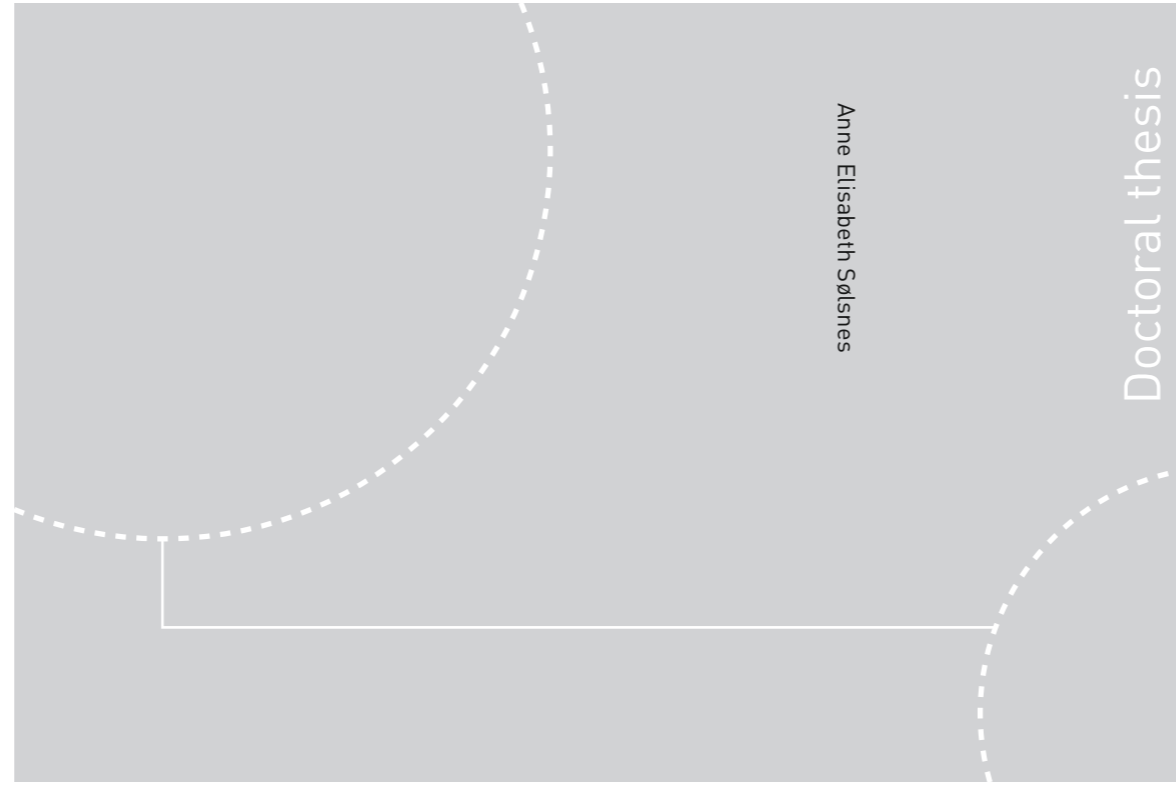


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Norwegian University of
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Thesis for the Degree of
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Trondheim, December 2015

Norwegian University of Science and Technology
Faculty of Medicine
Department of Laboratory Medicine, Children's
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“Straight ahead does not take anyone very far...”
Le Petit Prince
Antoine de Saint-Exupéry

IQ, eksekutive funksjoner og hjernefunn hos barn og unge voksne født prematurt med veldig lav fødselsvekt

Medisinske fremskritt innen nyfødtdisjon har ført til økt overlevelsesrate av prematurt fødte barn de siste to tiår. Majoriteten av de mest umodne og sykeste for tidlig fødte spedbarna som før døde, overlever nå nyfødtprioden. Dette er gode nyheter, men dessverre må noen av barna betale en høy pris med hjerneskadene og vedvarende avvik i hjerneutvikling. De prematurt fødte barna løper en større risiko for å utvikle alvorlige sekveler som utviklingshemming og cerebral parese (CP). I tillegg har de økt risiko for reduserte kognitive evner som blant annet kan lede til lærevansker, oppmerksomhets- og eksekutive vansker samt en økt prevalens av psykiske lidelser. Insidensen av alvorlige fokale hjerneskadene som store intraventrikulære blødninger og cystisk periventrikulær leukomalasi (PVL) er redusert ved forbedret medisinsk behandling av syke for tidlig fødte spedbarn, men fortsatt har de økt risiko for å få hjerneskadene som oppstår før, under eller etter fødselen hvor både hvit substans, gråsubstans og subkortikale strukturer kan bli negativt påvirket. Disse skadene oppstår som resultat av en kompleks og sammensatt prosess som påvirker nevronenes vandring og modning, samt nervebaner og hjernens nettverk. Denne formen for hjerneskade er ofte diffus og utstrakt og beskrives i litteraturen som «Encephalopathy of prematurity».

Kognisjon, målt med bruk av standardiserte nevropsykologiske tester og intelligenskvotient (IQ), har vist seg å være et robust mål på et individs intelligens og kognitive evner. Reduserte evner, eller problemer innen ulike eksekutive funksjoner, være seg arbeidsminne, hukommelse, oppmerksomhet eller evne til å organisere og planlegge, kan ha store innvirkninger på et menneskes liv både innen utdanningsløpet, innen arbeidslivet og sosialt. Oppfølgingsstudier knytter mange av disse vanskene opp til ulike hjerneavvik samt kliniske variabler som gestasjonsalder, fødselsvekt og sykdom i nyfødtprioden hos for tidlig fødte.

