the same participant's T_1-weighted image.

We also conducted tractography pointwise analysis by calculating the expected value of FA, MD, RD, or AD as a function of position at each cross-section along each white matter pathway in each participant's native space.

Quality control

Paper 1

The T_1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) images were reviewed for image quality, and low quality images were excluded. The quality of the FreeSurfer image processing was reviewed by image analyzers blinded to group adherence, checking the quality of the cortical reconstruction and applying minimal manual editing in a few cases.

Paper 2

Each MPRAGE series and the diffusion-weighted MRI (dMRI) data were visually inspected. Only scans with no or minimal movement artifacts were included. Calculation of head motion during dMRI was done as a part of the TRACULA quality control processing (Yendiki et al., 2014).

Paper 3

Each MPRAGE series was visually inspected using FreeSurfer's tkregister2 tool and Aeskulap Viewer (http://aeskulap.nongnu.org) to identify artifacts and evaluate Talairach alignment. Only scans with no or minimal movement artifacts were included. The FreeSurfer package QA Tools was run on all participants for visual inspection of segmentation.

Statistical analysis

Statistical analysis of morphometry data was performed within the Matlab software suite, version 2011b (papers 1 and 2) and Matlab 2015b (paper 3) (The MathWorks, Inc., Natick, Massachusetts, US). IBM SPSS version 21 (papers 1 and 2) and version 24 (paper 3) (Chicago, USA) was used for analysis of group differences in demographic, cognitive, and cross-sectional volumetric data, as well as correlational analyses with subcortical volumes.

Cross-sectional analysis

Paper 1

To investigate the relationship between visual-motor scores and cortical morphometry, a general linear model was fitted at each vertex, with cortical surface area or cortical thickness as dependent variable, and adjusted for sex and age at MRI, with one of the VMI tests (copying, motor, and visual) as continuous predictor. Group differences in age at exam, socioeconomic status, and maternal age at childbirth were investigated. A general linear model with age at MRI, sex, and socioeconomic status as covariates was used for analysis of the three VMI tests.

Paper 2

General linear models were fitted for group comparisons of subcortical brain structure volumes and dMRI data, controlled for age at scan, sex, and IQ; subcortical volume analyses were additionally controlled for eTIV. Partial correlation tests, controlled for age at scan and sex, were used to investigate the relationships between morphometry and dMRI and IQ and perinatal data. Tests for group × age interaction effects were performed for all subcortical structures and for FA, MD, RD, and AD in the white matter tracts. Pointwise analysis was used to locate segments along each tract showing group differences in diffusion parameters.

Paper 3

General linear models were fitted for cross-sectional cortical thickness and surface area analyses, controlled for age at scan and sex, and for subcortical brain structure volumes, controlled for age at scan, sex, and ICV. General linear models were also fitted to assess relationships between cortical surface area or thickness with IQ and the three executive function scores, between and within groups, at each timepoint. Differences in demographic and clinical variables were assessed, as well as partial correlation tests, controlled for age at scan, sex, and ICV, to investigate the relationships between morphometry and cognitive and perinatal data. Raw cognitive test scores were adjusted for age.

Longitudinal analysis (paper 3)

For longitudinal neuroimaging analysis, linear mixed effects models are useful to adjust for variation in conditions between timepoints for each study participant, such as non-uniform time intervals and including subjects who only have data from one timepoint, which can improve the statistical power of the overall analysis (Bernal-Rusiel et al., 2013b). Longitudinal analyses of changes in cortical morphometry from timepoint 1 to 2 were adapted from the linear mixed effects module in FreeSurfer 5.3.0 (Bernal-Rusiel et al., 2013a). A linear mixed effects model was fitted in each location (vertex) across the reconstructed cortical surface, with cortical area or cortical thickness as the dependent variable; intercept, time from baseline, age at baseline, group, sex, and interaction (group × time) as independent variables; and intercept as random factor. Contrast vectors were set in order to test for an interaction effect between group and time and for each of the three executive function tests and IQ. Effects of time were assessed within each group for each of the cognitive scores.

Correction for multiple comparisons

Neuroimaging analysis involves thousands of statistical tests, and the risk for false positives and non-reproducible results can be high if correction for multiple comparisons is not taken into account (Lindquist and Mejia, 2015). For all morphometric data, *p*-maps were thresholded to yield an expected false discovery rate (FDR) of 5%, which was applied co-jointly across the hemispheres to correct for multiple comparisons. Holm–Bonferroni step-down (Holm, 1979) was used to correct for multiple comparisons for tests of group difference and correlations in subcortical volumes (papers 2 and 3) and diffusion data (paper 2). For

pointwise analyses in paper 2, we chose to report findings only if they showed significant group differences ($p < 0.05$) over a contiguous segment of length greater than 2 cm along a given pathway, in order to control the false positive rate.

Figures

Cortical reconstruction images were exported from the software tools TkSurfer and FreeView. For paper 2, TRACULA white matter tract images were acquired in FreeView, and subcortical structures were visualized in 3D Slicer (www.slicer.org). Gimp and Adobe InDesign Creative Cloud 2017 were used for layout of figures and flowcharts.

Clinical data

Paper 1 is part of a long-term ongoing follow-up study with rich clinical data; however, only birth weight, gestational age, maternal age at birth, days spent in NICU, days on ventilator, and days before birth weight regained were used as clinical variables here. Birth weight, gestational age, Apgar scores at 1 and 5 minutes, number of days in the NICU, and number of neonatal days on mechanical ventilator were the clinical variables in the VLBW group used in papers 2 and 3. For paper 3, birth weight and gestational age for MoBa participants were retrieved from medical registry data (not available for two participants, for whom parent-reported birth weight was used).

Socioeconomic status

Hollingshead's (1957) two factor index of social position based on education and occupation of one parent or the mean index of both parents was used to calculate socioeconomic status.

Ethics

Written, informed consent was obtained from the participating young adults for paper 1, and from parents/guardians of participants for papers 2 and 3. The Regional Committee for Medical Research Ethics approved the study protocols (project number: 4.2005.2605 for paper 1; project number 2010/2359 for papers 2 and 3). For the long-term follow-up in paper 1, the Data Inspectorate assigned a license for keeping a data register with personal information; families were referred for follow-up assessment/treatment if indicated by test results.

Results

Paper 1

Among young adults born in the 1980s, the preterm/VLBW group scored significantly worse on the copying and motor coordination tests compared to term-born peers. Visual perception scores showed positive relationships with cortical thickness in the preterm group, primarily in the lateral occipito-temporo-parietal junction, the superior temporal gyrus, insula, and superior parietal regions (yellow to orange area in **Figure 7**). Lower VMI scores also were related to reduced surface area in the superior temporal gyrus, insula, and medial occipital lobe in conjunction with the posterior ventral temporal lobe (yellow area in **Figure 7**). In the preterm group, visual-motor performance correlated positively with fractional anisotropy especially in the corpus callosum, inferior fronto-occipital fasciculus bilaterally, and anterior

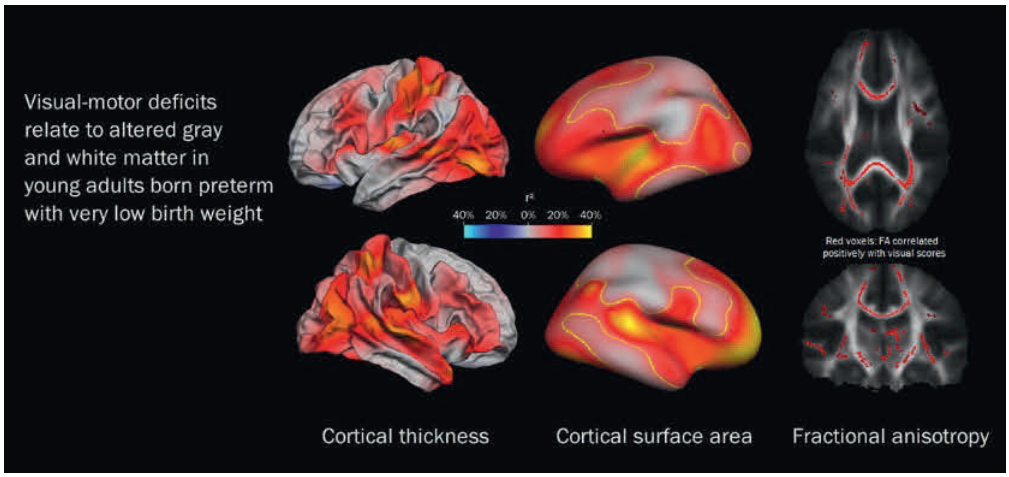

Figure 7. *NeuroImage* graphical abstract for paper 1.

thalamic radiation bilaterally, driven primarily by an increase in radial diffusivity. Our results indicate that visual-motor integration problems persist into adulthood for preterm/VLBW individuals, and visual–motor deficits appear related to reduced surface area of motor and visual cortices and disturbed connectivity in long association tracts containing visual and motor information.

Paper 2

Among children born in the 2000s, the preterm/VLBW group showed smaller volumes of thalamus, globus pallidus, corpus callosum, cerebral white matter, ventral diencephalon, and brain stem, with a larger ventricular system, after controlling for age, sex, IQ, and eTIV. Group differences in FA and diffusivity in the 18 white matter tracts were not significant at the whole-tract level after correction for multiple comparisons, though pointwise analysis found shorter segments affected in forceps minor and left superior longitudinal fasciculus-temporal bundle. Gestational age and birth weight in the VLBW group were generally not associated with subcortical volumes, and IQ did not correlate with either subcortical volumes or dMRI measures in the VLBW group. We also explored cortical thickness in projected endpoints of white matter tracts and did not find significant group differences.

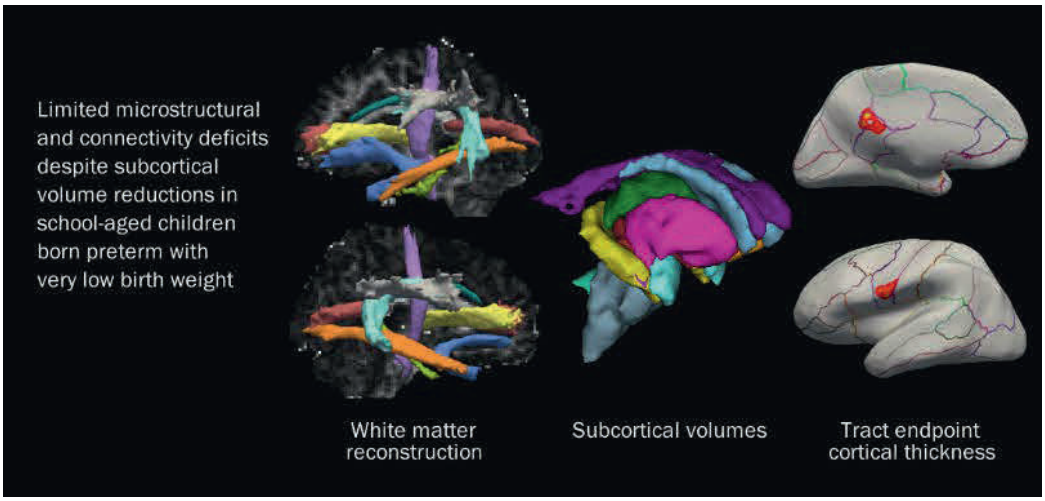

Figure 8. *NeuroImage* graphical abstract for paper 2.

Paper 3

No longitudinal group × time effects in cortical thickness, surface area, or subcortical volumes were seen, indicating similar brain growth trajectories in the preterm and term-born study groups in middle childhood among children born in the 2000s. Reduced cortical surface area in multiple cortical regions and thicker cortex occipitally and frontally and thinner in lateral parietal and posterior temporal areas persisted over time among preterm/VLBW children. Corpus callosum, left amygdala, right globus pallidus, left hippocampus, and bilateral thalamus were smaller in the VLBW group at both timepoints. Higher IQ scores in the VLBW group were associated with greater surface area in left parieto-occipital and inferior temporal regions in cross-sectional analyses, suggesting an altered structure-function relationship. VLBW children had on average IQ scores one standard deviation below term-born peers, had significantly different scores on NEPSY Visual Attention and WMS-III Spatial Span, and did not improve with time in visual attention as their term-born peers did. Executive function scores did not show differential associations with morphometry between groups cross-sectionally or longitudinally. The absence of group × time effects in conjunction with evidence of altered cognitive networks in preterm-born children may indicate that their brain development is significantly altered already by middle childhood, but thereafter follows a similar trajectory to term-born peers, giving support to the “different, not delayed” hypothesis of preterm brain development.

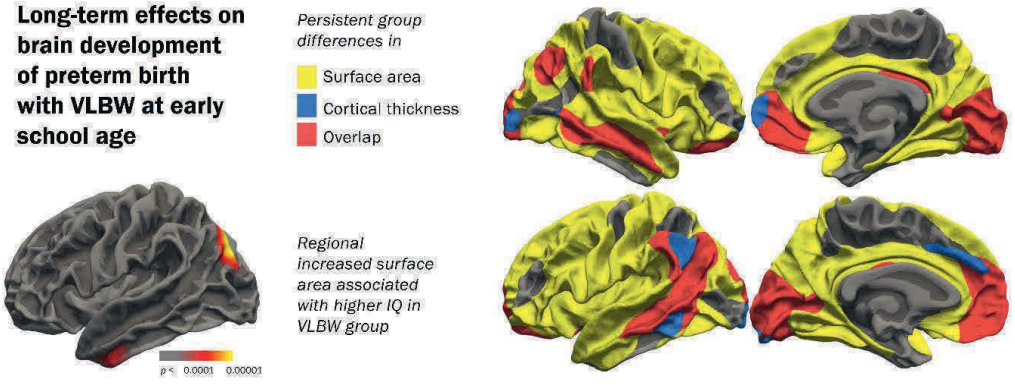

Figure 9. Graphical abstract submitted for paper 3.

Discussion

Summary

The studies in this PhD thesis identified long-term alterations in brain structure and function following preterm birth with VLBW, using structural MRI of gray and white matter and neuropsychological assessment. In a group of young adults born preterm with VLBW between 1986 and 1988, worse performance on visual-motor integration tasks was associated with reduced surface area and thickness in cortical regions, as well as reduced FA in corpus callosum and intrahemispheric white matter tracts. Longitudinal findings from cohorts born between 2001 and 2007 did not indicate group × time differences in cortical surface area, thickness, or subcortical structure development, indicating similar growth trajectories in middle childhood, although widespread reduced cortical surface area and altered cortical thickness in the preterm/VLBW group persisted over time. IQ scores were approximately one standard deviation lower in the preterm/VLBW group and showed a positive association to surface area in parieto-occipital and inferior temporal regions, while executive function did not show interactions with brain morphometry.

How this thesis builds upon previous research

This thesis builds on years of research in our group combining MRI and long-term follow-up of neurocognitive outcomes following preterm birth/VLBW (Hanch-Hansen et al., 1989; Skranes et al., 1992; Skranes et al., 1993; Skranes et al., 1997). Paper 1 is a multimodal study of the relationship between sensory-motor performance and gray and white matter structure at the young adulthood assessment in a three-decade long-term follow-up cohort study. Paper 2

broke new ground for our research group by implementing the novel diffusion MRI methods in the FreeSurfer software tool TRACULA – namely measuring cortical thickness in white matter tract endpoints, and pointwise analysis along reconstructed tracts. Paper 3 was the first study in our group to assess longitudinal changes in cohorts born in the 2000s, as well as the first study in our group using longitudinal data from the MoBa study.

Neuroplasticity in the preterm/VLBW population is of key importance, as it may indicate the neuroprotective potential for early life interventions. Longitudinal follow-up and cohort study design has therefore been central to the research goals of our group. Between ages 15 and 20, the cohort born in the 1980s did not demonstrate divergent trajectories compared to term-born peers, in terms of either cortical thickness or surface area (Rimol et al., 2016). Paper 3 expands upon that conclusion by not finding evidence for catch-up structural growth in the 2000s cohort at early school age in cortical thickness, surface area, or subcortical gray matter volumes.

Our group has been particularly interested in the cascading effects of both focal and diffuse white matter injury on neurocognitive function in the years following preterm birth/VLBW. White matter findings from paper 2 show that the more severe white matter abnormalities seen in the older cohort (Eikenes et al., 2011; Skranes et al., 2007) were not as prominent in the cohort born in the 2000s. However, direct comparison between the two cohorts in this PhD thesis is difficult given differences in data acquisition, age at scan, and software used for analysis. Continued follow-up of children born after the turn of the millennium will provide a stronger basis for comparison.

Altered structure-function relationships

Beyond identifying group differences in size, area, and thickness, this thesis also identified structure-function relationships that appear to be altered in the preterm brain.

In paper 1, VMI scores explained 35 to 40% of surface area reductions in widespread regions and, to a lesser extent and only for visual test scores, group differences in cortical thickness. All three VMI scores correlated positively with FA in corpus callosum, long range association tracts, and optic and thalamic radiation, and correlated negatively with MD

though less widespread, driven primarily by radial diffusivity. None of the associations in the preterm group were significant in the term-born group.

In paper 3, no significant group × score interactions for surface area or cortical thickness were found for any of the three executive functions, longitudinally or cross-sectionally. In the term-born group, surface area change in three regions correlated with improvements in executive function scores over time, and these correlations were not seen in the preterm/VLBW group. However, higher IQ score in the VLBW group was associated with greater surface area at the border of the left parietal and occipital lobes and to a lesser extent in the left inferior temporal cortex. Moreover, the parieto-occipital regions where greater surface area was associated with higher IQ in the preterm group also showed significantly reduced surface area compared to the term-born group, which could indicate a high level of sensitivity in the preterm group to perinatal insult, although the timing and cause-and-effect is difficult to discern.

Corpus callosum, particularly in the middle and posterior segments, was implicated in a number of findings in the VLBW group. In paper 1, VMI copying, motor, and visual perception scores were positively correlated with FA in the corpus callosum, in line with findings of worse visual acuity associated with lower FA in splenium and midbody of the corpus callosum in the adolescent VLBW cohort (Lindqvist et al., 2011). In papers 2 and 3, corpus callosum volume was significantly reduced by an average of approximately 14% compared to the MoBa group, and volume of the posterior subsegment of corpus callosum correlated positively with improved clinical variables in the preterm group. Bjuland et al. (2014) also found reduced volume of posterior corpus callosum in the 1980s cohort in young adulthood. Damage to corpus callosum has been reported to have long-term effects on language and cognitive processing (Allin et al., 2004). Kapellou et al. (2006) suggest that executive function deficits may relate more to white matter damage than primary cortical injury and, in fact, suggest that reduced growth of the cerebral cortex derives not from having fewer cortical neurons, but from reduced connectivity, where the corpus callosum plays a key role.

Considerations for using structural MRI to study preterm birth/very low birth weight

This thesis combined T_1-weighted MPRAGE imaging and diffusion-weighted imaging to paint a comprehensive picture of the alterations seen in the preterm/VLBW population. MRI is a complex method that requires validated data acquisition protocols, image analysis and quality control, and not least the cooperation (and limited head movement) of study participants.