Dette doktorgradsarbeidet består av to studier som inkluderer to ulike kohorter bestående av prematurt fødte med svært lav fødselsvekt (≤ 1500 gram) inkludert jevnaldrende terminfødte kontroller. Det er produsert 2 artikler fra hver av studiene.

Den ene kohorten er en del av en studiepopulasjon som er fulgt fra 80-tallet i en longitudinell studie, og deltakerne var mellom 18 og 20 år da datamaterialet benyttet i denne studien ble samlet inn (totalt 55 VLBW og 81 kontroller). Den andre kohorten er født etter år 2000 og var mellom 4 og 10 år da de ble testet for første gang. De to kohortene er født med nesten 20 års mellomrom, og ett av avhandlingens mål var å undersøke hvordan forbedret nyfødtdisjon kan ha virket inn på kognitive funksjoner og hjernefunn hos prematurt fødte med svært lav fødselsvekt.

For de unge voksne premature var vi interesserte i å observere om de opplevde å ha mer problemer i hverdagen enn sine jevnaldrende terminfødte. Vi benyttet et selvrapporteringskjema, BRIEF-A, for å kartlegge deres egen opplevelse av hverdagens krav som omfatter eksekutive funksjoner. Vi fant at det var lite samsvar mellom testresultater på eksekutive tester og mengden opplevde vansker, og spekulerer på om dette kan ha ulike årsaker som underrapportering eller manglende evne til å observere egne evner. Et annet alternativ er at selvrapportering ved bruk av BRIEF-A ikke er et godt mål til å fange opp disse reduserte evner innen eksekutive funksjoner funnet ved bruk av nevropsykologiske tester. Den samme gruppen unge voksne premature skåret lavere på de fleste av de nevropsykologiske tester av eksekutive og oppmerksomhets funksjoner i et massivt

testbatteri. Positive korrelasjoner ble funnet mellom eksekutive funksjoners domeneskåre og hjerneoverflate i medial frontale områder.

I populasjonen med førskole og skolebarn (totalt 37 VLBW og 104 kontroller) i studie 2 fant vi, som hos de unge voksne, reduserte kognitive evner med lavere IQ, men det er viktig å nevne at VLBW barna hadde en gjennomsnitt IQ som var innen normalområdet. De premature barna hadde mindre overflate areal i frontale, temporale og parietale områder i hjernebarken samt tykkere områder i frontale og occipitale deler av hjernen sammenlignet med de terminfødte barna. Økt overflateareal var forbundet med økt IQ i begge grupper, og hos VLBW barna var økt tykkelse av hjernebark frontalt og tynnere hjernebark temporo-parietalt forbundet med lavere IQ skårer. Korrelasjonene mellom IQ og hjernebarkforandringer var ikke signifikante i VLBW gruppen, mest sannsynlig på grunn av liten størrelse på studie populasjonen. De premature barna hadde også redusert volum i ulike hjernestrukturer og økt volum av ventrikkelssystemet sammenlignet med kontrollene. Kun volumet av bakre deler av corpus callosum korrelerte med gestasjonsalder, ingen andre volumer korrelerte med de kliniske variablene. Det var heller ingen korrelasjon mellom IQ og volumer verken i VLBW gruppen eller hos de terminfødte. Vi fant også indikasjoner på en endret mikrostruktur i hvit substans i VLBW gruppen ved bruk av diffusjonsvektede hjernebilder. VLBW barna hadde signifikant økt aksial diffusjon i superior longitudinal fasciculus og arcuate fasciculus. Også andre nervebaner var endret med økt radial- og gjennomsnitt diffusjon i VLBW gruppen, men gruppeforskjellene i disse banene overlevde ikke korreksjon for multiple sammenligninger. Resultatene fra denne avhandlingen indikerer at forbedret nyfødttmedisin og endringer i prosedyrene i nyfødtperioden har ført til økt overlevelsesrate og synes også å ha hatt positiv innvirkning på modningen av hjernens banesystemer. Robuste funn vedrørende vedvarende kortikale avvik og reduserte subkortikale volumer i begge VLBW kohortene indikerer at den umodne hjernen fortsatt er sårbar for effekten av prematur fødsel og medisinske problemer tidlig i livet.

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Veiledere: Professor Jon Skranes, Professor Asta Kristine Håberg, Post doc Gro Løhaugen

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List of papers

Paper 1

Anne Elisabeth Søsnes, Jon Skranes, Ann-Mari Brubakk, Gro C.C. Løhaugen
Executive Functions in Very-Low-Birth-Weight Young Adults – a comparison between self-report and neuropsychological test results
Journal of International Neuropsychological Society, 2014 May; 20(5):506-15.

Paper 2

Heidi Furre Østgård, Anne Elisabeth Søsnes, Lars Morten Rimol, Knut-Jørgen Bjuland, Marit Martinussen, Ann-Mari Brubakk, Asta Kristine Håberg, Jon Skranes, Gro Christine Christensen Løhaugen
Executive function relates to changes in frontal and temporal cortices in very-low-birth-weight late teenagers
Early Human Development (Submitted 2015-08-31)

Paper 3

Anne Elisabeth Søsnes, Kristine H. Grunewaldt, Knut J. Bjuland, Elisabeth M. Stavnes, Irén A. Bastholm, Synne Aanes, Heidi F. Østgård, Asta Håberg, Gro C.C. Løhaugen, Jon Skranes, Lars M. Rimol.
Cortical morphometry and IQ in VLBW children without cerebral palsy born in 2003-2007
Neuroimage Clinical. 2015 Apr 14;8:193-201.

Paper 4

Anne Elisabeth Søsnes^{*}, Kam Sripada^{*}, Anastasia Yendiki, Knut Jørgen Bjuland, Heidi Furre Østgård, Synne Aanes, Gro C. Løhaugen, Live Eikenes, Asta Håberg, Lars M. Rimol, Jon Skranes^{*} contributed equally
Limited microstructural and connectivity deficits despite subcortical volume reductions in school-aged children born preterm with very low birth weight
NeuroImage (Submitted 2015-08-31)

Abbreviations

AD	Axial Diffusivity
ADHD	Attentional Deficit /Hyperactivity Disorder
APIC	Adults Born Preterm International Collaboration
BRIEF	Behavior Rating Inventory of Executive Function
BRIEF-A	Behavior Rating Inventory of Executive Function - Adult version
BW	Birth Weight
CAB	Cingulum – angular bundle
CFA	Confirmatory Factor Analysis
CHC	Carroll-Horn-Cattell
CSF	Cerebrospinal Fluid
CP	Cerebral Palsy
DC	Diencephalon
D-Kefs	Delis–Kaplan Executive Function System
DTI	Diffusion Tensor Imaging
ES	Effect Size
ELBW	Extremely Low Birth Weight (<1000 grams)
FA	Fractional Anisotropy
FDR	False Discovery Rate
FGR	Fetal Growth Restriction
GA	Gestational Age
GLM	General Linear Model
HIE	Hypoxic-ischemic encephalopathy
ICV	Intra Cranial Volume
IUGR	Intrauterine Growth Restriction
IVH	Intraventricular Hemorrhage
IQ	Intelligence Quotient
LBW	Low Birth Weight
MD	Mean Diffusivity
MPRAGE	Magnetization-Prepared RApid Gradient-Echo
MRI	Magnetic Resonance Imaging
NEPSY	A Developmental NEuroPSYchological Assessment
NICU	Neonatal Intensive Care Unit
OLs	Oligodendrocytes

OR	Odds Ratio
PVL	Periventricular Leukomalacia
RD	Radial Diffusivity
SD	Standard Deviation
SES	Socioeconomic Status
SGA	Small-for-Gestational-Age
SLFP	Superior longitudinal fasciculus -parietal
SLFT	Superior longitudinal fasciculus –temporal
TRACULA	TRActs Constrained by Underlying Anatomy
VLBW	Very Low Birth Weight (<1500 grams)
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
λ	Lambda / Eigen value
Δ	Glass' Delta

Summary

Advances in neonatal clinical medicine have led to increased survival rates of the most preterm born infants in the past two decades. A majority of the most immature and sickest neonates, who died before, now survive the neonatal period. This is good news, but unfortunately some of the children still have to pay a high price with brain injuries and persisting deviations in brain development. The preterm children have a greater risk of developing severe neurological disabilities like intellectual disability and cerebral palsy (CP). In addition, they have an increased risk of cognitive impairments including learning disabilities, attention and executive function deficits as well as increased prevalence of mental health disorders. The incidence of severe focal brain injuries like large intraventricular hemorrhages (IVH) and cystic periventricular leukomalacia (PVL) has been reduced by improvements in perinatal medicine, but very preterm born babies are still in danger of more subtle early brain injuries where the normal development of the cerebral cortex, white matter and subcortical gray matter nuclei may be adversely affected. These injuries may occur as a result of a multifaceted and complex process that affects neuronal migration, connectivity and neural- and cellular maturation and growth. This type of brain damage is often diffuse and widespread and described in the literature as "encephalopathy of prematurity."

Assessments with standardized neuropsychological tests and especially of the full-scale intelligence quotient (IQ) have proven to be robust measures of an individual's cognitive abilities. Reduced IQ, or more specific problems with various executive functions, like working memory, general memory, attention or the ability to organize and plan, can have a major impact on a person's life both in education, at the workplace, in daily life functioning and in social interaction. Follow-up studies of preterm born populations have associated many of these difficulties with various brain alterations as well as clinical variables such as gestational age, birth weight and morbidity in the neonatal period.

This doctoral thesis is divided into two parts and includes two different cohorts of preterm born individuals with very low birth weight (≤ 1500 grams), each with a group of age-matched term born controls. Four papers have been produced with 2 papers based on data from each of the cohorts.

One of the cohorts is part of a study population that was born and followed since the late 1980s in a longitudinal study. The participants were between 18 and 20 years of age when the

data used in this study were collected (from a total of 55 VLBW and 81 control participants). The second cohort was born after the millennium and the VLBW and control children were between 4 and 10 years old when they were tested for the first time. This means that the two cohorts were born nearly 20 years apart, and one of the aims of the thesis was to investigate whether and how improved neonatal medicine during the last two decades may have affected cognitive outcome and brain morphometry in VLBW survivors.