Diffusion-weighted imaging is considered more sensitive and can show abnormalities earlier than cranial ultrasonography or conventional MRI, as early as the first 24 to 48 hours after birth, making it an important clinical tool (Volpe, 2008). This thesis employed diffusion-weighted imaging in long-term follow-up, and in papers 1 and 2, diffusion findings provided an important complement to the volumetric and cortical analyses. In paper 1, visual-motor test scores correlated positively with FA and negatively with MD in corpus callosum and association tracts in the preterm/VLBW group, while no significant correlations were found in the control group. In paper 2, group differences in diffusion measures in the 18 tracts were not significant (after Holm-Bonferroni correction for multiple comparisons), despite significantly smaller subcortical gray matter volume in the preterm/VLBW group.
At the same time, it is important to not overstep our current ability to interpret the mechanisms behind alterations in diffusion measures. It is not possible, for example, to equate a diffusion measure, such as FA or MD, to a specific neurobiological quality, such as thinner axons, abnormal axonal packing, or more myelination (Beaulieu, 2014), and cautious interpretation of axial and radial diffusivity is advised especially in clinical populations (Wheeler-Kingshott and Cercignani, 2009). However, group differences and longitudinal changes in the same individual can provide insight into deviations from typical development (Beaulieu, 2014).

For volumetric analyses (papers 2 and 3), we chose to correct for ICV to account for individual variability in skull size. A larger head will, for example, most likely have a larger hippocampus, but what interested us was whether the hippocampus was proportionately larger in one group compared to the other. Children and adolescents born preterm typically have reduced cerebral brain volume compared to term-born peers (Kesler et al., 2004; Nosarti

et al., 2002; Peterson et al., 2000). Consistent with this, in our 2000s cohort, mean ICV was 1416 cm^3 in the preterm/VLBW group compared to 1502 cm^3 in the term-born group ($p=0.02$). Some research has shown that, by term-equivalent age, preterm-born neonates have approximately the same cerebral tissue volume as neonates born at term, suggesting that reduced volume may not be caused by prematurity itself, but rather that postnatal events and risk factors, such as the need for prolonged supplementary oxygen, may exert an environmental influence on brain growth (Boardman et al., 2007).

For the longitudinal morphometry analysis, we implemented linear mixed effects models and mass univariate analysis. Advantages of this approach over other spatiotemporal statistical models for neuroimaging time series data include the ability to manage unequal time intervals between scans, incorporate participants with only one scan to improve the overall model, and explicitly model the effect of time (Bernal-Rusiel et al., 2013a).

Neuromarkers and predictive modeling

Whether subtle changes in gray and white matter have a clinical significance is difficult to assess (Mathur et al., 2010). Research is still in the early phases of understanding the links between abnormalities visible on early MRI and later neurocognitive outcomes. Both gray and white matter neuroimaging have been used to identify early biomarkers associated with cognitive deficits that may emerge months or years later (de Vries et al., 2011; Woodward et al., 2006). MRI, combined with cranial ultrasound, has been shown to have predictive value for motor outcomes in high-risk neonates (de Vries et al., 2011).

In a recent systematic review, Parikh (2016) identified 47 predictive neuroimaging studies in the very preterm population, and found that a majority reported novel neuromarkers for later impairment, with corpus callosum, cerebellum, centrum semiovale, sensorimotor cortex, subcortical nuclei, and posterior limb of the internal capsule being the most frequently cited structures. Parikh underscored the need to develop more powerful tools, including volumetric MRI, dMRI, magnetic resonance spectroscopy, and resting-state functional connectivity MRI, to be more sensitive to subtle physiological changes.

In another systematic review of follow-up studies from 18 months to 9 years corrected age, in children born very preterm (≤ 32 weeks) or with birthweight ≤ 1500 grams, white matter abnormalities predicted cerebral palsy and motor function with moderate sensitivity and specificity; however the predictive value for other neurocognitive and behavioral outcomes was limited (Van't Hooft et al., 2015). Howe et al. (2016) recently used four predictive factors at and before 2 years of age (namely medical complications at birth, maternal education, early motor assessments, and cognitive assessments) to predict 50% of full-scale intelligence and 30% of both motor performance and adaptive behavior at the age of 5, in children born ≤ 32 weeks' gestation with VLBW. Combinations of MRI data and clinical assessment are likely more effective than either alone.

Neuropsychological assessment and considerations

Overall, neurocognitive outcomes for children born preterm/VLBW have improved over the last three decades. In our case, this is demonstrated by the improvement in IQ scores from the cohort in paper 1 (two standard deviations below term-born peers) and the cohort in papers 2 and 3 (one standard deviation below term-born peers). One meta-analysis indicated that preterm delivery is associated with an almost 12 point drop in IQ score, while another meta-analysis estimated that individuals born with low birth weight (< 2500 grams) had an average of 7.63 IQ points lower than those born with birth weight ≥ 2500 grams. Whether IQ scores are improving in this population over time is challenging to determine (Kerr-Wilson et al., 2012), as survival rates for the most immature and consequently the highest risk infants have improved and influence the characteristics of the group as a whole.

Several considerations related to neuropsychological assessment for the studies in this thesis should be mentioned, particularly for the longitudinal analyses in paper 3.

This thesis used standardized neuropsychological assessments to estimate cognitive function in multiple domains at different ages. In papers 2 and 3, due to the age span of the participants and alignment with multi-site data collection in a larger study, it was not possible to use a single IQ assessment tool for all participants. In paper 3, participants took the same NEPSY and WMS Spatial Span tests twice, with testing timepoints an average of 14 to 16

months apart, which may have resulted in practice effects. Estimates of learning effects on these executive function assessments in pediatric populations is very limited. The WMS Spatial Span has been shown to have insignificant learning effects in adults (Lo et al., 2012). Both groups were administered the same executive function tests, and while it is difficult to speculate whether performance in the preterm group was affected by practice differently from the term-born group, it is unlikely that practice effects compensate for baseline group differences (Goldberg et al., 2007). The short interval between the two timepoints may also have influenced our lack of interaction findings between change in executive function scores and cortical and subcortical growth.

Researchers and clinicians are eager to determine the best tools to assess executive function in young children (Mahone and Schneider, 2012). For this, paper 3 used the NEPSY Visual Attention and Statue subtests and the WMS Spatial Span. The NEPSY has been used in various clinical groups, including children with spina bifida (Riddle et al., 2005) and children exposed to gestational diabetes mellitus (Nomura et al., 2012). However, some tests are considered more clinically meaningful than others, and results on the NEPSY Visual Attention subtest for example may not be seen as useful for clinicians (Mahone and Schneider, 2012). The NEPSY Statue subtest is typically administered to children three to six years old but was used here with older children as part of the longitudinal design and to increase standardization across the entire age span of participants. In a study of preschoolers, the NEPSY Statue subtest was the only neuropsychological assessment that showed significant predictive power of mother-reported hyperactivity and behavioral problems, with high specificity and low sensitivity (Youngwirth et al., 2007).

In paper 3, study participants were administered a battery of tests that included age-appropriate IQ, NEPSY, and Spatial Span – the scores which were presented in the paper – as well as the Rey Complex Figure Test and Recognition Trial, Strengths and Difficulties Questionnaire, Vineland Adaptive Behavior Scales, California Verbal Learning Test, and Behavior Rating Inventory of Executive Function. However, not all test scores were available for all participants, or at both timepoints. To create the most robust dataset focusing on longitudinal change in both morphometry and neuropsychological data, we opted to analyze only the IQ, NEPSY, and Spatial Span scores due to their higher numbers of completions at both timepoints and in both groups, compared to the other tests. The data not used in this PhD

thesis can be useful for further work describing the neuropsychological profile of the cohort and for developing predictive models.

Promise and challenges of longitudinal cohort studies

Longitudinal, cohort-based study design can provide unique insights into sequences of change, stability, and prediction of events over time, as well as allowing within-individual analysis of individual change, rather than between-individual differences cross-sectionally (Farrington, 1991). However, a number of factors conspire to make longitudinal research difficult, including mortality, disease, medication use, and drop-out of participants through the years, all of which can introduce bias into the study. Moreover, methods used at a later timepoint are not necessarily compatible with those used to acquire data at earlier timepoints due to advances in technology, such as a newer MRI sequence or scanner. More generally, the effects of nature versus nurture are impossible to control for fully, so even the most carefully designed longitudinal cohort study will not be able to account for all change drivers.

For survivors of high-risk pregnancies and their families, participating in follow-up studies may offer them an opportunity to maintain a relationship to the hospital that saved their lives (Tansey et al., 2007). Achieving high retention in clinical research requires giving participants individual attention, time, and respect. Data collection for both studies in this thesis was time- and resource-intensive, requiring a team collaborating on recruitment, communication, neuropsychological assessment, and MRI scanning – all of which required thoughtful interaction with each participant and, in many cases, their families.

The second study – part of a multi-site collaboration with the University of Oslo – included participants from MoBa, a national birth cohort study which recruited pregnant Norwegian-speaking mothers between 1999 and 2008 from 50 of Norway's 52 hospitals and maternity units with more than 100 annual births (Magnus et al., 2006). A total of 114,622 children were recruited to the study – a 41% initial participation rate – and MoBa participants have voluntarily provided biological samples and responded to detailed questionnaires, starting in pregnancy. As of the cohort update in 2016, questionnaire response rate had fallen from nearly 100% at birth, to 78.5% at the 6 month follow-up, to 36.4% at the 5 year follow-up

(Magnus et al., 2016). Furthermore, MoBa is not an exactly representative sample of the Norwegian population, with self-selecting participants who may have a slightly healthier lifestyle (Nilsen et al., 2009). For example, 80.9% of MoBa participants identify as nonsmokers, compared with 74.1% in the total population. Likewise, mean birthweight among MoBa participants was 3570 grams, compared to 3528 grams in the total population. In paper 3, which excluded preterm-born and low birth weight participants, mean birthweight in the MoBa group was 3679 grams. Overall, there may be some selection bias in this neuroimaging substudy compared to the entire MoBa cohort, as well as to the general population, as a factor of both self-selection bias and drop-out over time. Nonetheless, it is rare that national cohort studies include a neuroimaging component at all, and the ability to link neuroimaging data to detailed longitudinal questionnaire data (Walhovd et al., 2016), while not a part of this thesis, is an asset of this MoBa neuroimaging substudy.

Advances in pre- and neonatal medical care

Medical treatment and outcomes for high-risk pregnancies changed significantly between the births of the two cohorts included in this PhD thesis. This included increased antenatal and postnatal steroid use, surfactant therapy, cesarean section delivery, decreased sepsis, types of assisted ventilation, and changing attitudes towards resuscitation and intensive care, which among other outcomes resulted in a striking increase in the survival of babies born before gestational week 28 by the mid-1990s (Aylward, 2014; Fanaroff et al., 2003; Hack and Fanaroff, 1999; Wilson-Costello et al., 2007).

A recent study of all 1,612,789 infants born between 1967 and 2011 in Norwegian hospitals with neonatal departments examined the reasons behind Norway's hugely increased postnatal survival rates in the last 40 years (Grytten et al., 2017). The decline of about 50% in early neonatal mortality and infant mortality was explained by four interventions: ventilators, antenatal steroids, surfactant, and "insure" (*in*tubate, *sur*factant, *e*xtubate). For infants with birthweight 1001 to 1500 grams, the proportion of early mortality fell from 50% to 10%; for infants with birthweight 1000 grams and less, the rate dropped from nearly 100% to 30% (**Figure 10**).

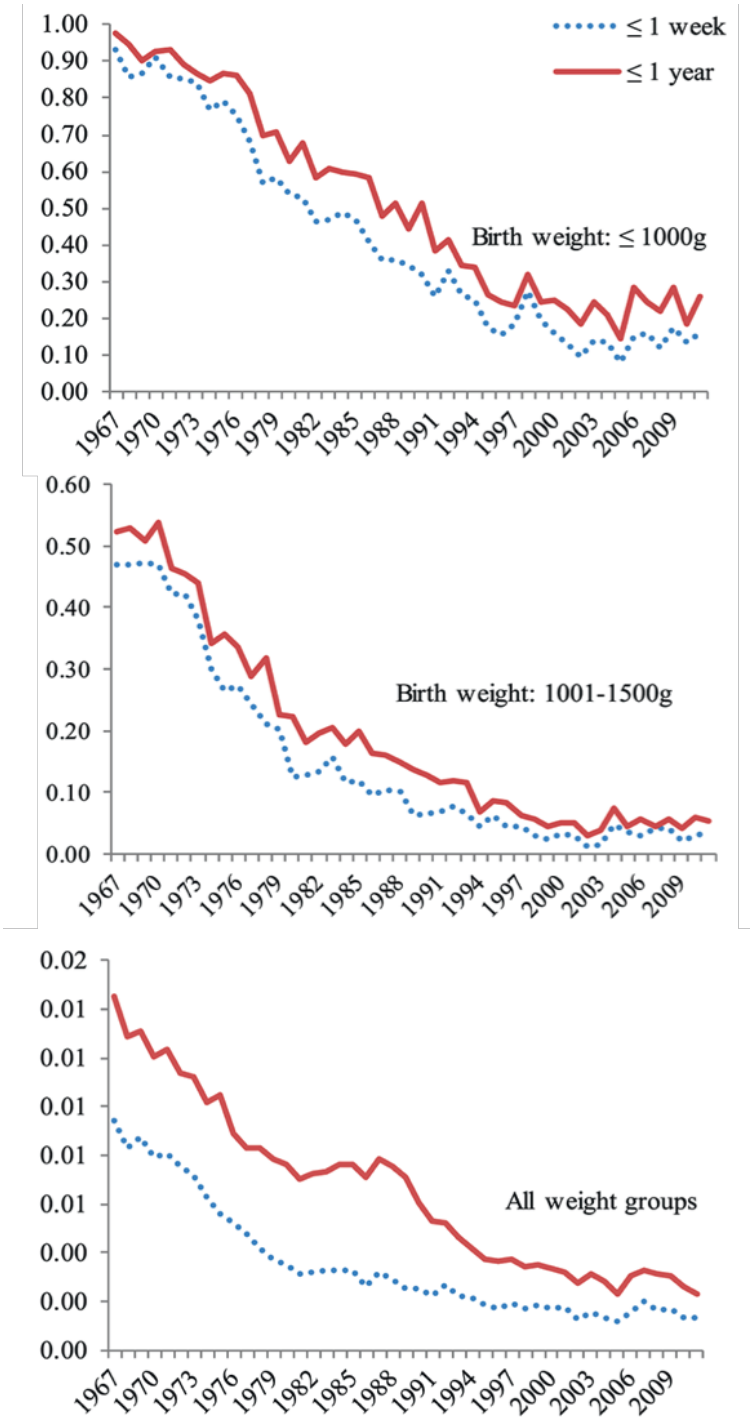

Figure 10. Proportion of infant deaths during the first week and the first year of life by year, among over 1.6 million births in Norway, 1967–2011. Data shown for birthweight ≤1000 grams, 1001-1500 grams, and all weights. Figure adapted from Grytten et al. (2017), reproduced here with permission.

The relationship between perinatal medical care and neurodevelopmental health is complex. Use of mechanical ventilator during a stay in the NICU, for example, is not necessarily correlated with outcomes later in childhood (Andrews et al., 2012). Recently, intubation for extremely preterm neonates has been increasingly replaced with less-invasive methods of ventilation, such as increased surfactant use, early continuous positive airway pressure, and nasal synchronized intermittent mandatory ventilation (Stoll et al., 2015). Postnatal corticosteroids, which expedite lung development in high-risk neonates, have also been examined for their potential effects on neurodevelopmental outcomes (Cheong et al., 2013). Several reviews of the long-term neurodevelopmental effects of postnatal steroids following preterm delivery have found links to higher risks for cerebral palsy, growth delays, and neurodevelopmental disability, and their use in clinical settings has been widely discussed (Barrington, 2001; Halliday et al., 2003; Yeh et al., 2004). Number of days spent in the neonatal intensive care unit and on a mechanical ventilator were used as clinical variables in this PhD thesis, but additional analysis on postnatal steroid use may have provided additional detail to the findings linking brain structure and functional changes to events and possible risk factors in the neonatal period.

While neonatal care has advanced tremendously, there is much ground still to cover in optimizing care for high-risk newborns. Preterm-born neonates often experience painful and stressful procedures in the NICU, such as skin-breaking procedures, use of respiratory devices, and the unpleasant odors of disinfectants, adhesive removers, and other chemicals (Carbajal et al., 2008). A study of 49 neonatal departments across France estimated that a neonate born prematurely at 28 weeks of gestation and discharged at week 40 would be exposed to odors 3448 times during their hospital stay (Kuhn et al., 2011). Exposure to stressors among preterm-born neonates in the NICU has been correlated with reduced brain size in frontal and parietal regions, reduced FA and altered connectivity in right temporal lobe (Smith et al., 2011), and altered cortical response (Frie et al., 2017). Exposure to more stressors in the neonatal period may also have long-lasting impacts on behavior (Ranger et al., 2014; Vinall et al., 2014). A recent study of 155 very preterm neonates (born at 24 to 32 weeks of gestation) reported that early pain was associated with slower thalamic growth, microstructural alterations in thalamocortical pathways, and decreased thalamic N-acetylaspartate/choline, suggesting a sensitive period in development of the somatosensory system related to lasting structural changes and cognitive and motor outcomes (Duerden et

al., 2017). Measures of early stress were not a part of this PhD thesis, but reducing pain and noxious stimuli in the NICU environment should be a consideration as new treatments are developed and brought into practice.

Pre- and post-natal medical care is still evolving. In Europe, there is still a gap in the actual implementation of evidence-based practices for infants born very preterm (Zeitlin et al., 2016). At the same time, Stoll et al. (2015) suggest that new frontiers in neonatal medicine hold promise for effective interventions, including advances in neuroimaging, genome sequencing to accelerate diagnosis, minimally invasive delivery of aerosolized surfactant, tissue engineering for injury repair, and clinical applications of growth factors and cellular therapies. Improved precision in understanding the timing of periventricular white matter injury and its influence on pre-oligodendrocyte vulnerability may also be an opportunity to develop prenatal intervention strategies to promote the survival and maturation of oligodendrocyte progenitors (Back et al., 2007). Development and implementation of new care strategies should include long-term follow-up assessment of neurodevelopmental outcomes.

Interventions after preterm birth with very low birth weight

Our research field is motivated to translate research findings into improvements for daily life for those born preterm/VLBW. Examples of interventions include home visits by educators, nurses, or other trained clinicians; parent training on developmental milestones and age-appropriate activities; physical therapy, hospital-based programs; video training; and computer-based working memory training (Pascoe et al., 2013; Spittle et al., 2015). A meta-analysis of 25 intervention studies following preterm birth found a clinically relevant improvement in cognitive outcomes following early intervention in infancy and preschool age, with no difference at school age or adulthood and only a small effect on motor development (Spittle et al., 2015).

Our group has also tested interventions, including computer-based working memory training in childhood and adolescence (Grunewaldt et al., 2013; Løhaugen et al., 2011), and the effects of melatonin in a rat model of hypoxic-ischemic neonatal injury (Berger et al., 2017).

A hope is that the findings from this PhD project can contribute to the ongoing efforts to map the causes and effects of preterm birth/VLBW to improve neuroprotective treatment options, especially for the highest risk individuals.

Limitations and generalizability

A number of specific limitations of this PhD thesis have already been described, including in the neuroimaging methods, neuropsychological assessment, limited data on pre- and perinatal experiences, selection bias, and challenges with longitudinal research. Several "big picture" limitations to the generalizability of these studies will be discussed here.

It is difficult to turn the clock back to identify specific causal and neurobiological mechanisms underlying long-term outcomes. For instance, an individual's *in utero* exposure to hypoxic insults and hypoxemia, altered endocrine and growth factor status, placental insufficiency, or infection can affect their neurodevelopmental outcomes (Rees et al., 2011), but these data are not easily acquired in human research. Neonates who experienced intrauterine growth restriction, for example, have shown not merely delayed but also discordant developmental trajectories, particularly in reduced cortical surface area and high level of sulcation compared to typical newborns, and these alterations can be predictors of neurobehavioral development (Dubois et al., 2008). Serial ultrasound during pregnancy can be used to estimate intrauterine growth restriction. This technique has been used by our research group on a cohort born at term small for gestational age (Løhaugen et al., 2013; Østgård et al., 2014; Rogne et al., 2015) but was not part of this PhD thesis. Viewing findings in light of information on which individuals experienced intrauterine growth restriction or other insults would have added precision to the timing and type of prenatal insult involved and may ultimately be necessary to translate long-term MRI findings into early interventions. In the case of altered structure-function relationships described in papers 1 and 3, it is not possible to determine whether these are specifically related to premature birth, VLBW, environmental × genetic interactions, differences in pre- and postnatal care, or other factors.

Another limitation comes in the form of the constantly changing landscape of MRI technology and analysis techniques. Advanced acquisition methods, such as high-angular

resolution diffusion imaging and diffusion spectrum imaging, are more sensitive than diffusion tensor imaging for investigating fiber orientations in areas with crossing fibers (Abhinav et al., 2014; Groeschel et al., 2014) but require longer scan times to measure more diffusion directions, which increases the risk of data loss due to movement artifacts, especially in children. Paper 2 in this thesis used innovative tools in TRACULA for analysis of diffusion-weighted data, and other automated methods for structural segmentation are continually in development. Tract-specific analysis (Pecheva et al., 2017) and spatial independent component analysis (O'Muircheartaigh and Jbabdi, 2017) may provide new options for improved segmentation of white matter tracts, especially for large datasets. Moreover, graph theory has already helped link functional and structural neuroimaging data, including among preterms (Bullmore and Sporns, 2009; Kim et al., 2014; Scheinost et al., 2017). Finally, many scans, especially in the study of children born in the 2000s, could not be used due to motion artifacts. Drop-out analysis showed that older children and those with higher IQs were more likely to have usable T_1- and diffusion-weighted MRI, as might be expected due to the need for greater self-control or motivation for lying still in the scanner; morphometry analyses included age as a covariate. The imaging methods employed in this thesis were based on the time and place of study planning and data collection, and future work will no doubt be able to shed light on the questions that these methods were not detailed enough to answer.

The generalizability of the findings presented in this PhD thesis should be approached with caution. Moreover, comparing the results of this PhD thesis to other research in the field is challenging, given the diverse neuropsychological assessments used, inconsistent inclusion criteria for gestational age (e.g., extremely preterm vs all preterm) and weight (e.g., cutoffs at 1000, 1500, or 2500 grams), and different ages evaluated. Finally, it is challenging to compare outcomes at different ages in cohorts who were born in different decades, and where standards of care vary from hospital to hospital and country to country. That means that the findings presented here may not be applicable to all children born preterm with VLBW in Norway and other high-income countries, and to an even lesser extent to neonates born in lower-income regions, who constitute the majority of preterm births globally each year.

Future directions

The effects of nature versus nurture are extremely challenging to disentangle in human neuroscience. However, several methods that were not employed in this PhD project could help unravel their shared and independent etiologies and cascading effects. Recent neuroimaging studies linked to genetic data have sought to delineate the contributions of genetic, epigenetic, and environmental influences. For example, Boardman et al. (2014) found that certain gene alleles related to neuronal migration and fatty acid synthesis were associated with white matter abnormalities, and Sparrow et al. (2016) found preterm birth to be associated with altered methylation at sites relevant for neural development in neonates born before 32 weeks of gestation. Moreover, twin and sibling studies have long been considered a gold standard in cognitive research for their unique ability to control for genetic and environmental variation. This PhD thesis did include several twins, and an interesting follow-up would be to recruit additional siblings and assess outcomes with this added level of group matching.

Sex differences in structural development and cognitive outcomes have been a topic of interest in this field. Boys have in some studies demonstrated a greater degree of neurocognitive impairments compared to girls following preterm birth/VLBW (Kapellou et al., 2006; Marlow et al., 2005). This may indicate a greater susceptibility of boys to the long-term effects of prematurity. This PhD thesis does not specifically address the topic of sex differences, and all morphometric analyses used sex as a covariate. However, further research on gender-related risk factors would be valuable.

Moreover, research in this field, including in this PhD thesis, discuss *group-level* differences and risk factors in the preterm/VLBW population; almost no focus is paid to individual development. For example, although the preterm/VLBW groups scored *on average* lower on IQ and cognitive tests, there were high performers in the preterm groups and poor performers in the term-born groups. The findings of this PhD thesis should therefore be interpreted with care. Unique *individual-level* influences in family structure, educational support, environmental exposures, and personal experiences contribute to a full picture of brain and behavior development (Fox et al., 2010; Nosarti et al., 2010; Shonkoff et al., 2012).

On a more theoretical level, another challenge for improving outcomes for children born preterm/VLBW emerges in light of the concept of "normal" development and function. To what extent can – and *should* – outcomes for this high-risk population approach the "typical" neurological, cognitive, and behavioral norms of their term-born/typical gestational weight peers? The neurocognitive outcomes explored in this thesis do not represent the full spectrum of meaningful aspects of life, and therefore likely undervalue the ways in which preterm/VLBW individuals may achieve day-to-day satisfaction and contribute positively to society (Saigal et al., 2006). One systematic review found that effects of preterm birth/VLBW on health-related quality of life diminished over time (Zwicker and Harris, 2008). A 27-year follow-up study found that parents of very preterm or VLBW adults had similar quality of life to parents of adults born at term (Wolke et al., 2017). These findings may reflect adapting definitions of quality of life, differences in self-report versus assessed quality of life, and/or resilience over time.

Preterm birth and very low birth weight in a global context

Preterm birth is a growing public health issue internationally (Chang et al., 2013; Howson et al., 2012). Each year, there are 11 million neonates born in high-income countries with intensive care universally available, like those included in this PhD project; 34 million births in middle-income countries, the majority in hospitals but not always with access to intensive care; 40 million births in low-income countries in facilities; and another 50 million births in low-income countries at home (Lawn et al., 2013). By week 24, pregnancies in high-income countries have passed the 50% mark for survival; in low- and middle-income countries, a pregnancy must reach 34 weeks to achieve the same chance (Blencowe et al., 2012). Moreover, there is significant variation in the types of interventions and follow-up services available to children around the world (Odom, 2003).

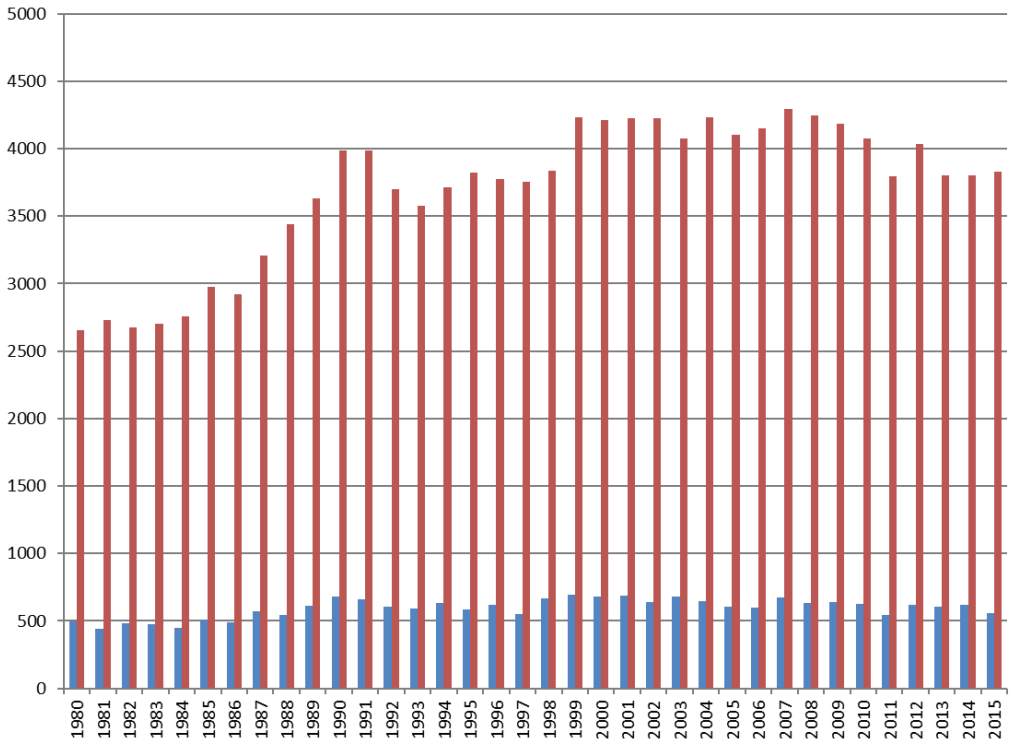

Figure 11. Preterm births in Norway, 1980-2015. Red bars show total number of children born preterm in Norway per year (< 37 weeks of gestation). Blue bars indicate the subset of children born preterm with VLBW. Data courtesy Rupali Akerkar at the Norwegian Institute of Public Health (Folkehelseinstituttet).

In Norway, nearly 4000 neonates are born preterm each year, of whom over 500 also have VLBW (**Figure 11**). These neonates are some of the most vulnerable hospital patients when they are born and are entitled to specialized follow-up services (Grytten et al., 2017; Norwegian Directorate for Health and Social Affairs, 2007). This small but stable preterm/VLBW population will continue to require neonatal intensive care services of hospital staff, close follow-up by trained clinicians and psychologists, and specialists at preschool and school to support them and their families.

Conclusions

This PhD thesis sought to advance our understanding of the long-term anatomical and cognitive sequelae of preterm birth with VLBW. Group differences in gray and white matter structures persisted longitudinally in childhood and were also evident in young adulthood, and performance on visual-motor, executive function, and IQ testing was affected in the preterm/VLBW groups. We did not find evidence for "catch up" growth in the preterm brain but did find evidence of altered structure-function relationships in cortical and subcortical structures, which lends support to the hypothesis of a neurocognitive developmental trajectory that is different, rather than merely delayed, in this population.

The goals of biomedical research go beyond describing the deficits that may accompany a particular condition. Improving lives through effective early interventions, advanced technology – especially noninvasive solutions – and facilitating more informed decision-making is how this line of research can actually make a difference in the lives of those born at high risk. The findings included in this PhD thesis will hopefully contribute to a more comprehensive understanding of the preterm/VLBW brain at various developmental stages and support the progress of neuroprotection and early intervention research.

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Paper I

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Visual–motor deficits relate to altered gray and white matter in young adults born preterm with very low birth weight

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ABSTRACT

Individuals born preterm and at very low birth weight (birth weight ≤ 1500 g) are at an increased risk of perinatal brain injury and neurodevelopmental deficits over the long term. This study examined whether this clinical group has more problems with visual–motor integration, motor coordination, and visual perception compared to term-born controls, and related these findings to cortical surface area and thickness and white matter fractional anisotropy. Forty-seven preterm-born very low birth weight individuals and 56 term-born controls were examined at 18–22 years of age with a combined cognitive, morphometric MRI, and diffusion tensor imaging evaluation in Trondheim, Norway. Visual–motor skills were evaluated with the Beery–Buktenica Developmental Test of Visual–Motor Integration—V (VMI) copying test and its supplemental tests of motor coordination and visual perception. 3D T_1-weighted MPRAGE images and diffusion tensor imaging were done at 1.5 T. Cortical reconstruction generated in FreeSurfer and voxelwise maps of fractional anisotropy calculated with Tract-Based Spatial Statistics were used to explore the relationship between MRI findings and cognitive results. Very low birth weight individuals had significantly lower scores on the copying and motor coordination tests compared with controls. In the very low birth weight group, VMI scores showed significant positive relationships with cortical surface area in widespread regions, with reductions of the superior temporal gyrus, insula, and medial occipital lobe in conjunction with the posterior ventral temporal lobe. Visual perception scores also showed positive relationships with cortical thickness in the very low birth weight group, primarily in the lateral occipito-temporo-parietal junction, the superior temporal gyrus, insula, and superior parietal regions. In the very low birth weight group, visual–motor performance correlated positively with fractional anisotropy especially in the corpus callosum, inferior fronto-occipital fasciculus bilaterally, and anterior thalamic radiation bilaterally, driven primarily by an increase in radial diffusivity. VMI scores did not demonstrate a significant relationship to cortical surface area, cortical thickness, or diffusion measures in the control group. Our results indicate that visual–motor integration problems persist into adulthood for very low birth weight individuals, which may be due to structural alterations in several specific gray–white matter networks. Visual–motor deficits appear related to reduced surface area of motor and visual cortices and disturbed connectivity in long association tracts containing visual and motor information. We conjecture that these outcomes may be due to perinatal brain injury or aberrant cortical development secondary to injury or due to very preterm birth.

Introduction

Though their survival rates have risen greatly in recent decades, individuals born preterm with very low birth weight (VLBW: birth weight ≤ 1500 g) are at an increased risk of perinatal brain injury, including focal and diffuse periventricular leukomalacia (Volpe, 2001), and neurodevelopmental deficits over the long term (Aarnoudse-Moens et al., 2009). While the behavioral and cognitive outcomes of preterm birth and VLBW have been well-documented, the patterns of neurodevelopmental changes in both gray and white matter underlying visual–motor performance in young adulthood remain an open question.

Periventricular leukomalacia is strongly associated with motor problems, such as cerebral palsy, cognitive deficits, and perceptual impairments, and periventricular deep white matter damage can affect

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projection fibers, such as the corticospinal tract, and association fibers including the long association tracts and the optic radiations (Staudt et al., 2003; Krageloh-Mann et al., 1999; van den Hout et al., 2004; Platt et al., 2007; Sullivan and Margaret, 2003; Evensen et al., 2004; Davis et al., 2005; Hard et al., 2000; McGrath and Sullivan, 2002). Visual–motor function includes multiple components: visual perception, eye-hand coordination, fine motor skills and speed, and visual–motor integration (Aylward, 2005). Thus, assessment of visual–motor function is complex, and poor visual–motor performance may reflect deficits associated with one of these components alone or a combination. The latter has been reported for preterm-born children (Evensen et al., 2009). Poorer visual function, including reduced visual acuity and visual–motor problems, has been reported to be more prevalent among VLBW children and adolescents (Lindqvist et al., 2007, 2008; Hellgren et al., 2007; Goyen et al., 1998). Moreover, preterm-born children are at risk for developing motor function deficits and have demonstrated significantly higher rates of motor impairment compared to controls (Spittle et al., 2011; Williams et al., 2010).

Morphometric magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) sequences are sensitive to distinct but complementary layers of structural organization, and by combining them it is possible to paint a more detailed picture of brain development (Dubois et al., 2014). Cortical surface area and thickness analyses are seen as increasingly important datapoints in clinical MR research for characterizing gray matter (Panizzon et al., 2009). By contrast, DTI makes possible the study of microstructural changes and white matter connectivity and is one of few approaches available today to trace white matter connectivity in vivo non-invasively in the human brain (Le Bihan and Johansen-Berg, 2012). Brownian motion of water molecules in the brain is hindered by cell membranes, and diffusion MRI can indicate the axial and radial diffusivity of water along white matter fiber bundles (Johansen-Berg and Behrens, 2009; Vasung et al., 2013).

Morphometric MRI techniques have yielded insights about gray matter alterations related to preterm birth (Lax et al., 2013), and likewise DTI has demonstrated microstructural differences in the brains of VLBW and term-born children and the persistence of these effects through childhood and into early and late adolescence (Ment et al., 2009; Mento and Bisiacchi, 2012; Skranes et al., 2007; Eikenes et al., 2011). In a recent study, Kim et al. (2014) combined graph theory analysis and DTI tractography and reported that longer gestational periods in typically developing children enhanced efficiency of both local and global structural brain networks. However, little neuroimaging research employing both morphometric and DTI data in the preterm-born population has focused on on visual–motor function (Tao and Neil, 2014).

MRI research has identified sequelae of preterm birth and VLBW, ranging from reductions in white matter, gray matter, and overall brain volume in childhood and adolescence (de Kieviet et al., 2012; Giménez et al., 2004) to brain correlates of behavioral problems, such as inattention and hyperactivity in childhood (Bora et al., 2014) and socialization problems in adolescence (Healy et al., 2013). Diverse cortical and subcortical structures have been implicated in patterns of altered brain development following preterm birth. Previous long-term follow-up studies comparing VLBW and term-born individuals have demonstrated alterations in gray matter structure, including reductions in cortical surface area in ventrolateral prefrontal, temporal and parietal regions in VLBW individuals by age 19 (Skranes et al., 2013), differential patterns of cortical thickness between VLBW and controls by early adulthood (Bjuland et al., 2013), and regions of increased and decreased structural covariance between the groups by adolescence (Nosarti et al., 2011).

White matter studies with VLBW individuals have identified reduced posterior corpus callosum surface area (Nosarti et al., 2004), lower FA in bilateral uncinate fasciculi (Mullen et al., 2011), external capsules, corpus callosum splenium (Constable et al., 2008; Vangberg et al., 2006; Eikenes et al., 2011), and other intrahemispheric association fibers. A smaller subset of these have begun to identify associations between specific white matter tract alterations and diverse cognitive functions, such as language processing (Reidy et al., 2013; Mullen et al., 2011), IQ (Iwata et al., 2012), and perceptual and motor functions (Skranes et al., 2007; Chau et al., 2013).

Previous reports on this cohort (Eikenes et al., 2011; Skranes et al., 2007, 2013; Bjuland et al., 2013, 2014; Lindqvist et al., 2011; Vangberg et al., 2006) have documented alterations in gray and white matter structures in VLBW individuals. The current study expands on these by investigating MRI data in the context of visual–motor integration at entry to adulthood and assessing specific cortical regions and white matter structures that may be sensitive to VLBW.

Aim

This study assesses visual–motor function in the context of brain development by combining cognitive assessment with structural MRI and DTI. The first aim of this study was to evaluate visual–motor abilities for copying figures, fine motor tasks, and visual perception in young adults born with VLBW compared to age-equivalent term-born controls. The second aim was to relate visual–motor and visual–perceptual abilities in the VLBW group to morphometric and DTI findings. Our hypothesis was that the VLBW adults would achieve lower scores than controls on these visual–motor tests and demonstrate corresponding gray and white matter alterations.

Methods

Study design

This study is part of a hospital-based prospective follow-up study of three year cohorts of children. A total of 121 VLBW infants were admitted to the neonatal intensive care unit (NICU) at the university hospital in Trondheim, Norway, between 1986 and 1988. The control infants were born to mothers living in the Trondheim area and were enrolled in a multi-center study before week 20 of pregnancy, between January 1986 and March 1988. All the births in a 10% random sample of mothers (paras 1 and 2) were included for follow-up during pregnancy. Neuroimaging and cognitive data collection for the present study was carried out between January 2007 and December 2008.