For the VLBW young adults, we investigated whether they experienced and reported more problems in everyday life than their peers born at term. We used a self-report form, BRIEF-A, to map their own experience of the everyday demands involving executive functions. We found that there was weak correlation between results on executive tests and self-experienced difficulties, and we speculated whether this could have various explanations, including underreporting, inability to observe their own shortcomings, or if self-report using BRIEF-A may not be a good measure to capture expected problems based on poorer scores on the neuropsychological tests. The same group of VLBW young adults scored lower on most neuropsychological tests of attention and executive function when assessed with a comprehensive test battery. Positive correlations were observed between the executive function domain score and cerebral cortex surface area in medial frontal and temporal areas, i.e., inferior scores were associated with reduced surface area in brain regions known to take part in higher order cognitive functions.

In the second cohort, consisting of preschool and school aged children (a total of 37 VLBW and 104 control children), we found, as in the VLBW young adult group, reduced cognitive abilities shown as lower mean full IQ score in the VLBW children compared to controls. However, the VLBW children had an average IQ in the normal range. The VLBW children had reduced cortical surface area in the frontal, temporal and parietal areas and cortical thickening primarily in frontal and occipital areas of the brain compared to their term born peers. Larger surface area was associated with higher IQ scores in both groups; in addition, increased frontal cortical thickening and temporo-parietal thinning was associated with lower IQ scores in the VLBW group. The VLBW children had smaller volumes of several brain structures and enlarged volume of the ventricles compared with controls. We also found indications of altered white matter integrity in the VLBW group using diffusion-weighted brain imaging. The VLBW group had significantly increased axial diffusivity in the superior longitudinal fasciculus and arcuate fasciculus. In addition, several white matter tracts were altered with increased radial diffusivity and mean diffusivity among the VLBW children, but

these differences did not survive correction for multiple comparisons. The changes seen in white matter integrity that was much less pronounced in the VLBW children born in the 2000s may still affect connectivity and reduce the effectiveness in neural networks in VLBW children.

The results from this thesis indicate that while improved neonatal treatment and care for the most immature neonates has resulted in higher survival, it seems also to have had a positive effect on white matter maturation. However, the robust findings regarding persistent cortical deviations and reduced subcortical volumes in both VLBW cohorts indicate that the immature brain is still vulnerable to the effects of premature birth and concomitant medical problems at the early start of life.

Definitions

Prematurity is a term for the broad category of neonates born at less than 37 weeks' gestation (definition from the World Health Organization). Preterm neonates are further subdivided into categories based on their gestational age (GA) and birth weight (BW). Children born before 28 full weeks of gestation are defined as “extremely preterm”, whereas children born between weeks 28 and 32 are termed “very preterm.” In the last category the children born during the 32-37 full weeks of gestation are defined as “late preterm.” Children with birth weight at or below 1000 grams are defined as extremely low birth weight (ELBW); the very low birth weight (VLBW) category is used on the children weighing 1500 grams or less and finally the low birth weight (LBW) children have a birth weight of 2500 grams or less.

Prevalence

According to the United Nations Children's Fund (UNICEF) (1), an estimated 15.5% (>20 million infants) of all births were LBW (<2500 g) worldwide in the year 2000. The prevalence of LBW infants in developing countries (16.5%) is more than double than in developed countries (7%). Of all living births in Norway in 2012 6.4% were born with ELBW (0.5%), VLBW (1.5%) or LBW (4.9%) (data from Norwegian Institute of Public Health, 2012). LBW increases morbidity and mortality (2) (3) , and preterm infants are 7 to 13 times more likely to die during the neonatal period than full-term infants (4, 5). The two main reasons for LBW are preterm birth and intrauterine or fetal growth restriction (IUGR/FGR). Term born with LBW (small-for-gestational-age, or SGA) infants are likely to have growth failure and an increased risk of morbidity and mortality in infancy (6) and are also likely to remain small during childhood and to experience more developmental deficits than term born

infants with normal birth weight (7). However, the survival rate in developed countries, like the United Kingdom, has increased for preterm children born between 22 -25 weeks, from 36% in 1994-1999 to 47% between 2000 and 2005 (8).

Brain development in normally developing children

The formation of the neural tube from the neural plate starts already around day 16 after conception and is the early part of the development of the central nervous system (9). The regional differentiation within the neural tube starts by week 4 of gestation and the rostral part forms three brain vesicles; the forebrain (prosencephalon), midbrain (mesencephalon) and hindbrain (rhombencephalon). Further, at week 5 of gestation the neuronal proliferation starts within the ventricular zone, and by week 8 of gestation the neuroblast differentiation starts and the cells develop into specific neuronal cell-types or non-neural cells – macroglia, which include astrocytes and oligodendrocytes (10).