Study population

VLBW group

Of the 121 VLBW infants admitted to the NICU, 33 died, and nine had moved before follow-up. One child with Down's syndrome and two children with severe cerebral palsy were excluded from follow-up due to inability to perform the tests. Of the remaining 76, 54 (71%) participated in follow-up evaluation at age 18–22, and 47 (61%), including 3 individuals with mild bilateral spastic cerebral palsy, had successful cognitive assessments and MRI acquisitions. Twelve of the VLBW participants were twins.

Control group

The control group comprised 120 infants from the 10% random sample born at term, with birth weight ≥ 10th percentile for gestational age. At age 18–22, 10 had moved and two were excluded due to congenital malformations. Of the remaining 108, 81 (75%) participated at the follow-up, and 66 were examined with MRI. Seven DTI scans were excluded due to image artifacts, leaving 59 with successful DTI scans. Three of these did not have VMI assessment or had a poor morphometric MRI, leaving 56 (52%) who were successfully evaluated with cognitive testing, morphometric MR, and DTI.

MRI acquisition

MRI data were acquired on a 1.5 T Siemens Magnetom Symphony (Siemens, Erlangen, Germany) with Quantum gradients (30 mT/m) and a quadrature head coil. A structural T_1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was acquired with TR = 7.1 ms, TE = 3.45 ms, TI = 1000 ms, flip angle 7°, FOV 256 × 256, slab thickness 170 mm, and acquisition matrix 256 × 192 × 128, reconstructed to 256 × 256 × 128, giving a reconstructed voxel resolution of 1 × 1 × 1.33 mm. The DTI sequence was a single-shot balanced-echo EPI sequence acquired in 12 non-collinear directions with b = 1000 s/mm^2 using the following parameters: TR = 10,400 ms, TE = 100 ms, FOV 280 × 280 mm, slice thickness 2.2 mm, and acquisition matrix 128 × 128, giving isotropic voxels of 2.2 mm. Fifty-five transversal slices with no gap were acquired, giving full brain coverage. The slices were obtained parallel to the anterior/posterior commissural line. For each slice, two images without diffusion weighting (b = 0), and 12 images with diffusion gradients were acquired. The DTI sequence was repeated six times for an increased signal-to-noise ratio.

Morphometric image analysis

The MPRAGE images were reviewed for image quality, and low quality images were excluded. The quality of the FreeSurfer image processing was reviewed by image analyzers blinded to group adherence, in order to check the quality of the cortical reconstruction and apply minimal manual editing in a few cases.

Cortical reconstruction for cortical thickness and surface area measurements was performed with the FreeSurfer 5.1.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu). The technical details of these procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 1999a,b, 2001, 2002, 2004a,b; Han et al., 2006; Jovicich et al., 2006; Ségonne et al., 2004). Briefly, this processing includes motion correction and averaging (Reuter et al., 2010) of multiple volumetric T_1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, intensity normalization (Sled et al., 1998), tessellation of the gray and white matter boundary, automated topology correction (Fischl et al., 2001; Ségonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid (CSF) borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl et al., 1999a), registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across individuals (Fischl et al., 1999b), parcellation of the cerebral cortex into units with respect to gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004b), and creation of a variety of surface-based data. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity.

The two cerebral hemispheres were processed separately. The surfaces were smoothed with a full-width-half-maximum Gaussian kernel of 30 mm (662 iterations) and averaged across participants. Each surface consisted of 163,842 vertices arranged in a triangular grid, and estimates of cortical area were obtained by computing the area of each triangle in the standardized, spherical atlas space surface tessellation when mapped into the individual subject space. Vertex-wise estimates of relative areal expansion for each individual in atlas space were then computed by assigning one-third of the area of each triangle to each of its vertices (Rimol et al., 2012). The cortical surface for each individual was automatically parcellated using defined gyri and sulci as landmarks, and the surface was divided into 34 anatomical regions for each brain hemisphere defined in FreeSurfer (Fischl et al., 2004b; Desikan et al., 2006), which were used to anatomically identify affected regions after significance testing.

Morphometry statistical analysis

All statistical analyses of morphometry data were performed within the MATLAB software suite 2011b (MATLAB and Statistics Toolbox Release 2011b. The MathWorks, Inc., Natick, Massachusetts, US). A general linear model was fitted in each of the 163,842 vertices per cerebral hemisphere, with cortical surface area or cortical thickness as dependent variable, and adjusted for sex and age at MRI, with one of the VMI tests (copying, motor, or visual) as continuous predictor. The appropriate contrast vectors were set to test for a relationship between performance on each of the VMI tests and cortical morphology. The hemispheres were analyzed separately, and effect size and *p*-maps were generated. Effect size was obtained as explained variance (r^2 = (F / (f + df))). To correct for multiple comparisons, the two *p*-maps from left and right hemisphere were combined and thresholded to yield an expected false discovery rate (FDR) of 5% across both hemispheres.

DTI analysis

DTI analysis was performed with the FMRIB software library (FSL, Oxford Centre for Functional MRI of the Brain, Oxford, UK; www.fmrib.ox.ac.uk/fsl). All DTI acquisitions were registered to the b = 0 image using affine registration in order to minimize image artifacts caused by motion and eddy current distortions. FMRIB's Diffusion Toolbox was used to fit a diffusion tensor model to the raw diffusion data in each voxel (Basser and Pierpaoli, 1996) and create voxelwise maps of the eigenvalues (λ_1, λ_2, and λ_3), FA, and mean diffusivity (MD) for both the VLBW and control groups.

FSL's Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) was used for voxel-based analysis of the DTI data. Randomise was used to study the relationship between the skeletonized FA, MD, and eigenvalues (λ_1, λ_2, and λ_3) and scores on the three VMI tests (copying, motor, and visual) in the VLBW and control groups separately. Randomise performs nonparametric permutation tests with a correction for multiple comparisons, here corrected for sex and age at MRI ($p < 0.05$) (Nichols and Holmes, 2002). Anatomical locations were identified using the Johns Hopkins University International Consortium of Brain Mapping-DTI-81 White-Matter Labels and Johns Hopkins University White-Matter Tractography atlases within FSL (Wakana et al., 2007; Hua et al., 2008) and human white matter atlases by Oishi et al. (2011) and Mori et al. (2005).

Visual–motor integration evaluation

Visual–motor integration was assessed with the Beery–Buktenica Developmental Test of Visual–Motor Integration—V (VMI) and its two supplemental tests. VMI is a widely used standardized test that requires both motor and perceptual skills (Beery et al., 2004). In the copying test (hereafter referred to as "copying"), the participant is instructed to copy 30 geometric designs in increasing order of difficulty without a time limit. The designs are scored according to the VMI manual based on accuracy and quality standards. If the participant fails to copy three consecutive designs, the test may be stopped. The first supplemental test, visual perception ("visual"), requires the participant to match visual shapes within a 3-minute time limit. Total number of correctly

matched designs is the raw score. The second supplemental test, motor coordination ("motor"), requires the participant to trace the designs with a pencil without leaving the double-lined paths in which the designs are presented, within 5 min. For the supplemental tests, the participants are allowed to continue throughout the time allotted, regardless of failed tasks. Thirty points is the maximum raw score for each of the three tests.

Cognitive data analysis

The software package IBM SPSS 21 (Chicago, USA) was used for statistical analysis of the cognitive data. Differences between groups in age at exam, socioeconomic status, and maternal age at childbirth were investigated with t-tests, and effect of twin status on VMI scores was assessed with univariate ANOVA. A general linear model with age at MRI, sex, and socioeconomic status as covariates was used for analysis of the three VMI tests. Demographic and clinical data are presented in Table 1.

Socioeconomic status

Socioeconomic status was calculated using Hollingshead's two factor index of social position based on education and occupation of one parent or the mean index of both parents (Hollingshead, 1957).

Ethics

Written, informed consent was obtained from the participating young adults, and the Data Inspectorate assigned the license for keeping a data register with personal information. The Regional Committee for Medical Research Ethics approved the study protocol (project number: 4.2005.2605).

Results

Group characteristics

Demographic and clinical characteristics of the study groups are shown in Table 1. Birth weight and gestational age were selection criteria for the two groups. In the VLBW group, mean birth weight was 1221 g and mean gestational age was 29.3 weeks. There was no difference in age at exam ($p = 0.90$), socioeconomic status ($p = 0.12$), or maternal age at childbirth ($p = 0.08$) between the groups.

Cognitive test results and group differences

The VLBW group had lower scores than controls on the copying and motor tests but not on the visual test after adjusting for age, sex, and socioeconomic status. Raw scores for the three VMI tests are presented with age, sex, and socioeconomic status as covariates in a general linear model in Table 2. The univariate ANOVA yielded no significant effect of twin status on VMI scores.

Table 1
Demographic and clinical information. Mean values ± standard deviation, [95% confidence intervals].

Characteristics	VLBW (n = 47)	Control (n = 56)
Birth weight (g)	1221 ± 231, [1153, 1289]	3694 ± 495, [3561, 3826]
Gestational age (weeks)	29.3 ± 2.5, [28.5,30.0]	39.8 ± 1.3, [39.4,40.1]
Sex (male/female)	20/27	21/35
Age at exam (years)	19.7 ± .9	19.7 ± .6
Socioeconomic status (1–5)	3.4 ± 1.3, [3.0,3.8]	3.8 ± .88, [3.5,4.0]
Maternal age (years)	29.0 ± 4.7, [27.6,30.3]	30.5 ± 3.9, [29.4,31.5]

Abbreviations: VLBW, very low birth weight.

Table 2
Results of the three VMI tests in the two study groups. Mean raw scores ± standard deviation, [95% confidence intervals].

VMI assessment	VLBW (n = 47)	Control (n = 56)	*p*-value
Copying	24.6 ± 3.6, [23.7, 25.4]	26.7 ± 2.4, [25.9, 27.5]	.001
Motor	27.4 ± 2.7, [26.8, 28.1]	29.2 ± 1.8, [28.6, 29.8]	<.001
Visual	27.6 ± 2.0, [27.0, 28.3]	27.9 ± 2.3, [27.3, 28.4]	.609

Abbreviations: VLBW: very low birth weight; VMI: Beery–Buktenica Developmental Test of Visual–Motor Integration—V.

Structural MRI

Cortical surface area

In the VLBW group, there were widespread cortical regions in both hemispheres showing a significant relationship between each of the three VMI tests and cortical surface area. Table 3 lists all regions with significant findings in the VLBW group as determined by the general linear model (after FDR correction), with several regions significant across the VMI tests (Fig. 1). The explained variance reached 35–40% in several highly correlated regions (yellow in Fig. 2) and was as high as 48% in the right lingual and lateral occipital gyri for the copying test. Explained

Table 3
Proportion (%) of surface area in cortical regions of interest showing significant relationship with VMI tests (copying, motor, visual) in the VLBW cohort.

Cortical region of interest	Copying		Motor		Visual	
	Left	Right	Left	Right	Left	Right
Banks of the superior temporal gyrus	68	70	100	77	77	82
Caudal anterior cingulate gyrus	0	8	22	100	79	81
Caudal middle frontal gyrus	36	20	95	64	58	54
Cuneus	100	31	100	48	100	63
Entorhinal cortex	0	0	2	0	100	0
Fusiform gyrus	63	47	95	74	96	78
Inferior parietal gyrus	30	34	52	80	57	70
Inferior temporal gyrus	11	4	51	38	41	25
Insula	94	99	67	100	100	99
Isthmus cingulate	44	42	42	63	63	100
Lateral occipital gyrus	74	51	96	85	88	98
Lateral orbitofrontal gyrus	73	73	85	100	100	96
Lingual gyrus	100	100	100	94	100	100
Medial orbitofrontal gyrus	17	44	100	86	100	93
Middle temporal gyrus	48	25	59	83	82	31
Parahippocampal gyrus	76	69	68	76	100	90
Paracentral gyrus	7	13	90	76	22	34
Pars opercularis	76	28	100	83	100	41
Pars orbitalis	0	100	100	100	100	100
Pars triangularis	1	74	95	100	100	77
Pericalcarine sulcus	100	84	100	79	100	100
Postcentral gyrus	9	13	21	19	14	16
Posterior cingulate	32	88	71	100	84	97
Precentral gyrus	40	21	58	73	55	34
Precuneus	41	47	70	54	43	62
Rostral anterior cingulate	0	46	82	100	95	100
Rostral middle frontal gyrus	49	55	100	81	95	83
Superior frontal gyrus	69	47	98	87	94	91
Superior parietal gyrus	32	38	61	88	38	44
Superior temporal gyrus	85	86	92	99	83	100
Supramarginal gyrus	1	8	38	12	8	39
Frontal pole	33	0	100	41	100	100
Temporal pole	25	4	93	76	100	57
Transverse temporal gyrus (Heschl's gyrus)	100	100	100	100	100	100

The table presents the percentage of surface area in each of the parcellations (from the FreeSurfer Desikan–Killiany parcellation scheme) that showed a significant result (after FDR correction) in the GLM testing for a relationship between the VMI tests and cortical surface area in the VLBW cohort. The GLMs were fitted with cortical surface area as dependent variable, sex as categorical predictor, and age at MRI scan and one of the VMI test scores as continuous predictors. Contrast vectors were set to test for a relationship between performance on each of the VMI tests (copying, motor, visual) and cortical surface area.
Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight; VMI, Beery–Buktenica Developmental Test of Visual–Motor Integration—V.

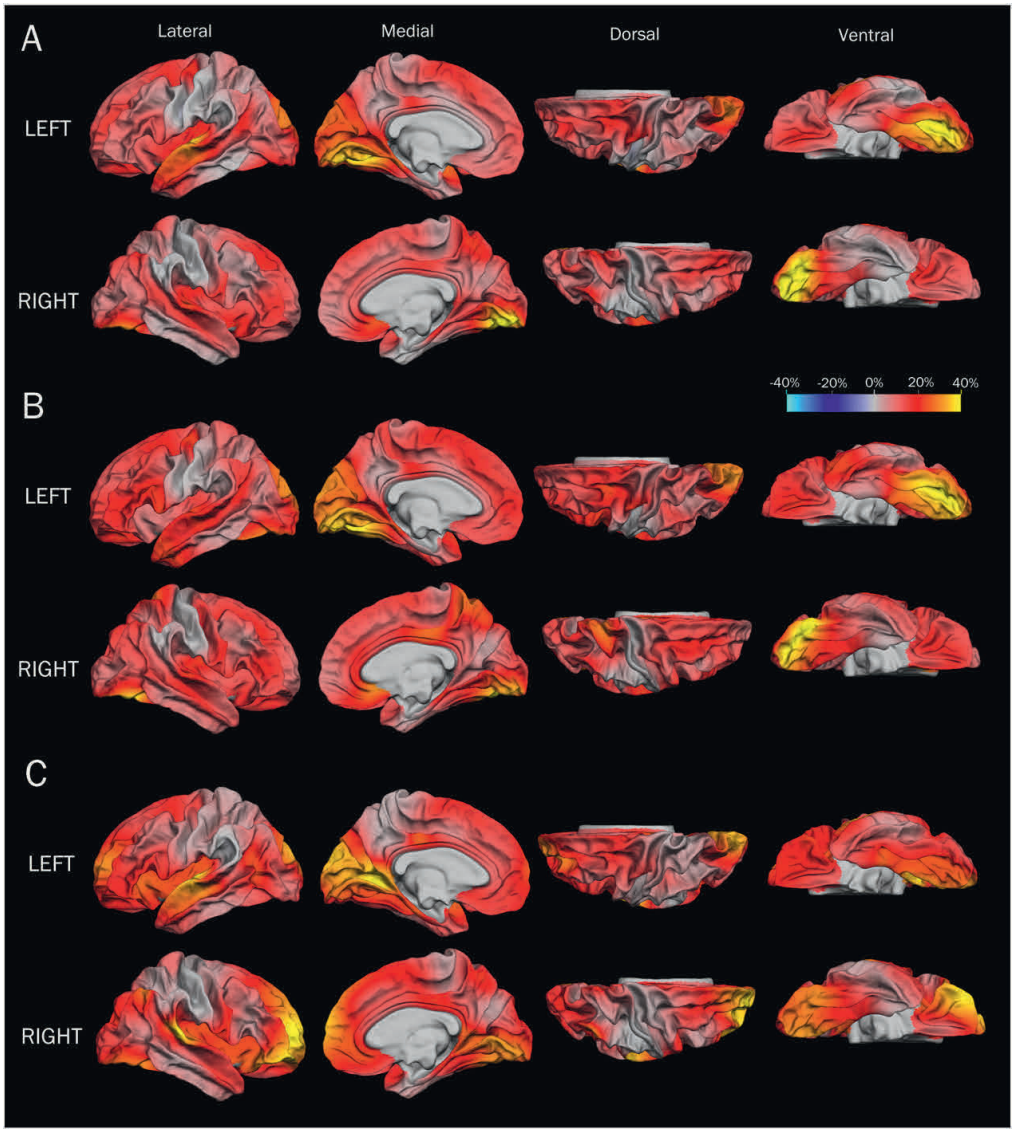

Fig. 1. Cortical surface area maps of explained variance in VLBW group. Maps of explained variance (r^2) for the association between test scores on the three VMI tests (A: copying, B: motor, C: visual) and cortical surface area in the VLBW sample. The r^2 is based on a GLM with cortical surface area as dependent variable, sex as categorical predictor, and age at MRI scan and one of the VMI test scores as continuous predictor. $r^2 = (F / (F + df))$. Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight; VMI, Beery–Buktenica Developmental Test of Visual–Motor Integration—V.

variance values were as low as 10% in the least correlated regions that survived significance testing. There were no significant findings in the control group.

Cortical thickness

In the VLBW group, the general linear model identified regions with a significant relationship between cortical thickness and visual test scores but not the other two VMI tests (Fig. 3). The findings were mainly in the lateral occipito-temporo-parietal junction, the superior temporal gyrus and insula (extending into inferior frontal gyrus), as well as superior parietal regions including superior parietal gyrus and postcentral gyrus. There were fewer findings on the medial side, in particular some in the left precuneus, cuneus, and medial occipital gyrus. There were no significant findings in the control group.