Neuronal migration

Brain development is characterized by early overproduction of neurons and glial cells, neural processes and synapses, and neuronal migration takes place from week 12 of gestation and lasts until weeks 26 to 29 (10). The cells migrate from the ventricular zone to form cortical laminae in an inside-out manner, where the deeper cortical layers develop first and form the sub plate and the cortical plate (10). When neurons have reached their “final destination” they start to form axons and dendrites to connect to other neurons. The synapse formation (synaptogenesis) and the selective programmed cell-death (apoptosis) take place after week 16 of gestation. This massive increase in brain connections is followed by a process of dendritic “pruning” and synapse elimination, which leads to a more efficient set of connections remodeled throughout life and which are particularly plastic during the postnatal and preschool years (11).

Myelination

Between weeks 20 and 28 of gestation, myelination can be detected. Myelination starts in subcortical regions and extends into the cortex (10), and even though it starts as early as the second and third trimester, it continues into the second and third decade of life. The layer of insulating lipids on axons causes the conduction speed of fibers that interconnect different brain regions to increase ~100-fold. During the period of initial myelination, many excess oligodendrocytes undergo apoptosis within a few days after differentiating (12). It has been

suggested that this process of apoptosis depends on signals from nearby axons so that the number of surviving oligodendrocytes matches the local axonal surface area (12). Many of the oligodendrocyte progenitors begin to differentiate by extending processes and up-regulate myelin protein expression, forming the membrane that wraps around the nearby axons, when they have reached their destination. The increased myelination does not only have an effect on axonal conduction velocity, but the functional interactions between oligodendrocytes and neurons also appear to contribute to the maintenance of axonal integrity and neuronal survival (13, 14).

Cortex

During the third trimester, the basic organization of the subcortical regions are in place (15) and the cortical volume has increased four-fold with a disproportionate increase in thickness in the upper cortical layers (16). This increase in the upper cortical layers consists of later-arriving interneurons (17). Gray matter volume increases linearly by about 1.4 percent per week during the last trimester in the perinatal period (18). Gyration, the folding of the brain, occurs by the second month of fetal development and continues through the end of pregnancy and after birth, and is considered a reliable estimate of gestational age and maturation of the fetal brain (19, 20).

The human brain consists of ~100 billion neurons at birth; however, the brain of the newborn child is only one-quarter to one-third of its adult volume. During development the brain will continue to grow and specialize according to a precise genetic program, with modifications driven by environmental influences, both positive and negative (21). With stimulation, learning and experience, the dendritic branching of neurons greatly increases, as do the numbers of synaptic connections (22), and the potential and many of the vulnerabilities of the brain are in part determined by the first two decades of life (11).

A developmental change in the cortical surface area has been seen as a significant expansion during preschool years at 4 to 6 years of age and extends into school age (23). The greatest expansion occurs in higher order cortical regions like the prefrontal cortex and temporal association areas, and by the age of 10 years some cortical regions, like occipital and superior parietal lobes, start to show a decrease in surface area, most probably due to pruning and increased neural complexity (23). In contrast to cortical surface area, the cortical thickness

does not increase during the preschool years; instead a decrease is observed throughout the cortex. This decrease continues into young adulthood (23).

Several studies have investigated normal development of gray matter volumes that, in contrast to white matter volumetric changes, increase in the developing years and then decrease (11, 24-30). In a longitudinal study of children from 5 to 11 years of age Sowell et al. (30) found that the pattern of progressive cortical thinning varies across development, where the areas presumed to develop earliest showed evidence of maximal thinning, and the areas showing thickening were the later developing areas. More specific, the observed thinning was located in dorsolateral frontal regions particularly in the right hemisphere, and in parietal-occipital region, and the gain in cortical thickness was seen in perisylvian regions of ventral frontal lobe and superior temporal lobe (30). The pattern of progressive cortical thinning is thought to reflect the underlying subtractive processes of synapse retraction, associated with elimination of exuberant connections and the stabilization of more mature neural pathways (30).

Prematurity, brain development and injuries

The period during which premature children are born is a time where the immature brain undergoes massive developmental changes. Early and sometime harsh environmental exposures, immature blood vessels and circulatory systems, underdeveloped intestinal systems and immature lungs are examples of some of the medical challenges the premature child faces when meeting the world. Gray and white matter volumes increase dramatically during the third trimester, and because the immature neurons are particularly vulnerable to degenerative change, brain development is susceptible even in the absence of specific traumatic events. During the last decades the medical treatment for preterm born children has improved substantially and the survival rate has increased dramatically (31-33). The gestational age and birth weight of the children surviving has dropped, so that more children with ELBW and gestational age less than 25 weeks survive the early start of life. However, despite improved medical treatment and neonatal care, these very immature children have increased risk of brain insults due to prematurity.

Encephalopathy of prematurity

Early brain insults caused by episodes of hypoxia ischemia and/or infection and inflammation are the reason for many of the developmental neuroimpairments seen in premature children. One of the frequent injuries of the preterm brain is the intraventricular hemorrhage (IVH);

however, in recent decades the number of preterm born children with IVH has declined from an incidence of 35 to 50% in the early 1980s (34) to 20 to 25% in the late 1990s (35). Particularly at 23 to 32 weeks postconceptional age, premature infants are at an increased risk for brain injuries. One reason for the higher risk is the incomplete state of development of the vascular supply to the cerebral white matter and impairment in autoregulation of cerebral blood flow. Hypoxic-ischemic encephalopathy (HIE) can cause cell death deep within the brain in the so-called watershed areas and the premature infants are more susceptible to injuries like deep white matter infarction or periventricular leukomalacia (PVL). In addition, germinal matrix IVH, periventricular hemorrhagic infarction, and post-hemorrhagic ventricular dilatation (36) are more common brain injuries in preterm than term born infants.

“Encephalopathy of prematurity” is a term introduced by Joseph Volpe (17) describing injury of the preterm brain as a “complex amalgam of primary destructive disease and secondary maturational and trophic disturbances.” Even in the absence of severe hypoxic-ischemic events, PVL or IVH, preterm birth is characterized by a potential disturbance in the typical temporal and spatial progress of development of brain structures. Insults occurring during these sensitive periods in brain development may cause this disruption (37), and many of these processes happen during the infant’s hospital stay in the neonatal period (38). During these sensitive periods, several vulnerable brain processes occur like the establishment and differentiation of subplate neurons, the alignment, orientation, and layering of cortical neurons in addition to dendritic and axonal elaboration, synaptic formations, cell death, selective sculpting of neuronal processes and synapses and glial cell development (37-39).

Immature cerebrovascular system - haemorrhages

The immature cerebrovascular system may have episodes of impaired auto-regulation of cerebral perfusion that can lead to fluctuations in cerebral blood flow (40), and blood pressure (41), which increase the possibility of brain injuries like hemorrhages and infarction. The capillaries in the germinal matrix are extremely sensitive to changes in cerebral blood flow and rupture easily (42). The germinal matrix is located in proximity to the ventricular wall and reaches its maximum volume around week 25 of gestational and involutes around weeks 32 to 34 of gestational. This region, in addition to the ventricular- and subventricular zones, is the site of the neuronal and glial cell proliferation (17) and in preterm born children, 80 to 90% of the IVHs are associated with and usually start as a germinal matrix hemorrhage (43).

The risk of rupture of the capillaries is especially high during the first 2 to 3 days after birth, and bleeding in the germinal matrix ruptures easily into the lateral ventricular system where the blood in the cerebrospinal fluid (CSF) might block the resorption of CSF, resulting in increased intraventricular pressure and hydrocephalus (42). Germinal matrix hemorrhage can in addition result in disturbed neuronal and glial cell proliferation (42). If the hemorrhage in the germinal matrix is severe, it might lead to an obstruction of the terminal veins and subsequently the medullary veins, resulting in a periventricular hemorrhagic infarction (PHI) in the deep white matter, usually as a unilateral lesion (42, 44). The incidence of PHI in extremely low birth weight neonates has been stable at 5 to 8% over the last few decades (45).

Inflammation

Perinatal hypoxia and/or infections can initiate a cascade of destructive processes in the immature brain (46) which may lead to excitotoxicity (47), inflammation (48) and oxidative stress that may cause neuron loss (49). One reason for the increased risk for inflammation of the brain can be traced back to the immature blood-brain barrier. Before 27 weeks of gestation, the blood-brain barrier does not function efficiently due to immaturity of endothelial and ependymal cells. This increases the risk of the blood-brain barrier to allow toxins to enter into the infant's brain. Myelination in particular is highly susceptible to disruption due to the circulation of pro-inflammatory cytokines and their damaging effect on pre-oligodendrocytes, which in turn, would have subsequent negative impact on oligodendrocyte maturation and thereby myelination (50).

White and gray matter lesions in the preterm brain

Cerebral white matter lesions are the most frequent injuries in the preterm brain (39, 51, 52). White matter injury consists of two basic components: focal necrosis and diffuse gliosis (36, 53). The focal necrosis in the periventricular zone is characterized by loss of all cellular elements causing so-called cystic or non-cystic focal PVL. The diffuse form is characterized by widespread white matter injury, including diffuse gliosis and axonal damage, which may affect the microstructural integrity of white matter and tract connectivity (17).

Less than 5% of the very preterm born children are diagnosed with the focal form of PVL, but it is associated with the most severe disabilities like cerebral palsy, blindness and intellectual disability (35, 54, 55). The more diffuse form of PVL, where the white matter lesions are microscopic and may extend beyond the periventricular areas, resulting in glial scars and abnormal tract connectivity, is a more common pathological finding in the preterm brain than

the focal PVL. There is a possibility that this diffuse form of white matter damage can, at least to some extent, explain the high incidence of mild to moderate neurological deficits and motor, perceptual, cognitive, and behavioral impairments reported in preterm children. The white matter injury is often accompanied by neural and axonal pathologies that can affect cerebral gray matter — both cortex and subcortical gray matter nuclei. Cortical involvement may be seen already at term-equivalent age as less cortical surface area and less complex cortices compared to healthy controls (56). Furthermore, the growth of cortical surface area has been shown to be related to the degree of prematurity at birth where the growth in cortical surface area was significantly related to gestational age at birth but not to gender, birth weight, or body weight at the time of scan (57). The close relationship between prematurity, cortical growth, and neurodevelopmental functioning reported in this study suggests that aberrant cortical development may be a neural substrate for the abnormal functions observed in preterm infants (57).

Injuries to the subcortical gray matter are commonly found in preterm infants with cystic PVL (58), as well as in children with diffuse white matter abnormalities (59). Gray and white matter lesions could be connected by the gray matter involvement taking place secondary to white matter injury, but they may also be concomitant injuries. White matter injury might impact the connectivity of the developing neuronal systems and consequently influence the development of subcortical gray matter nuclei like basal ganglia and thalamus (59).