Group differences

There were significant differences in cortical surface area between the VLBW group and the control group. The VLBW group showed reduced cortical surface area primarily in frontal, temporal, and parietal lobes. Cortical thinning was observed in the left parietal and temporal

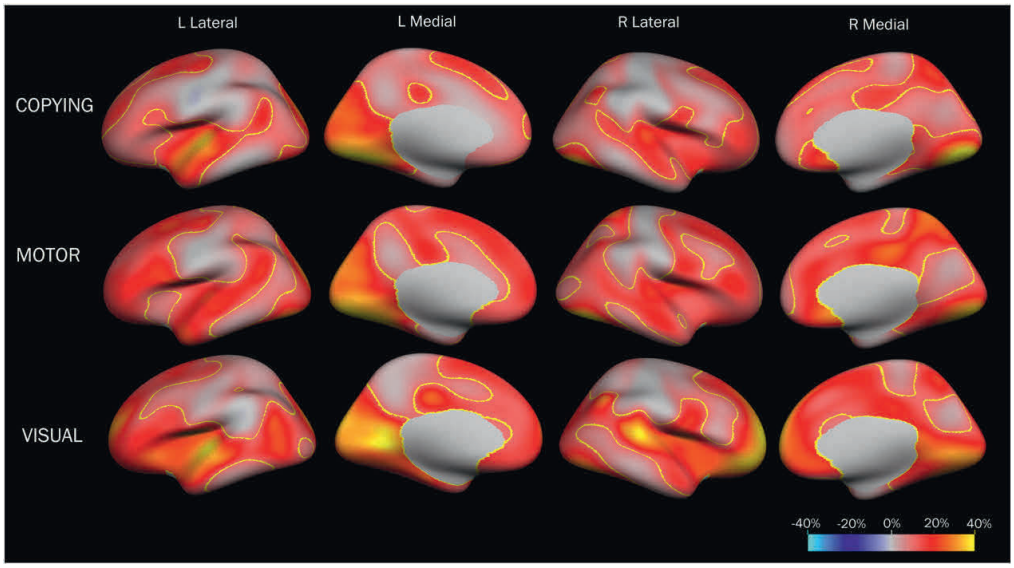

Fig. 2. Labeled cortical surface area maps of explained variance in VLBW group. Maps of explained variance (r^2) for the association between test scores on the three VMI tests and cortical surface area in the VLBW sample, with suprathreshold regions outlined in yellow. Suprathreshold regions are cortical regions that survived the significance test and a subsequent 5% FDR correction. The significance tests and the effect size estimates (r^2) are based on fitting GLMs with cortical surface area as dependent variable, sex as categorical predictor, and age at MRI scan and one of the VMI test scores as continuous predictor. Contrast vectors were set to test for a relationship between performance on each of the VMI tests (copying, motor, visual) and cortical surface area. The *p*-maps were thresholded and multiple comparisons were corrected for with a 5% FDR that was applied co-jointly across the hemispheres. To create a map illustrating both effect sizes as well as which regions contain statistically significant findings, a label was created in FreeSurfer containing vertices that survived the significance test (including FDR). This label was subsequently overlaid on the effect size map. Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight; VMI, Beery–Buktenica Developmental Test of Visual–Motor Integration—V.

lobes and cortical thickening in frontal regions bilaterally; however there was no significant difference in mean global cortical thickness between groups. These group differences have previously been reported by our group (Skranes et al., 2013; Bjuland et al., 2013) and are therefore not presented here.

DTI findings

Fractional anisotropy in VLBW group

In the VLBW group, all three visual–motor test scores correlated positively with FA ($p < 0.05$; red voxels in Fig. 4). DTI analysis demonstrated

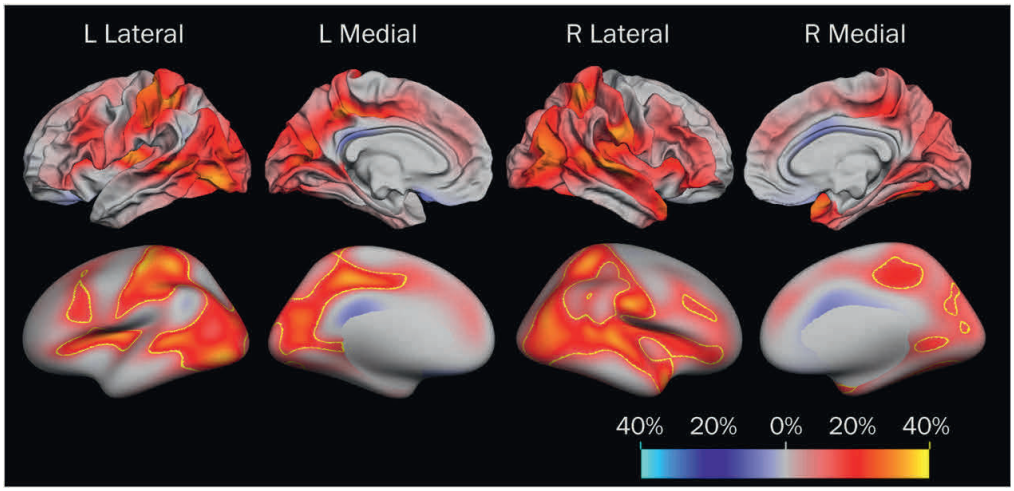

Fig. 3. Cortical thickness maps of explained variance in the VLBW group for VMI visual test scores, shown without and with suprathreshold labeling. Maps of explained variance (r^2) for the association between test scores on the VMI visual test and cortical thickness in the VLBW sample (top row), with suprathreshold regions outlined in yellow (bottom row). The maps were produced from GLMs with cortical thickness as dependent variable at each location (vertex) across the surface, and visual test scores as independent variable, covarying for age and sex. To create a map illustrating both effect sizes as well as which regions contain statistically significant findings, a label was created in FreeSurfer containing vertices that survived the significance test (including FDR). This label was subsequently overlaid on the effect size map, as shown in the bottom row. Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight; VMI, Beery–Buktenica Developmental Test of Visual–Motor Integration—V.

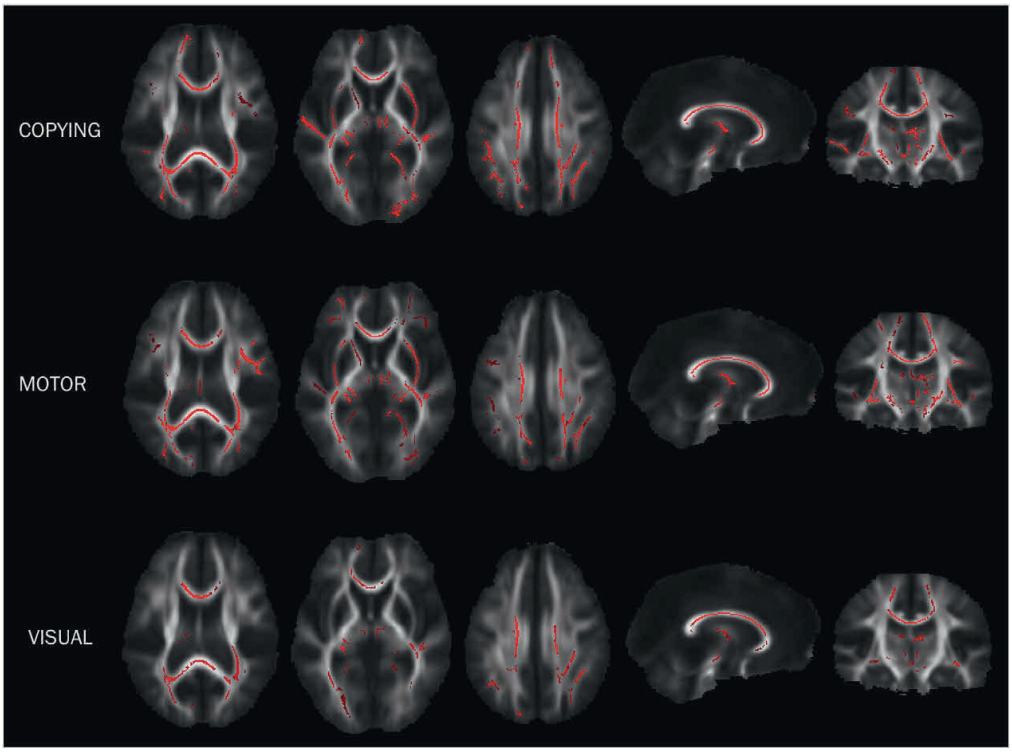

Fig. 4. Fractional anisotropy and visual–motor score correlations in the VLBW group. White matter areas demonstrating a positive correlation (voxels in red) between VMI test scores and fractional anisotropy in the VLBW group, based on DTI analysis in TBSS and Randomise ($p < 0.05$, nonparametric permutation test, corrected for multiple comparisons, gender and age at MRI). Images are displayed in radiological convention (right brain on left side). Abbreviations: DTI, diffusion tensor imaging; TBSS, Tract-Based Spatial Statistics; VLBW, very low birth weight; VMI, Beery–Buktenica Developmental Test of Visual–Motor Integration—V.

significant positive correlations between FA and copying scores in the corpus callosum (extending rostrally in the right hemisphere), optic radiation, bilateral inferior longitudinal fasciculus, bilateral inferior fronto-occipital fasciculus (more strongly in the right hemisphere), bilateral uncinate fasciculus, bilateral external capsules, and to some extent bilaterally in the anterior thalamic radiation, as well as in the left superior longitudinal fasciculus and right internal capsule. For the motor test, reduced scores correlated with FA reductions in corpus callosum, bilateral inferior longitudinal fasciculus (more strongly in the right hemisphere), bilateral inferior fronto-occipital fasciculus (more strongly in the right hemisphere), bilateral uncinate fasciculus, and bilateral external capsules, as well as left superior longitudinal fasiculus, right internal capsule, and somewhat in the right anterior thalamic radiation and to lesser extent in the left anterior thalamic radiation. For the visual perception test, correlation between FA and score was less widespread compared to the other two tests and were mainly found in the corpus callosum, particularly in the body, and bilaterally in the posterior inferior fronto-occipital fasciculus and the anterior thalamic radiation.

Mean diffusivity and eigenvalue analysis in the VLBW group

In the VLBW group, MD was negatively correlated to all visual–motor test scores in white matter structures similar to but less widespread than the FA findings. Separating the three eigenvalues, the radial diffusivities λ_2 and λ_3 reflecting radial diffusivity showed negative correlations to scores in all three visual–motor test scores. The axial diffusivity λ_1 indicated a negative correlation in very few white matter structures in relation to copying scores, but none with the motor or visual tests.

Findings in control group

FA, MD, and λ_1, λ_2, and λ_3 eigenvalues did not demonstrate significant correlations with any of the visual–motor test scores in the control group (data not shown). In a previous report on a subset of the same study population, Eikenes et al. (2011) showed group differences between preterm-born VLBW young adults and controls, examining relationships between DTI parameters, cognitive performance, and perinatal clinical data.

Discussion

In our VLBW young adult group, poorer visual–motor integration performance was related to thinner cortex in several regions, reduced cortical surface area in all four cerebral lobes, including regions important for visual association and motor function, and reduced FA in several association tracts. We have thus identified gray and white matter structures that appear to be sensitive to perinatal injury and visual–motor integration. These structural alterations related to perceptual and motor coordination deficits persist even at entry to adulthood and underscore the importance of these gray and white matter structures for normal visual–motor functioning in the VLBW population.

VLBW individuals performed significantly worse on the VMI copying and motor tests than the control group, and their scores on all three VMI tests had significant relationships to surface area in widespread cortical regions, with the superior temporal gyrus, the insula, and the medial

occipital lobe in conjunction with the posterior ventral temporal lobe (lingual gyrus and fusiform gyrus to a lesser extent) being the most consistently significant regions across the three VMI tests. FA in the corpus callosum, bilateral inferior fronto-occipital fasciculus, and bilateral anterior thalamic radiation correlated positively to scores on all three VMI tests, and radial diffusivities λ_2 and λ_3 showed negative correlations to all three test scores in the VLBW group. There were no significant relationships between VMI test scores and cortical morphometry or DTI in the control group.

Cortical surface area and thickness

Morphometric analyses on cortical surface area and thickness identified several cortical regions that showed significant relationships to visual–motor performance. The regions that showed the highest explained variance were similar across all three tests, including the superior temporal gyrus, insula, and medial occipital lobe in conjunction with the posterior ventral temporal lobe (Fig. 1). In VLBW individuals, it appears that these regions may experience injury related to preterm birth. Consistent with this, Nosarti et al. (2008) found that gestational age in very preterm adolescents was linearly associated with decreased gray matter bilaterally in portions of the superior temporal gyri and the insula, which has been linked to various cognitive functions, speech, and articulatory control processes (Ackermann and Riecker, 2010).

Cortical thickness in the VLBW group exhibited a significant relationship to visual scores, and several of the implicated cortical regions are believed to be involved in visual and motor function. Lesion studies have identified a possible role of superior parietal regions in visually guided movements and reaching (Vesia and Crawford, 2012), while the precuneus has diverse and as yet poorly demarcated functions ranging from visual–spatial imagery and mental representations of the self (Cavanna and Trimble, 2006) to proprioceptive input from the arm during tasks (Vesia and Crawford, 2012). The three VMI tests, which demand visual–spatial planning and fine motor execution, may therefore be expected to draw upon the functions of these cortical regions.

DTI findings

Lower FA was found to correlate to lower VMI scores in the VLBW group. However, when looking at the eigenvalues, only radial diffusivities were found to correlate negatively with VMI scores, while axial diffusivity was only found to correlate with the copying test in a few structures. This is in line with previous results, in which we demonstrated that the reduced FA in the same VLBW study group was driven primarily by an increase in radial diffusivity (Eikenes et al., 2011).

The corpus callosum was implicated in our analyses for each of the three VMI tests. This major white matter structure is widely reported to be impacted by preterm birth, and studies have demonstrated lower FA in the corpus callosum compared to controls at term-equivalent age (Lepomäki et al., 2012) and during adolescence and young adulthood (Nagy et al., 2009; Eikenes et al., 2011). Groeschel et al. (2014) found higher axial diffusivity in preterm-born adolescents in the corpus callosum body for fibers connecting premotor areas, while Thompson et al. (2012) found higher diffusivity in the splenium at term-equivalent age associated with impaired motor development at two years. Smaller corpus callosum size, especially posteriorly, has been associated with lower VMI copying scores (Rademaker et al., 2004). We have previously reported significant positive correlation between visual acuity and FA in the splenium and midbody of the corpus callosum in the VLBW group (Lindqvist et al., 2011).

In the optic radiation, we found a positive correlation between FA and the copying scores in the VLBW group, which expands upon our previous findings of significantly reduced FA and increased MD in optic radiation in VLBW young adults compared to controls (Eikenes et al., 2011). DTI assessments of premature infants have indicated a significant positive correlation between optic radiation fractional anisotropy and visual function (Berman et al., 2009; Bassi et al., 2008). Thompson et al. (2013) also found higher diffusivity in the optic radiation of very preterm-born children at age seven compared to controls and suggested that optic radiation diffusion values may have a structure–function relationship with visual functions that rely on visual cortex processing.

FA in several major white matter structures, including long-range association tracts, correlated positively to VMI test scores. FA bilaterally in the uncinate fasciculus, a long-range white matter association tract that connects the orbitofrontal cortex to the anterior temporal lobes, correlated positively to scores on the copying and motor tests in the VLBW group. Moreover, FA in the inferior longitudinal fasciculus also correlated positively to copying and motor scores. Ortibus et al. (2012) found lower FA in the inferior longitudinal fasciculus in children with visual perceptual impairment compared to typically developing children and argued that this tract plays a role in object recognition. However, linkages between cognitive function and white matter findings in the inferior longitudinal fasciculus should be interpreted with caution, as it is believed to be involved in wide-ranging capacities including thought disorders, visual emotion, cognitive impairments, and language (Ashtari, 2012; Mandonnet et al., 2007). In addition, we identified positive correlations between copying and motor scores with FA in the external capsule and left superior longitudinal fasciculus, which along with the uncinate fasciculus have been shown to have lower FA in preterm-born individuals compared with controls (Duerden et al., 2013; Eikenes et al., 2011; Skranes et al., 2007). Integrity in these white matter structures may therefore be particularly sensitive to persistent white matter disturbances related to preterm birth.

It is difficult to translate DTI measures into specific physiological features (Pandit et al., 2013). However, it is possible that the reduced FA in these regions in the VLBW group is caused by decreased or aberrant myelination, as evidenced by increased radial diffusion (Cheong et al., 2009; Song et al., 2005). Nonetheless, white matter imaging may be able to detect structural alterations in motor pathways even where standard MRI does not indicate brain injury in preterm-born infants (Anjari et al., 2007; Hüppi and Dubois, 2006) and adolescents (Groeschel et al., 2014) and is therefore an important clinical neuroimaging tool for the preterm-born population.

Potential relationships between gray and white matter findings in the VLBW group

This study raises several important questions about the relationship between gray and white matter development in VLBW individuals through adolescence and into adulthood. Several white matter structures implicated in our DTI analysis connect to cortical regions in which VMI test scores were significantly related to surface area and cortical thickness, including in regions implicated in visual association and motor processing. Thus, by connecting gray and white matter analyses to cognitive data, we have identified putative gray–white matter networks in which structural integrity appears to relate to visual–motor performance in the VLBW population.

Copying and motor scores in the VLBW group correlated to FA in the inferior longitudinal fasciculus, an association pathway whose fibers connect the occipital and anterior temporal lobe and originates from the cuneus, lateral occipital gyrus, and posterior lingual and fusiform gyri (Catani et al., 2003), cortical regions which showed a high proportion of surface area significantly related to VMI test scores (Table 1). Long inferior longitudinal fasciculus fibers connect visual association with parahippocampal areas, while its short fibers connect regions related to primary visual processing and visual association including the inferior parietal lobe (Aralasmak et al., 2006). Both of these cortical targets also showed strong relationships between surface area and test scores in the VLBW cohort.

Scores on all three VMI tests correlated positively to FA in the inferior fronto-occipital fasciculus, a white matter tract important for connecting visual association areas with primary motor frontal eye fields, as well as for relaying elementary visual information (Aralasmak et al., 2006). The inferior fronto-occipital fasciculus connects the posterior temporal, orbito-frontal, and occipital regions (Ashtari et al., 2012), and we found large proportions of surface area in occipital regions, especially in the left hemisphere, significantly related to scores on all three visual–motor tests.

Finally, we identified significant DTI correlations in several other major association tracts and white matter structures which have cortical targets important for visual and motor function. The uncinate fasciculus, a major long association tract with FA significantly related to scores on the copying and motor tests in our study, links the frontal and temporal lobes including regions involved in multimodal association and event-related memory (Catani et al., 2002). The superior longitudinal fasciculus, where FA in the left hemisphere positively correlated with copying and motor scores, is another major association bundle connecting the external surface of the temporoparieto-occipital regions with the frontal lobe and is thought to be related to visuospatial processing and spatial attention (Thiebaut de Schotten et al., 2011). The internal capsule contains corticofugal motor and thalamocortical sensory projection fibers (Aralasmak et al., 2006) and was in the right hemisphere also positively correlated with copying and motor scores.

We speculate that the structural deviations seen in the VLBW group may be due to perinatal injury and cause reduced scores on these visual–motor tests. It is also possible that the widespread findings for cortical surface area reflect a more general relationship between cognition and aberrant brain development in the VLBW group. These relationships may be stronger in some regions with regard to perceptual functioning but may suggest larger-scale relationships across the cortex.

Cognitive findings and clinical implications

The VLBW group performed significantly worse on the copying and motor tests than term-born individuals, as expected. This finding is consistent with earlier literature concerning preterm birth, although most studies have evaluated school-aged children in contrast to our young adults (Geldof et al., 2012; Davis et al., 2005; Hard et al., 2000; Goyen et al., 1998; Molloy et al., 2014). Preterm-born individuals have demonstrated worse performance on simple visual–motor tasks and are thought to have a different, rather than merely delayed, developmental trajectory for visual–motor processes compared to controls (Van Braeckel et al., 2010; Narberhaus et al., 2009; Sullivan and Margaret, 2003; Martinussen et al., 2009).

Visual–motor impairment can have far-reaching consequences, including in the classroom, where motor coordination and fine motor skills are fundamental for everyday tasks. Preterm-born school-aged children have demonstrated worse handwriting performance, including significantly lower legibility and slower speed (Feder et al., 2005). Recent studies have begun to highlight the role of white matter (Saygin et al., 2013; Aeby et al., 2013) and cortical thickness (Clark et al., 2014) structural alterations as biomarkers of latent developmental problems, such as dyslexia. Our results indicate that diminished motor coordination in the VLBW cohort evident at earlier ages persists even through early adulthood.