Thalamus, Basal ganglia and Globus pallidus

The subplate neuron layer is important in the cerebral organization because the subplate neurons guide descending axon projections from the cortex to sub-cortical targets, including thalamus and corpus callosum. The subplate is a temporary structure that is located beneath the cortical plate and peaks in activity between 22 and 36 weeks of gestation (60). Afferent axons from the thalamus and distant cortical sites grow and linger in the subplate pending the development of their ultimate neuronal targets in the cortical plate (60). Gray matter nuclei abnormalities comprise different structures that play a role within working memory and learning (61) and the volumes of thalamus, basal ganglia and globus pallidus have been found to be reduced in the VLBW population compared to term born controls (62, 63). At 20 weeks of gestation, the thalamocortical and cholinergic afferents start to form synapses with upper subplate neurons and the thalamocortical axons enter the primary somatosensory cortex by 24 weeks of gestation (64). This makes the thalamus especially sensitive to damages

in the ventricular zone and/or the germinal matrix since it receives neurons from these regions early in the second trimester and also in later gestational age (65, 66). An insult during these sensitive periods may lead to a reduction of the second wave of neurons from the telencephalon (67) and can affect the thalamo-cortical circuits (68).

The thalamus receives neural inputs from the basal ganglia and globus pallidus where the basal ganglia is thought to register or negate sensory contexts into working memory, and the globus pallidus has been identified as contributing to the filtering of irrelevant information and through this can exert attentional control over access to working memory capacity (69). The striatum, a part of the basal ganglia, is a component of the feedback loop that modulates cortical function. Damage to the striatum can lead to a disruption of cortico-striato-thalamic pathways which can have a negative effect on neurobehavioral functions such as modulation of attention and regulation of behavior (70). Reduction of subcortical volume in these structures can contribute to the understanding of cognitive problems seen in preterm children (55).

Cognitive outcome

Intelligence Quotient and neuropsychological tests

There are several theories about what general cognitive abilities, or Intelligence Quotient (IQ), actually denote. In the Carroll-Horn-Cattell (CHC) theory, intelligence is defined as “a mental quality that consists of the abilities to learn from experience, adapt to new situations, understand and handle abstract concepts, and use knowledge to manipulate one’s environment” (71). The most frequently and commonly used tools to assess IQ are the Wechsler tests (72). Cognitive abilities measured by IQ have been shown to be reduced in the VLBW population (73-77) as well as poorer performance on other neuropsychological tests measuring abilities like learning and memory (78), visual-motor function (79), and executive functions (80-82).

Executive functions

In addition to lower IQ scores, the premature children more often display difficulties with executive functions and increased attentional problems than term born controls. Executive functions refer to higher order cognitive functions that are important to control and regulate goal directed behavior and coordinate other cognitive functions, and include self-regulation,

impulse control, working memory, allocation of attention, initiation of activity, mental flexibility and utilization of feedback in addition to planning, organization and selecting efficient problem-solving strategies (83). Executive dysfunction reflects a range of impairment phenotypes such as decreased conceptual reasoning, verbal working memory, spatial conceptualization, planning, and inhibition. Deficits in executive functions can lead to inability to execute plans successfully and independently, problems with social interactions and with controlling emotions. Children born prematurely have been found to have higher prevalence of executive dysfunction than term born peers (80-82).

Even though deficits in executive functions may be subtle, they can have a substantial impact on the individual's cognitive, social, and academic functioning. It will also have generalized effect on IQ and impacts the child's knowledge acquisition, which may explain the limited social competence and adaptive behavioral skills observed in preterm born children (84).

Using the Behavioral Rating Inventory of Executive Functions (BRIEF), ELBW children were found to have inferior scores on the initiate, working memory, planning/organizing, and monitoring subscales, suggesting problems in metacognition (85).

Executive dysfunction has been found in preterm born adolescents (86); and young adults (87). Parents reports more inattentiveness in preterm born offspring at 20 years of age (88), and in a study using self-report, Strang-Karlson et al. (89) found an increased prevalence of inattention and executive problems at 22 years of age in those born preterm with VLBW and SGA (birth weight < 10th centile).

Academic achievement

Studies have shown that more than half of VLBW and between 60 and 70% of ELBW children require special assistance at school (90). However, an accurate estimation of the true magnitude of this problem is difficult because of different definitions in various countries. In addition, special education services and eligibility criteria may also differ. However, studies have shown that by middle school age, ELBW children are three to five times more likely than full-term peers to have learning problems in reading, spelling, mathematics, and writing (91). Particularly, mathematics and broad reading are more disrupted (92), and these rates are independent of IQ scores. Furthermore, by adolescence, there is an 8- to 10-fold increase in use of educational help in comparison to term born controls (92, 93).