By contrast, scores on the visual matching subtest were nearly the same between the groups. In a recent functional MRI study on visual–perceptual function, Narberhaus et al. (2009) found that very preterm-born adolescents did not demonstrate performance deficits on a visual–perceptual learning task inside the MRI scanner yet showed different patterns of brain activation compared to controls. It may therefore be possible that preterm VLBW individuals develop compensatory connections to improve visual processing, especially in the absence of a stronger demand on motor function.

Visual–motor integration, motor coordination, and visual–perceptual impairments may have a common etiology in preterm VLBW individuals. Perinatal brain injury that affects posterior deep white matter connectivity may have consequences for both visual and perceptual cortical regions (Skranes et al., 2007). Preterm-born individuals are at risk for periventricular leukomalacia (Volpe, 2001), and subsequent damage to the developing sensory, motor, and cognitive pathways may result in modified target regions or tract directions which are different from what is observed in term-born individuals (Tzarouchi et al., 2011).

Important developmental events unfold during 24 to 40 weeks of gestation and may enhance the fetus's vulnerability to ischemia, inflammation, excitotoxicity, and free-radical attack, and possibly other exogenous insults like drugs and undernutrition (Volpe, 2009; Dobbing, 1974). Groppo et al. (2014) posit that the developing visual system undergoes significant maturation and vulnerability between 32 weeks of gestation and term–equivalent age. Events during this timeframe may also contribute to visual–motor integration abilities.

Strengths and limitations

A strength of this study is the long-term follow-up of the two study groups, which were recruited at birth and equivalent in terms of maternal age at childbirth and socioeconomic status. The groups have been followed prospectively with comprehensive multidisciplinary clinical, cognitive, and MRI assessments at different ages. Through a drop-out analysis, we found no differences in background characteristics between those who participated and those who chose not to participate in the early adolescence and early adulthood follow-up sessions, which reduces the likelihood that the results were influenced by selection bias. In order to reduce the risk of information bias, the cognitive testing was performed by two trained examiners blinded to group adherence and former medical history.

About 56% of those eligible from the cohort participated at the early adulthood follow-up with a full perceptual assessment and MRI. While this percentage is lower than ideal, it is comparable to other long-term follow-up studies assessing adolescents and young adults, where high drop-out rates are common (Hille et al., 2005). Cases lost to follow-up are often selective, and mothers with low educational attainment and those with children with serious developmental delays or disabilities are most likely to drop out (Wolke et al., 1995). If that is the case in our study, this would most likely have led to an underestimation rather than an overestimation of the prevalence of problems reported.

Furthermore, in the control group, we did not find significant relationships between gray and white matter structure and VMI scores, consistent with previous reports from our group. However, a few studies do report significant structure–function relationships in healthy controls (see e.g., Squeglia et al., 2013), so it is thinkable that such correlations may also exist in term-born children.

Finally, our relatively small number of participants means that we have limited power to detect minor group and sex differences and must therefore interpret non-significant results with caution. Because of the limited sample size, differences in VLBW subgroups based on cut-off values for birth weight, gestational age, and other perinatal variables, were not investigated. Additional details on the reasons behind the VLBW would have been interesting to assess; for instance, whether individuals who experienced fetal growth restriction exhibit differential perinatal injuries or developmental trajectories.

Conclusions

Our results indicate an increased risk of visual–motor integration deficits in early adulthood for individuals born preterm with VLBW. Alterations in white matter tracts containing primary and secondary visual and motor fibers and reduced surface area of visual–perceptual cortical regions, both of which correlated to reduced test scores, may indicate a structure–function relationship that entails both long-lasting

effects of early perinatal brain injury and persistent visual–motor perceptual deficits in VLBW individuals who have reached young adulthood.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.01.019.

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Supplementary Material

Supplementary Table S1. Newborn clinical information for the VLBW group. Data available on n, range, mean values ± standard deviation.

	VLBW (n=47)		
	n, data available	Range	Mean ± SD
Days spent in NICU	46	23-386	75.3 ± 57.2
Days on ventilator	46	0-63	4.5 ± 11.5
Days before birth weight regained	37	3-39	16.2 ± 8.3

Abbreviations: NICU, neonatal intensive care unit; VLBW, very low birth weight.

Supplementary Table S2. Proportion (%) of cortical surface area in regions of interest showing significant relationships between cortical thickness and scores on VMI tests (copying, motor, visual) in the VLBW cohort.

Cortical region of interest	Copying		Motor		Visual	
	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
Banks of the superior temporal gyrus	0	0	0	0	88	98
Caudal anterior cingulate gyrus	0	0	0	0	0	0
Caudal middle frontal gyrus	0	0	0	0	34	7
Cuneus	0	0	0	0	76	27
Entorhinal cortex	0	0	0	0	0	32
Fusiform gyrus	0	0	0	0	22	52
Inferior parietal gyrus	0	0	0	0	65	70
Inferior temporal gyrus	0	0	0	0	21	7
Insula	0	0	0	0	43	63
Isthmus cingulate	0	0	0	0	11	4
Lateral occipital gyrus	0	0	0	0	75	43
Lateral orbitofrontal gyrus	0	0	0	0	2	10
Lingual gyrus	0	0	0	0	34	25
Medial orbitofrontal gyrus	0	0	0	0	0	0
Middle temporal gyrus	0	0	0	0	24	29
Parahippocampal gyrus	0	0	0	0	1	1
Paracentral gyrus	0	0	0	0	25	29
Pars opercularis	0	0	0	0	58	12
Pars orbitalis	0	0	0	0	0	78
Pars triangularis	0	0	0	0	36	35
Pericalcarine sulcus	0	0	0	0	75	20
Postcentral gyrus	0	0	0	0	82	69
Posterior cingulate	0	0	0	0	31	17
Precentral gyrus	0	0	0	0	14	7
Precuneus	0	0	0	0	62	26
Rostral anterior cingulate	0	0	0	0	0	0
Rostral middle frontal gyrus	0	0	0	0	5	13
Superior frontal gyrus	0	0	0	0	3	0
Superior parietal gyrus	0	0	0	0	46	40
Superior temporal gyrus	0	0	0	0	12	94
Supramarginal gyrus	0	0	0	0	33	32
Frontal pole	0	0	0	0	0	0
Temporal pole	0	0	0	0	0	96
Transverse temporal gyrus (Heschl's gyrus)	0	0	0	0	38	100

Table S1. The table presents the percentage of cortical surface area in each of the parcellations (from the FreeSurfer Desikan-Killiany parcellation scheme) that showed a significant result (after FDR correction) in the GLM testing for a relationship between the VMI tests and cortical thickness in the VLBW cohort. The GLMs were fitted with cortical thickness as dependent variable, sex as categorical predictor, and age at MRI scan and one of the VMI test scores as continuous predictors. Contrast vectors were set to test for a relationship between performance on each of the VMI tests (copying, motor, visual) and cortical thickness.
Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight; VMI, Beery-Buktenica Developmental Test of Visual-Motor Integration-V.

Paper II

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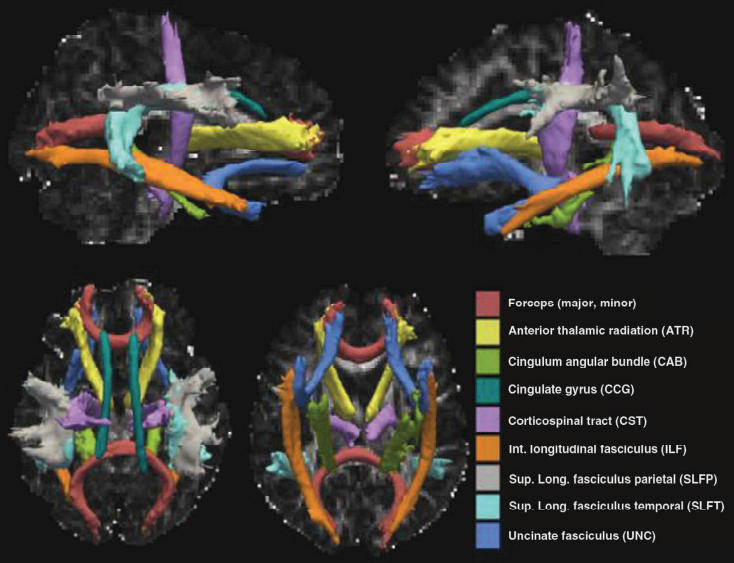

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Limited microstructural and connectivity deficits despite subcortical volume reductions in school-aged children born preterm with very low birth weight

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ABSTRACT

Preterm birth and very low birth weight (VLBW, ≤1500 g) are worldwide problems that burden survivors with lifelong cognitive, psychological, and physical challenges. In this multimodal structural magnetic resonance imaging (MRI) and diffusion MRI (dMRI) study, we investigated differences in subcortical brain volumes and white matter tract properties in children born preterm with VLBW compared to term-born controls (mean age = 8 years). Subcortical brain structure volumes and cortical thickness estimates were obtained, and fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were generated for 18 white matter tracts. We also assessed structural relationships between white matter tracts and cortical thickness of the tract endpoints. Compared to controls, the VLBW group had reduced volumes of thalamus, globus pallidus, corpus callosum, cerebral white matter, ventral diencephalon, and brain stem, while the ventricular system was larger in VLBW subjects, after controlling for age, sex, IQ, and estimated total intracranial volume. For the dMRI parameters, group differences were not significant at the whole-tract level, though pointwise analysis found shorter segments affected in forceps minor and left superior longitudinal fasciculus – temporal bundle. IQ did not correlate with subcortical volumes or dMRI measures in the VLBW group. While the deviations in subcortical volumes were substantial, there were few differences in dMRI measures between the two groups, which may reflect the influence of advances in perinatal care on white matter development.

Introduction

Preterm birth (gestational age < 37 weeks) is a worldwide problem, affecting 15 million newborns each year and burdening many survivors with lifelong cognitive, psychological, and physical challenges (Chang et al., 2013; Lawn et al., 2014; Saigal and Doyle, 2008). Advances in perinatal care, including the introduction of surfactant therapy for preterm infants, led to improved survival rates starting in the 1990s (Wilson-Costello et al., 2005). While survival rates have improved and prevalence of severe focal brain injuries, including intraventricular hemorrhages grades III and IV and cystic periventricular leukomalacia, has decreased, adverse long-term neurological outcomes are common in preterm-born individuals (Ferriero, 2004; Back et al., 2007). Low IQ and poorer attention/executive functions and academic outcomes have frequently been associated with very low birth weight (VLBW, birth weight ≤ 1500 g) and preterm birth (Løhaugen et al., 2010; Aarnoudse-Moens et al., 2009; Lund et al., 2012). Diffuse white matter injury including axonal abnormalities and gliosis is considered the dominant neuropathology in preterm-born infants and is believed to underlie many of these cognitive and sensorimotor deficits (Volpe et al., 2011; Haynes et al., 2011).

White matter near the lateral ventricles and in centrum semiovale has long been known to be especially vulnerable to perinatal injury

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among preterm-born individuals (Banker and Larroche, 1962), and hypoxia-ischemia and inflammation are considered the underlying causes behind periventricular white matter injury in preterms (Ortinau and Neil, 2015). Diffusion magnetic resonance imaging (dMRI), which measures Brownian motion of water diffusion of white matter bundles in the brain (Le Bihan and Johansen-Berg, 2012; Johansen-Berg and Behrens, 2014), has been used to identify white matter tracts that appear particularly sensitive to the effects of preterm birth and VLBW, such as corpus callosum and long-range association tracts (Counsell et al., 2008; Constable et al., 2008; Skranes et al., 2007; Eikenes et al., 2011; Ment et al., 2009; Mento and Bisiacchi, 2012; Hintz and O'Shea, 2008).

In line with the widely reported "encephalopathy of prematurity" of diffuse white matter injury and tissue loss typical among preterms, deviations in volumes of subcortical structures have also been reported in the VLBW population (Volpe, 2009; Boardman et al., 2010). Cerebral white matter, thalamus, globus pallidus, nucleus accumbens, and corpus callosum volumes may be vulnerable to neonatal risk factors such as VLBW (Bjuland et al., 2014). Deep gray matter abnormalities have been found in tandem with diffuse white matter injury among infants (Boardman et al., 2006), toddlers (Lowe et al., 2011), and school-aged children (Murray et al., 2014).

In a recent paper (Sølsnes et al., 2015), we reported significant differences in cortical architecture in our cohort of term-born controls recruited from the Norwegian Mother and Child Cohort Study and VLBW children born between 2001 and 2007, with increased cortical thickness frontally and occipitally, and reduced cortical surface area in widespread regions in the VLBW group, consistent with previous reports from year cohorts of VLBW teenagers born in 1986–88 (Skranes et al., 2007, 2013; Eikenes et al., 2011; Bjuland et al., 2013; Martinussen et al., 2005). It is not known whether these cortical deviations are secondary to the reported abnormalities in white matter tracts connected to these cortical regions or represent primary cortical injury.

This study therefore aimed to investigate subcortical volumes, white matter properties, and possible relationships between white matter tracts and the cortical changes previously reported in the same cohort of school-aged children. We explored group differences in fractional anisotropy and diffusivity using TRACULA, a novel tool for automated reconstruction of 18 major white matter tracts, as well as subcortical structure volumes using FreeSurfer. Moreover, we assessed structural relationships between white matter tracts of interest and cortical thickness of the tract endpoints. We also investigated possible relationships between neuroimaging findings and full-scale IQ scores and perinatal risk factors.

Methods

Participants

VLBW group

Preterm-born VLBW subjects (birth weight ≤ 1500 g), born between 2003 and 2007, were recruited based on admittance to the Neonatal Intensive Care Unit at St. Olav's University Hospital in Trondheim, Norway. Sixty-three children were invited and 57 agreed to participate in the study (Fig. 1). Age ranged from 5.0 to 10.5 years old (mean age =

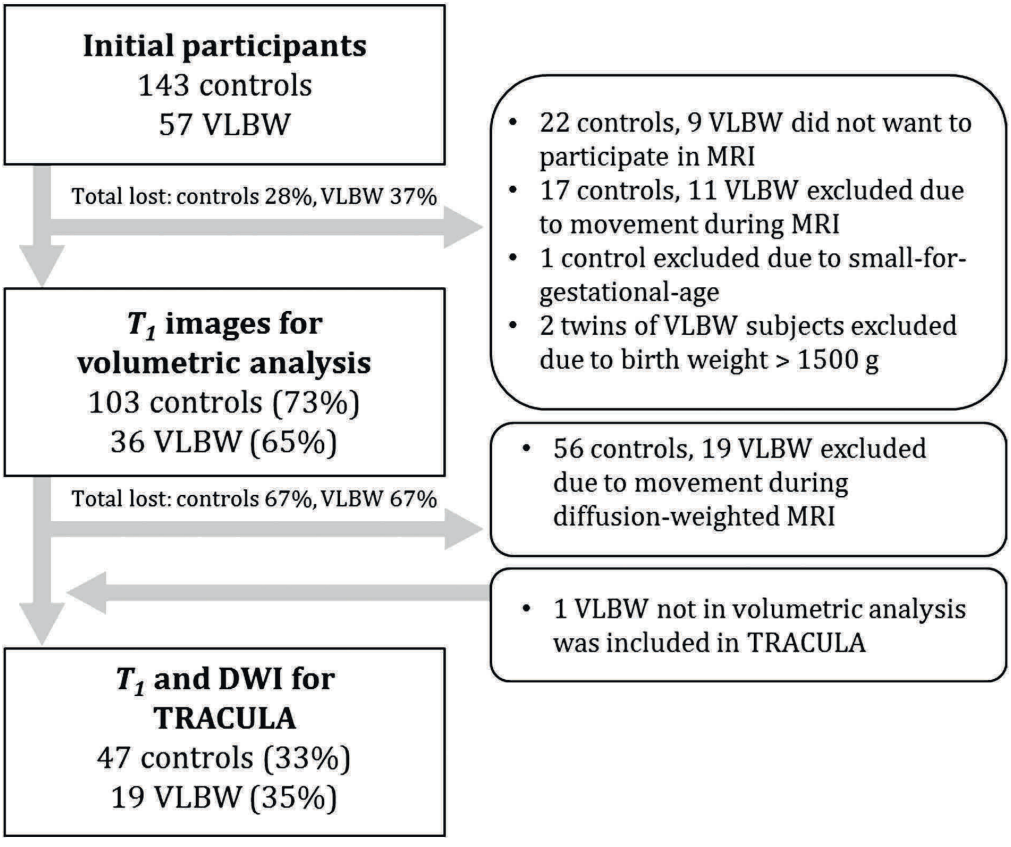

Fig. 1. Overview of participation and retention. Abbreviations: DWI: diffusion-weighted imaging; VLBW: very low birth weight.

7.8 years). Exclusion criteria were severe cerebral palsy (unable to complete neuropsychological testing and MRI), severe sensory impairments, and/or MRI contraindications. One child with retinopathy of prematurity and one with grade 1 intraventricular hemorrhage and mild cerebral palsy who successfully completed the neuropsychological assessments and MRI were included in the analyses. Perinatal health data collected included gestational age, birth weight, Apgar score (at 1 and 5 min), and number of days on mechanical ventilator after birth. Thirty-six VLBW subjects had successful structural MRI and were included in the subcortical volume analysis, and 19 with high-quality diffusion data were included in the dMRI analysis.

Control subjects

The control subjects were recruited from the national Norwegian Mother and Child Cohort Study, managed by the Norwegian Institute of Public Health (Magnus et al., 2006), and born between 2001 and 2007. Age ranged from 5.3 to 10.7 years old (mean age = 8.3 years). Control participants were living in the same geographical area as the VLBW participants and had normal/corrected vision and hearing. Exclusion criteria were current psychiatric treatment, use of psychoactive drugs known to affect central nervous system functioning, birth weight below 2500 g, and/or MRI contraindications. Subcortical volume analysis included 103 control subjects, and 47 controls were included in the dMRI analysis based on quality of their diffusion data (Fig. 1).

Cognitive measures

VLBW subjects were assessed with complete versions of age-appropriate standardized Wechsler intelligence tests: Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) (Wechsler, 2002) or Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler, 2003). Controls were assessed with short forms of the corresponding age-appropriate tests: WPSSI-III (four subtests) or Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Full-scale IQ scores were used for analysis. At neuropsychological assessment, parents reported whether children had received or planned to receive extra help, such as aid of an assistant or help with specific subjects, at school/preschool.

Socio economic status

Hollingshead's (1957) two factor index of social position based on education and occupation of one parent or the mean index of both was used to calculate socioeconomic status.

MRI

MRI data were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner (Siemens, Erlangen, Germany). The total scan time was on average 30 min. The pulse sequence used for morphometric analyses was a 3D T_1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) scan with the following parameters: TR = 2400 ms, TE = 3.61 ms, TI = 1000 ms; flip angle 8°, FOV 240 × 240 mm^2, and TA = 4 min and 18 min. Each volume consisted of 160 sagittal slices with voxel sizes of 1.25 × 1.25 × 1.20 mm^3.

dMRI was acquired using a conventional 2D single shot balanced-echo EPI sequence. The series acquired diffusion weighting along 30 non-collinear directions (b = 700 s/mm^2), and with 6 images acquired without diffusion weighting (b = 0). The acquisition parameters were: TR = 7700 ms, TE = 70 ms, FOV 256 × 256 mm^2, matrix size 128 × 128, TA = 4:22, BW = 1396 Hz/px, and GRAPPA acceleration factor 2, slice thickness 2 mm. Number of slices was 64 (no gap), with isotropic voxels of 2 × 2 × 2 mm^3.

Each MPRAGE series and the dMRI data were visually inspected, and only scans with no or minimal movement artifacts were included in the analyses. Calculation of head motion during dMRI was done as a part of the TRACULA quality control processing (Yendiki et al., 2013).

Image analysis

All image analysis, including subcortical volumetric segmentation and dMRI analysis, was performed with the freely available FreeSurfer image analysis suite version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). The technical details of the FreeSurfer image processing procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 1999a; Fischl et al., 1999b; Fischl et al., 2004b; Han et al., 2006; Jovicich et al., 2006; Ségonne et al., 2004). The subcortical volumetric analysis was based on MRI from 37 VLBW children and 103 controls. The subcortical brain structures included in the analyses (see Table 2) were based on the automated segmentation and labeling procedure in FreeSurfer (Fischl et al., 2002, 2004a), and each structure's volumes from both hemispheres were combined to generate a bilateral volume value. For subcortical volumes, analyses were controlled for estimated total intracranial volume (Buckner et al., 2004).

TRACULA

TRACULA (TRActs Constrained by UnderLying Anatomy), as implemented in FreeSurfer 5.3.0, was used for dMRI analysis and tractography (Yendiki et al., 2011). Briefly, TRACULA applies probabilistic tractography to diffusion data using an anatomical atlas of white matter tracts as well as the subcortical segmentation labels from FreeSurfer (Fischl et al., 2002, 2004a). TRACULA contains an algorithm for automated global probabilistic tractography that estimates the posterior probability of 18 pathways, based on a "ball-and-stick" model of diffusion (Behrens et al., 2007) as well as a pathway prior term, which incorporates prior anatomical knowledge on the pathways from a set of healthy adult training subjects. The prior term expresses the probability of each pathway to pass through, or lie adjacent to, each anatomical segmentation label, calculated separately for every point along the pathway's trajectory. The anatomical segmentation labels come from the cortical parcellation and subcortical segmentation of T_1-weighted MPRAGE images in FreeSurfer. Nineteen VLBW children and 47 controls were included in the TRACULA analyses based on quality of diffusion data. One subject was missing data for forceps major, right corticospinal tract, and right cingulate gyrus, but the remaining values were used for group-level analysis. Eighteen of 19 subjects from the dMRI analysis were also included in the subcortical volume analysis, while one VLBW subject with too poor subcortical data to be analyzed in the volume analysis could be included in TRACULA (see Fig. 1).

Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were assessed in the 18 white matter pathways reconstructed by TRACULA (see Fig. 2): anterior thalamic radiation (ATR) left and right, cingulum–angular (infracallosal) bundle (CAB) left and right, cingulum–cingulate gyrus, (supracallosal) bundle (CCG) left and right, corticospinal tract (CST) left and right, corpus callosum forceps major, corpus callosum forceps minor, inferior longitudinal fasciculus (ILF) left and right, superior longitudinal fasciculus–parietal bundle (SLFP) left and right, superior longitudinal fasciculus–temporal bundle (SLFT, also called arcuate fasciculus) left and right, and uncinate fasciculus (UNC) left and right.

Tract endpoint cortical thickness analysis

In order to explore the relationship between white matter tracts and cortical thickness, we projected the endpoints of the various tracts onto the cortical surface to assess the correlations between dMRI measures from those tracts and the corresponding patch of cortical thickness in the subjects' native space. We obtained regions of interest for the endings of the 18 pathways on the cortical surface by mapping the probability distribution of each of the two end regions of each pathway, as computed by TRACULA, from its native diffusion-weighted imaging (DWI) space to the space of the same subject's T_1-weighted image. We projected the tract endpoints onto the gray/white matter surface by sampling along the surface normal vector, anywhere within 6 mm

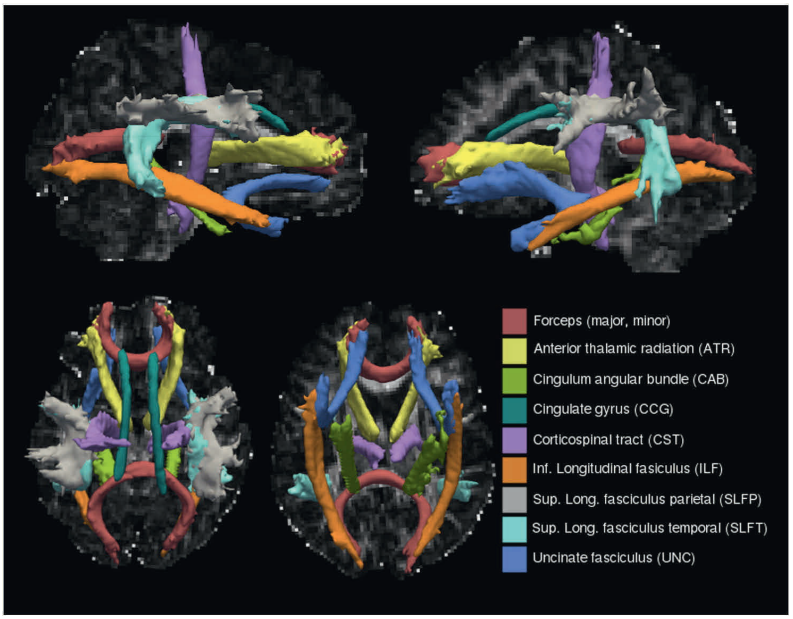

Fig. 2. Probabilistic reconstruction of 18 white matter tracts generated by TRACULA, illustrated here in a control subject.

(3 DWI-space voxels) of the gray/white junction, and then smoothing along the surface with a 2D Gaussian kernel of 6 mm full width at half max.

Tractography pointwise analysis

TRACULA estimates the posterior probability distribution of each pathway in the native DWI space of each subject and finds the maximum probability path, which is a 1D curve in that space. It then calculates the expected value of FA, MD, RD, or AD as a function of position along the pathway by performing a weighted average of the values of each of these four measures at each cross-section of the pathway. These cross-sections are defined at each voxel along the maximum probability path. This yields a 1D sequence of values for each of the four measures, computed in the native space of each subject. These sequences can be used for pointwise analyses of each measure along the trajectory of a pathway.

In order to control the false positive rate, we have chosen to report findings only if they showed significant group differences ($p < 0.05$) over a contiguous segment of length greater than 2 cm along a given pathway.

Statistical analysis

Matlab software suite 2011b (MATLAB and Statistics Toolbox Release 2011b. The MathWorks, Inc., Natick, Massachusetts, USA) was used for statistical analyses of subcortical and cortical morphometry and dMRI data. The software package IBM SPSS 21 (Chicago, USA) was used to generate group difference values and correlations between morphometric, dMRI, IQ, and clinical measures. General linear models were fitted for group comparisons of subcortical brain structure volumes and dMRI data, controlled for age at scan, sex, and IQ; subcortical volume analyses were additionally controlled for estimated total intracranial volume as computed by FreeSurfer. Partial correlation tests, controlled for age at scan and sex, were used to investigate the relationships between morphometry and dMRI and IQ and perinatal data. Data with non-equal variances were analyzed with non-parametric tests and Spearman's ρ. Group analysis for categorical data were tested for significance using Fisher's exact test. Tests for group × age interaction effects were performed for all subcortical structures and for FA, MD, RD, and AD in the white matter tracts. Holm–Bonferroni step-down (Holm, 1979) was used to correct for multiple comparisons for all tests of group differences and correlations.

Ethics

The Regional Committee for Medical Research Ethics approved the study protocol (project number: 2010/2359), and written, informed consent was obtained from the parents/guardians of all participants.

Results

Clinical and cognitive results

Clinical characteristics and full-scale IQ scores are presented in Table 1a and b. VLBW subjects were approximately 6 months younger than control subjects (7.7 vs 8.3 years) in the subcortical sample, while the groups had mean ages of 8.5 and 8.7 years, respectively, in the TRACULA sample. Additional perinatal characteristics for the VLBW group are presented in Table S1.

Full-scale IQ scores were significantly lower in the VLBW group than in controls by approximately 1 standard deviation from control mean, both in the subcortical volume analysis (99 vs 108) and in the dMRI analysis (97 vs 112). IQ scores were still significantly lower in the VLBW group after additionally controlling for socioeconomic status ($p < 0.001$). Controls in the TRACULA analysis had slightly higher IQ scores (4.0 points) than controls in the subcortical volume analysis, but VLBW IQ scores were similar between the analyses. The VLBW group received more help in school and preschool than controls ($p < 0.0001$). The control group had slightly higher average socioeconomic score than the VLBW group.

Subcortical volumes

Compared to controls and after controlling for age, sex, and estimated total intracranial volume, the VLBW group had significantly reduced volumes of thalamus, globus pallidus, hippocampus, cerebral white

Table 1
Overview of major clinical variables and full IQ scores in control and VLBW groups, shown for both (a) subcortical and (b) dMRI analyses.

1a. Subcortical analysis	VLBW (n = 36)			Control (n = 103)			*p*-value
	Mean	SD	Range	Mean	SD	Range	
Birth weight, grams	1019	361	416–1495	3661	485	2510–4950	<0.0001
Gestational age, weeks (days)	29 (0)	2 (6)	23 (4)–35 (1)	Term-born			–
Age at MRI, years	7.8	1.7	5.0–10.5	8.3	1.0	5.3–10.7	0.04
Full-scale IQ	99	9.9	82–132	108	13.6	73–139	<0.001
Socioeconomic status (n = 34, 84)	3.9	0.9	1–5	4.3	0.8	2–5	0.03
Sex: male/female	16/20			49/54			0.8
Subjects with twin	6			0			<0.0001
Received extra help at school, n (%)	10 (28%)			2 (1.9%)			<0.0001
1b. dMRI analysis	**VLBW (n = 19)**			**Control (n = 47)**			***p*-value**
	Mean	SD	Range	Mean	SD	Range	
Birth weight, grams	1103	365	500–1495	3692	531	2550–4950	<0.0001
Gestational age, weeks (days)	29(4)	3(1)	23(4)–35(1)	Term-born			--
Age at MRI, years	8.5	1.2	5.0–10.5	8.7	0.7	7.5–10.6	0.3
Full-scale IQ	97	8.1	82–117	112	13.7	73–134	<0.0001
Socioeconomic status (n = 18, 39)	4.0	0.9	2–5	4.4	0.8	2–5	0.07
Sex: male/female	9/11			22/25			0.9
Subjects with twin	4			0			0.005
Received extra help at school, n (%)	4 (21)			1 (2.1)			0.1

Displayed with *p*-values based on ANOVA between control and VLBW groups. Abbreviations: SD, standard deviation; VLBW, very low birth weight.

matter, ventral diencephalon, brain stem, and in 4 of 5 corpus callosum subsegmentations (Table 2). The ventricular system, comprising lateral, inferior, third, and fourth ventricles, was larger in VLBW subjects. Fig. 3 illustrates the extent of the volume reductions as a percentage of the control group mean for the brain structures that were significantly smaller in the VLBW group.

Partial correlation analysis examined relationships between subcortical volumes and birth weight, gestational age, and IQ, controlled for age and sex and with Holm–Bonferroni step-down. Among VLBW subjects, corpus callosum posterior subsegmentation volume correlated significantly to gestational age ($R = 0.55$, $p = 0.0007$), and cerebellum white matter volume correlated positively to birth weight ($R = 0.53$, $p = 0.001$). No other correlations to gestational age, birth weight, or IQ in the VLBW group reached significance. In controls, birth weight correlated significantly to volumes of cerebellar white matter ($R = 0.49$, $p < 0.0001$), cerebellar gray matter ($R = 0.36$, $p = 0.0002$) and brain stem ($R = 0.42$, $p < 0.0001$). IQ correlated to volumes of thalamus ($R = 0.37$, $p < 0.0001$), hippocampus ($R = 0.35$, $p < 0.0001$), and cerebral white matter ($R = 0.37$, $p < 0.0001$). In the VLBW group, receiving help at school was correlated negatively with corpus callosum volume ($R = -0.46$, $p = 0.008$, uncorrected), but this relationship was not seen in controls. Correlation in controls between IQ and hippocampus volume was not significant after correction for socioeconomic status, and correlations in both groups were not significant with correction for estimated total intracranial volume. There were no significant group × age interaction effects for subcortical structure volumes.

TRACULA results

Group differences

To assess differences in white matter microstructure between the groups, we compared the VLBW group to the control subjects in terms of FA, MD, RD, and AD in the 18 tracts generated by TRACULA. Means and *p*-values for the dMRI measures for tracts with significant group differences are presented in Table 3.

Table 2
Bilateral subcortical volumes (mm^3) in VLBW and control subjects with *p*-values for group differences.

Structure	VLBW		Control		*p*-value
	mean	95% CI	mean	95% CI	
Amygdala	2840	(2752, 2928)	2858	(2808, 2908)	0.73
Brain stem	17,854	(17,373, 18,333)	18,974	(18,700, 19,247)	0.00015*
Caudate	8099	(7811, 8386)	8128	(7963, 8291)	0.87
Cerebellar cortex	113,842	(110,519, 117,164)	113,978	(112,084, 115,872)	0.95
Cerebellar white matter	23,376	(22,552, 24,200)	24,527	(24,056, 24,996)	0.021
Cerebral white matter	400,892	(392,985, 408,799)	420,230	(415,722, 424,737)	7.5×10^{-5}*
Corpus callosum anterior	759	(719, 798)	806	(784, 828)	0.045
Corpus callosum central	317	(292, 341)	391	(377, 404)	9.4×10^{-7} *
Corpus callosum mid-anterior	349	(324, 373)	404	(390, 418)	0.00029*
Corpus callosum mid-posterior	301	(276, 325)	384	(370, 398)	9.6×10^{-8}*
Corpus callosum posterior	660	(619, 700)	774	(751, 796)	5.1×10^{-6}*
Globus pallidus	3499	(3383, 3614)	3751	(3684, 3816)	0.00040*
Hippocampus	7908	(7694, 8121)	8265	(8143, 8386)	0.0059
Nucleus accumbens	1356	(1293, 1418)	1395	(1359, 1430)	0.30
Putamen	11,722	(11,332, 12,111)	11,966	(11,743, 12,188)	0.30
Thalamus	14,039	(13,739, 14,338)	14,703	(14,532, 14,873)	0.00031*
Ventral diencephalon	6859	(6708, 7009)	7109	(7023, 7194)	0.0062*
Ventricular system	20,766	(18,306, 23,225)	11,932	(10,529, 13,333)	1.7×10^{-8}*

Group differences tested using the general linear model, controlled for age, sex, and estimated total intracranial volume. Holm–Bonferroni step-down used to determine significance threshold; significant results denoted by *. Abbreviations: CI, confidence interval; VLBW, very low birth weight.

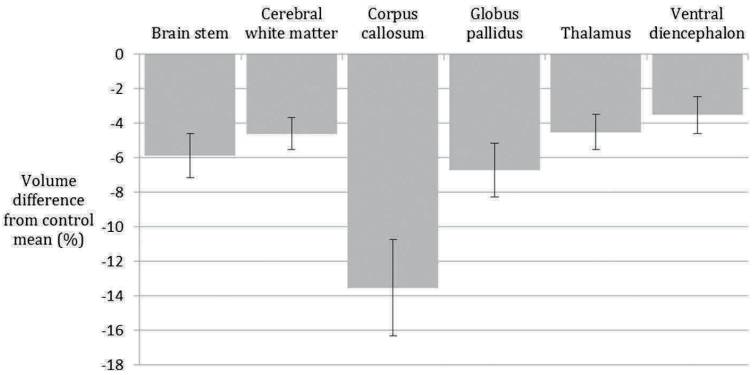

Fig. 3. VLBW subcortical volumes as percentage difference from control mean. Volumes controlled for age, sex, and estimated total intracranial volume. Corpus callosum volume aggregated from all 5 subsegmentations.

No group differences were significant after Holm–Bonferroni step-down, though group differences in several structures were nominally significant at the uncorrected $p < 0.05$ level. The VLBW group showed higher AD in the left SLFP and SLFT, left and right CST, and left CAB. The VLBW group had higher average FA in left CST and in left SLFT. RD was lower in the VLBW group in left CST. Control and VLBW groups did not differ in terms of head motion. There were no correlations after Holm–Bonferroni step-down between dMRI values and subcortical volumes in either group, and there were no significant group × age interaction effects for any of the tracts with nominally significant group differences.

Relationships between dMRI and clinical variables

In relating FA, MD, RD, and AD in all 18 tracts to full-scale IQ, birth weight, and gestational age, we found significant correlations after Holm–Bonferroni step-down in AD in left CAB in the VLBW group with gestational age ($R = 0.86$, $p < 0.0001$). In the control group, birth weight correlated with MD ($R = 0.49$, $p = 0.0009$) and AD ($R = 0.46$, $p = 0.002$) in the right SLFP and AD in the left uncinate fasciculus ($R = 0.52$, $p = 0.0004$). Post-hoc analysis revealed that the number of days VLBW subjects spent on a ventilator after birth correlated negatively with forceps major FA ($R = 0.89$, $p < 0.001$) and positively with forceps major RD ($R = 0.85$, $p < 0.001$), with the five subjects who were on mechanical ventilator in the neonatal period driving the correlations. No other correlations survived Holm–Bonferroni step-down.

Tract endpoint cortical thickness analysis

None of the correlations between dMRI measures and tract endpoint cortical thickness reached significance after Holm–Bonferroni correction for multiple comparisons. However, there were several nominally significant correlations ($p < 0.05$, uncorrected) (Fig. 4). In controls, cortical thickness in the left SLFP parietal endpoint correlated with mean tract MD ($R = 0.30$, $p = 0.046$) and RD ($R = 0.34$, $p = 0.024$), and cortical thickness in the right SLFT temporal endpoint also correlated with mean tract RD ($R = 0.32$, $p = 0.034$). In the VLBW group, right ATR frontal endpoint cortical thickness correlated with mean tract RD ($R = 0.56$, $p = 0.024$); left CCG cortical thickness in the posterior endpoint correlated with mean tract AD ($R = 0.67$, $p = 0.0044$), RD ($R = -0.51$, $p = 0.045$), and FA ($R = 0.61$, $p = 0.0013$); right ILF cortical thickness in the occipital endpoint correlated with mean tract

Table 3
Mean values for FA, MD, RD, and AD in both groups and Cohen's *d* and *p*-values for group differences.

White matter tract	FA				MD [$\times 10^{-4}$ mm^2/s]				RD [$\times 10^{-4}$ mm^2/s]				AD [$\times 10^{-4}$ mm^2/s]			
	VLBW mean	Control mean	d	*p*-value	VLBW mean	Control mean	d	*p*-value	VLBW mean	Control mean	d	*p*-value	VLBW mean	Control mean	d	*p*-value
ATR, left	0.44	0.45	−0.44	0.26	7.9	7.9	0.18	0.67	5.9	5.8	0.31	0.46	12.0	12.0	−0.10	0.82
ATR, right	0.44	0.44	−0.23	0.59	8.0	8.0	0.14	0.74	6.0	5.9	0.08	0.84	12.1	12.1	0.14	0.74
CAB, left	0.35	0.37	−0.78	0.07	8.4	8.5	−0.17	0.68	6.8	6.7	0.29	0.49	11.7	12.0	−1.01	0.018*
CAB, right	0.38	0.39	−0.20	0.63	8.3	8.3	−0.24	0.57	6.5	6.5	−0.02	1.00	11.8	11.9	−0.52	0.22
CCG, left	0.54	0.54	−0.05	0.90	7.8	7.7	0.44	0.29	5.3	5.1	0.35	0.40	12.9	12.8	0.18	0.67
CCG, right	0.47	0.47	0.03	0.92	7.8	7.8	0.19	0.64	5.6	5.6	0.10	0.81	12.1	12.0	0.14	0.73
CST, left	0.58	0.56	1.03	0.015*	7.9	7.9	−0.41	0.33	4.9	5.1	−1.00	0.018*	13.8	13.6	0.86	0.042*
CST, right	0.56	0.55	0.42	0.29	8.0	7.9	0.36	0.39	5.1	5.2	−0.19	0.65	13.7	13.5	0.85	0.045*
Forceps major	0.62	0.63	−0.25	0.55	8.2	8.2	0.09	0.83	4.8	4.7	0.24	0.56	15.0	15.1	−0.31	0.46
Forceps minor	0.59	0.61	−0.58	0.17	8.1	8.0	0.43	0.30	5.0	4.8	0.59	0.16	14.4	14.5	−0.27	0.51
ILF, left	0.52	0.51	0.23	0.57	8.4	8.4	−0.26	0.54	5.8	5.8	−0.24	0.56	13.6	13.7	−0.10	0.81
ILF, right	0.53	0.52	0.46	0.27	8.4	8.5	−0.29	0.49	5.7	5.8	−0.40	0.34	13.9	13.8	0.14	0.73
SLFP, left	0.45	0.44	0.44	0.28	7.9	7.8	0.59	0.16	5.9	5.9	0.07	0.87	11.9	11.6	1.17	0.0065*
SLFP, right	0.44	0.43	0.30	0.42	8.1	8.0	0.46	0.28	6.1	6.0	0.10	0.81	12.0	11.8	0.71	0.09
SLFT, left	0.49	0.47	0.93	0.034*	8.0	7.9	0.25	0.54	5.7	5.8	−0.32	0.45	12.5	12.2	1.23	0.0043*
SLFT, right	0.46	0.45	0.27	0.49	8.0	8.0	−0.04	1.00	5.9	6.0	−0.21	0.61	12.3	12.2	0.26	0.53
UNC, left	0.43	0.43	0.08	0.85	8.3	8.3	−0.10	0.82	6.3	6.3	−0.08	0.85	12.4	12.4	−0.05	0.90
UNC, right	0.45	0.46	−0.48	0.25	8.2	8.2	0.11	0.79	6.1	6.0	0.35	0.40	12.5	12.6	−0.37	0.37

* Denotes nominally significant (uncorrected) at the $p < 0.05$ level. Abbreviations: *d*, Cohen's *d*; AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; CST, corticospinal tract; ILF, inferior longitudinal fasciculus; UNC, uncinate fasciculus; ATR, anterior thalamic radiation; CCG, cingulum–cingulate gyrus bundle; CAB, cingulum–angular bundle; SLFP, superior longitudinal fasciculus–parietal bundle; SLFT, superior longitudinal fasciculus–temporal bundle; VLBW, very low birth weight.

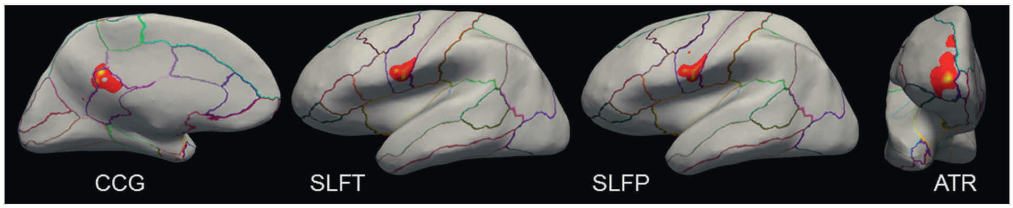

Fig. 4. Examples of projections of left CCG posterior endpoints, left SLFT frontal endpoints, left SLFP frontal endpoints, and right ATR frontal endpoints onto inflated cortical surface, illustrated in a control subject. The red–yellow overlays are the probability distributions of the position of the endings of the corresponding pathways on the surface. Cortical parcellations are outlined based on the Desikan–Killiany atlas (Desikan et al., 2006). Abbreviations: ATR, anterior thalamic radiation, CCG, cingulum cingulate gyrus; SLFP, superior longitudinal fasciculus–parietal bundle; SLFT, superior longitudinal fasciculus–temporal bundle.

MD ($R = 0.62$, $p = 0.011$) and RD ($R = 0.54$, $p = 0.030$); left SLFT cortical thickness in the frontal endpoint correlated with mean tract MD ($R = 0.64$, $p = 0.0076$) and RD ($R = 0.53$, $p = 0.036$); and cortical thickness in the left UNC orbitofrontal endpoint correlated with mean tract MD ($R = 0.57$, $p = 0.021$), RD ($R = 0.79$, $p = 0.00026$), and FA ($R = -0.76$, $p = 0.0007$). Group differences in cortical thickness based on the 34 anatomical regions for each brain hemisphere defined in FreeSurfer were previously reported by Sølsnes et al. (2015).

CCG posterior endpoints were primarily in the isthmus cingulate cortex, and to a lesser extent in adjacent posterior cingulate and precuneus. SLFT and SLFP frontal cortex endpoints were primarily in the precentral gyrus and to a very limited extent in nearby pars opercularis. Cortical ATR endpoints were found in the rostral middle frontal gyrus.

Tractography pointwise analysis

To better localize affected white matter along the various tracts, we conducted a pointwise analysis to identify tract segments with significant group differences ($p < 0.05$) contiguously along at least 2 cm of the tract. The forceps minor showed lower FA and higher RD in the VLBW group along a medial segment of the tract. Left SLFT along the middle of the tract showed higher AD in the VLBW group, which drove the nominally significant group differences in that tract. Additionally, AD in the VLBW group was also higher in two sections of the middle of the right SLFT but did not reach the 2 cm significance threshold.

Discussion

This follow-up study of school-aged children born in the 2000s, comparing those born preterm with VLBW and a term-born control group, found smaller volumes of thalamus, globus pallidus, hippocampus, cerebral white matter, ventral diencephalon, brain stem, and corpus callosum, along with an enlarged ventricular system, in the VLBW group. VLBW subjects had lower FA in a medial segment of forceps minor and higher AD in the middle of the left SLFT, but dMRI measures did not differ significantly between groups at the whole-tract level. Gestational age and birth weight in the VLBW group were generally not associated with subcortical volumes, and IQ did not correlate with either subcortical volumes or dMRI measures in the VLBW group.

Subcortical structure volumes

We found smaller subcortical volumes and larger ventricles in the VLBW group compared to controls, in agreement with earlier reports (Miller et al., 2005; Inder et al., 2003). The VLBW children had reduced volumes of subcortical gray matter, such as thalamus and globus pallidus, and of cerebral white matter including corpus callosum. The increase in ventricular size in preterms is likely due to perinatal deep white matter loss influencing the volume and microstructural characteristics of central white matter tracts (Volpe, 2009; Verney et al., 2012; Judas et al., 2005). Abnormal thalamus microstructure and smaller thalamus (Nagasunder et al., 2011), hippocampus (Aanes et al., 2015), globus pallidus (Lax et al., 2013), and cerebral white matter (Taylor et al., 2011) have been reported in the preterm-born population and may reflect neuron loss and injury to myelinated axons. At their young adulthood follow-up (Bjuland et al., 2014), our older study cohort born in 1986–1988 also showed significant volume reductions in thalamus, cerebral white matter, and the posterior parts of corpus callosum, similar to the findings presented here. This similarity may reflect the influence of *in utero* developmental processes, such as intrauterine growth restriction, on subcortical structures, with consequences for postnatal brain growth.

A complex constellation of neuropathological factors influences brain and cognitive development among preterm VLBW individuals through encephalopathy of prematurity (Volpe, 2009), affecting both gray and white matter. Boardman et al. (2010) described a "common neonatal image phenotype" among children born preterm, consisting of diffuse white matter injury and tissue loss localized to the dorsomedial nucleus of the thalamus, globus pallidus, white matter of the corona radiata, posterior periventricular white matter, and the central region of the centrum semiovale. Moreover, this abnormal phenotype was associated at 2 years of age with reduced developmental quotient, suggesting that the influence of white matter injury on the development of basal ganglia and thalami could have functional consequences (Boardman et al., 2010). Our findings related to lower IQ and greater need for help at school are consistent with this model of restricted growth of the preterm brain in terms of impacts on subcortical volumes and long-term functional deficits. We speculate that this persistent postnatal growth restriction of the brain may be due to a continuation of mechanisms causing intrauterine growth failure, in line with previous studies showing a relationship between lower IQ scores in young adults born small for gestational age with intrauterine growth restriction (Løhaugen et al., 2013; Østgård et al., 2014).

dMRI findings

In contrast to previous reports, the VLBW and control groups had similar FA, MD, AD, and RD values in the 18 white matter tracts assessed in this study. Group differences were only nominally significant and limited to left SLFT (for FA and AD), left SLFP (for AD), left CST (for FA and AD), right CST (for AD), and left CAB (for AD). We previously described (Sølsnes et al., 2015) in an overlapping group from the same cohort significant surface area reductions among VLBW children in the left precentral gyrus, where we found a portion of the SLFP to terminate. Cortical thickness in the white matter tract endpoints demonstrated nominally significant correlations to dMRI values in several regions in frontal, temporal, parietal, and occipital lobes. Our previous report (Sølsnes et al., 2015) found significant differences in surface area and cortical thickness between the VLBW and control groups in the several of the same regions implicated in our cortical endpoint analysis.

Using pointwise analysis, we also identified specific segments of white matter tracts in the forceps minor and SLFT that showed greatest differences between groups on diffusivity measures. While the clinical significance remains to be established, these findings may indicate the localization of the initial perinatal brain injury or delayed myelination.

Changes in FA and diffusivity in superior longitudinal fasciculus (SLF) among individuals born preterm have been frequently reported during infancy, childhood, adolescence, and adulthood (Skranes et al., 2007; Pandit et al., 2013). The SLFT, which corresponds to the arcuate fasciculus, links Wernicke's and Broca's areas (Catani et al., 2002), and the SLFP connects parietal cortex and ventral premotor cortex, including posterior Broca's area (Rushworth et al., 2014). SLFT has been linked to phonological awareness and reading skills in children (Saygin et al., 2013; Yeatman et al., 2011), and both SLFT and SLFP have been hypothesized to be involved in mathematical processing (Jolles et al., 2015). Myall et al. (2013) described possible axonal straightening and increased axonal density in the SLFT, among other tracts, in case studies of adolescents born preterm with ventricular dilation. In our cohort, AD differences in the VLBW group in these long-range association tracts were still evident at early school age. AD and RD have been interpreted in various ways in the neuroimaging literature, including as signifiers of axonal injury and myelin loss (Song et al., 2002), though cautious interpretation of AD and RD is advised especially in clinical populations (Wheeler-Kingshott and Cercignani, 2009).

Similar to our findings, several other studies have also reported very limited difference in FA in preterms compared to controls in childhood (Feldman et al., 2012), adolescence (Frye et al., 2010), and adulthood (Kontis et al., 2009). Thompson et al. (2014) found global increases in MD, RD, and AD in a very preterm group compared to full-term infants, while FA was similar across the groups. Taylor et al. (2011) showed that both structural abnormalities and neuropsychological deficits were more pronounced in VLBW adolescents who were at higher neonatal risk based on birth weight, small for gestational age, severe abnormality on cranial ultrasound, or chronic lung disease, and FA has recently been more associated with complications of preterm birth than with extreme preterm birth in itself (Bonifacio et al., 2010).

In general, the limited dMRI pathology observed here in the VLBW group was somewhat surprising based on previous reports of widespread differences between preterms and controls in white matter tracts among children (Nagy et al., 2003), adolescents (Skranes et al., 2007; Mullen et al., 2011), and young adults (Allin et al., 2011; Eikenes et al., 2011). Although total brain growth is affected in this cohort, with smaller volumes, reduced surface area, and signs of possible cortical reorganization with frontal and occipital thickening (Sølsnes et al., 2015), diffusion measures in the preterm-born children appear similar to their peers born at term. We speculate that perinatal morbidity especially influences white matter development, and that the less severe perinatal morbidity seen in the more recent VLBW cohorts has resulted in fewer deviations in the microstructure of the remaining white matter (Favrais et al., 2014; Gagliardi et al., 2009).

Associations with cognitive performance

Our VLBW group generally scored within the normal IQ range, which was higher than previous study cohorts (Løhaugen et al., 2010). We did not find any relationship between IQ scores and dMRI findings in this study, although diffusion properties in white matter tracts among VLBW individuals have previously been linked to diverse cognitive deficits, ranging from IQ scores (Yung et al., 2007; Eikenes et al., 2011), language skills (Mullen et al., 2011), learning and memory (Salvan et al., 2014), to visual-motor function (Sripada et al., 2015). Significantly more VLBW children in our study received extra help at school or preschool compared to controls ($p < 0.0001$), indicating affected cognitive abilities. Muetzel et al. (2015) showed that white matter microstructure was associated with visual–spatial ability independent of general intelligence in a large sample (n = 778) of normally developing children at 6 to 10 years of age. It is also possible that VLBW individuals exhibit plasticity to develop different neural network trajectories and compensatory connections related to certain cognitive functions (Mürner-Lavanchy et al., 2014; Gozzo et al., 2009; Narberhaus et al., 2009; Van Braeckel et al., 2010; Ment et al., 2009). Focusing on visual–spatial skills, working memory, motor skills, or language-specific tasks, rather than general intelligence, may have detected additional structure-function relationships in our study sample.

Several of the subcortical structures implicated in our group differences analysis are involved in working memory networks. McNab and Klingberg (2008) identify the globus pallidus as essential for controlling access to working memory, while functional and structural imaging of basal ganglia and thalamus have recently shown promise in predicting healthy children's visuospatial working memory two years later (Ullman et al., 2014).

In our cohort born in the late 1980s, Bjuland et al. (2014) found that in VLBW young adults (mean IQ = 89) subcortical volumes correlated strongly with cognitive performance on full-scale IQ. Subcortical volumes in that VLBW group were also strongly associated with birth weight and days in the neonatal intensive care unit. The current study identified volume reductions in nearly all the same subcortical structures, yet the close relationship in the VLBW group to IQ was not apparent. An explanation for this lack of relationship may be the moderate sample size and normal mean IQ scores in the VLBW group.

In Norway, high-risk preterm infants and their families are entitled to special follow-up developmental health services. A quarter of our VLBW participants have had extra help in school or preschool, compared to only 2% of controls. It is plausible that the normal mean IQ score and connectivity in our VLBW group, compared to previous cohorts, reflect in part the availability of such higher-quality educational interventions, although the mean IQ score among VLBW children is still approximately one standard deviation lower than mean IQ in controls. As training and cognitive interventions have been shown to affect white matter (Scholz et al., 2009; Sampaio-Baptista et al., 2013; Hu et al., 2011), it would be worthwhile to explore the direct impact of the combination of advanced medical care and childhood follow-up services on white matter development and connectivity in the high-risk preterm-born population.

Strengths and limitations

The results presented here will provide a useful baseline for follow-up research on these VLBW and term-born cohorts. All subjects underwent structural MRI and dMRI on the same scanner with standardized sequences and were assessed with age-appropriate, standardized cognitive tests. We used TRACULA for reconstruction of major white matter tracts in subjects' native spaces and were able to combine cortical thickness and dMRI data to investigate possible impacts at the transition between white and gray matter. TRACULA's automated reconstruction is based on healthy adult training subjects but has also been used in pediatric populations (Yendiki et al., 2013; Saygin et al., 2013; Koldewyn et al., 2014). The validity of the anatomical data processing stream used in TRACULA for automated surface reconstruction and segmentation of structural images and its lack of age-related bias have been shown previously for children aged 4 to 7 (Ghosh, et al., 2010).

TRACULA includes corpus callosum forceps major and minor, but full corpus callosum segmentation is not available in the current version. Corpus callosum has been implicated in previous studies of VLBW children showing deficits in diverse cognitive skills and would have been an important complement to the 18 tracts described here. Corpus callosum volume, however, is included in our subcortical analysis. While diffusion values for group differences were taken across the entire tract, we examined pointwise to better localize affected white matter segments. Moreover, we chose to control for age and sex; however, larger studies

have shown associations between certain subcortical volumes and age and sex (Koolschijn and Crone, 2013). However, this was a cross-sectional study not intended to identify specific developmental changes within this age range, and the study sample was too small to investigate sex differences within groups.

DWI is very sensitive to motion inside the scanner, which poses a challenge especially for pediatric research. Due to movement artifacts in both groups, the sample available in the TRACULA analysis was about 47% the size of the sample used for subcortical volume analysis. Moreover, a recent estimate suggests that up to 60–90% of all white matter voxels contain multiple fiber orientations (Jeurissen et al., 2013). High-angular resolution diffusion imaging (HARDI) and diffusion spectrum imaging (DSI) are more sensitive than diffusion tensor imaging (DTI) for investigating fiber orientations in areas with crossing fibers (Abhinav et al., 2014; Groeschel et al., 2014) but require longer scan times to measure more diffusion directions, which increases the risk of data loss due to movement artifacts, especially in children. DWI parameters for this study were designed to reduce scan time to accommodate our young subjects and also to improve compatibility with scans from other cohorts. TRACULA does not rely on tensors for tractography but instead uses a crossing-fiber model.

Subjects in the TRACULA sample were on average 5 to 18 months older than those in the volumetric analysis, probably due to more movement in the younger children. VLBW subjects had lower mean socioeconomic status, although very few children in the study had low socioeconomic status, and compared to controls the VLBW group still had significantly lower IQ scores after correction for socioeconomic status.

Conclusion

Consistent with previous reports, this study found significantly reduced volumes of gray and white matter structures including thalamus, globus pallidus, cerebral white matter, and corpus callosum, along with enlarged ventricles in the school-aged VLBW group. By contrast, group differences in dMRI measures were minor and mostly seen in higher AD in the preterm group. In addition, white matter tracts connected to brain regions with cortical deviations showed some evidence of abnormal diffusion measures. This VLBW cohort born in the 2000s showed subcortical volume deviations consistent with previous reports, while white matter connectivity seemed similar between the groups, potentially reflecting different mechanisms on gray and white matter during pre- and postnatal development.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.12.029.

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Supplemental Material

Table S1. Perinatal characteristics for children in the VLBW group (n=37, unless indicated).

	n	Mean
Apgar score 1 min, (SD)		7.4 (2.3)
Apgar score 5 min, (SD)		8.4 (2.2)
Received antenatal steroids, doses (%)	22	1.9 (59%)
Used mechanical ventilation, days (range)	17	5.4 (0-47)
Intraventricular hemorrhage		
- Grade 1, n (%)		2 (5.4%)
- Grade 3, n (%)		1 (2.7%)
Days in NICU, (SD)		64.6 (33.3)
SGA, n (%)		4 (10%)

Abbreviations: NICU, neonatal intensive care unit; SD, standard deviation; SGA, small for gestational age (birth weight below the 10th percentile). Data in this table were originally published in a previous report on this cohort (see Sølsnes et al., 2015).

Paper III

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