Magnetic resonance imaging

Cerebral magnetic resonance imaging (MRI) is a proven and well-established imaging modality in the evaluation and assessment of normal and abnormal conditions of the brain. The technique offers high sensitivity in exploiting inherent contrast differences of brain tissues as a result of variable magnetic relaxation properties and magnetic susceptibilities. Because the brain consists of large amounts of water, MR imaging is made possible by magnetic moment and spin of the atomic nuclei of the hydrogen molecule in a magnetic field (94). Every water molecule contains two hydrogen atoms where the atom consists of a proton nucleus, carrying a unit positive electrical charge, and a single electron, which has a negative electric charge equal to the magnitude of the proton. Hydrogen nuclei, which do not contain neutrons, are referred to as protons. The atomic nuclei of many atoms carry a small magnetic dipole moment and act as small magnets, and when subatomic particles, such as protons, are exposed to magnetic fields, the axis of the protons' rotation is changed. When placed into a magnetic field, body tissues change gradually from demagnetized state to magnetized state at a rate is determined by the magnetization time. The magnetization time of the different body tissues ranges from about 0.1 second (in fat) to 4.0 seconds (in cerebral fluid). The protons spin at a frequency that is directly proportional to the strength of the magnetic field (Tesla). The net magnetization of protons at equilibrium is called longitudinal magnetization, which is oriented in the same direction as the magnetic field of the imaging magnet. Conventional MRI generally refers to images whose signal is weighted by proton density or by relaxation times, which characterize how fast the water magnetization returns to equilibrium after the perturbation induced by electromagnetic waves. When excited by a radio pulse of identical frequency, the magnetization of spinning protons is rotated toward the transverse plane. The strength and duration of this excitation radio pulse determines how far this magnetization is rotated. A radio pulse that rotates the magnetization of spinning protons by 90° is referred to as a 90° pulse. Longitudinal (equilibrium) magnetization cannot be measured easily, and needs to be rotated into the transverse axis to be detected.

When the protons are rotated into the transverse plane, the protons begin "dephasing." The rate of which the protons dephase depends on the environment that each proton is in. When the protons are "re-phasing" they are realigning to the static magnetic field or the RF pulse. In so-called T1 weighted imaging, they all align again with the field, but in T2 they go back to the direction they are facing after the first RF pulse is generated. In T1-weighted imaging,

they recover/align with the magnetic field because the protons are trying to get back into equilibrium. The longitudinal relaxation time (t_1) is characterized by the proton interactions with its environment (“spin-lattice” interactions), while the transverse relaxation time (t_2) characterizes the interactions between protons (“spin-spin” interactions). Since relaxation times depend on tissue characteristics, T1-weighted and T2-weighted images both demonstrate high contrast between different tissues in the brain.

T1-weighted imaging is especially suited for structural analysis where areas with a high amount of water (like the cerebrospinal fluid, CSF) are dark, and the fatty areas (like white matter) are white, making the contrast and borders of the different brain tissues easier to detect. In T2-weighted scans the image signal is opposite from T1, i.e. the CFS has high intensity (bright white) and the fatty areas have darker color.

Structural Imaging

By using 3-dimensional MPRAGE T1-weighted images, we are able to measure cortical thickness, cortical surface area, subcortical structure volumes, total brain and ventricular volumes. Different software packages have been developed and can be used for analysis; the program FreeSurfer has been used in this thesis.

FreeSurfer bases its analysis on preprocessed images (which will be described in detail in the methods section), and the two cerebral hemispheres are processed separately.

White matter integrity

White matter consists mostly of glial cells and myelinated axons that transmit signals from one region of the brain to another. Myelin acts as an insulator, increasing the speed of transmission of all nerve signals and is made by different cell types, and varies in chemical composition and configuration. The myelin will hinder the water to move freely across the myelinated axon. Diffusion refers to the random (Brownian) motion of molecules in a fluid, where the relative amount of diffusion is expressed in terms of a parameter called the diffusion coefficient, D . Water is a homogeneous liquid, for example in a cup of water, the diffusion coefficient is the same in every direction, or isotropic (a sphere). In some biological tissues, like the myelinated axons, the diffusion coefficient varies in different directions, i.e. anisotropic (like an ellipsoid) (see Figure 1). Water molecules’ motion or diffusion is much faster along the white matter fibers than perpendicular to them (95-97). The difference between these two motions (parallel and perpendicular to the fibers) is the basis of diffusion tensor imaging (DTI). Even though the anisotropic nature of water displacement in white

matter has been observed since the early days of diffusion MRI (98-100), to quantify the different diffusion coefficients is complex.

As seen in Figure 1, the diffusion can be presented as an ellipsoid with the coefficients orientated in three different directions; the major, medium, and minor principle axes of the ellipsoid (eigenvectors). The measures of diffusivity in these three directions are called eigenvalues ($\lambda_1, \lambda_2, \lambda_3$). The long axis pointing along the axon direction is λ_1 and the two small axes are λ_2 and λ_3 . Mean diffusivity (MD) is a measure of mean diffusion in all these eigenvalues, $(\lambda_1 + \lambda_2 + \lambda_3) / 3$. Axial diffusivity (also called fractional diffusivity) measures the diffusivity along the principal axis, λ_1 , while radial diffusivity is the measure of the sum of the diffusivities in the two minor axes.

The measure fractional anisotropy (FA), which is commonly used in diffusion imaging, is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. A value of zero means that diffusion is isotropic, i.e., it is unrestricted (or equally restricted) in all directions, while a value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. In white matter FA is thought to reflect fiber density, axonal diameter and coherence, and the degree of myelination (101). Nearly all studies of myelination with normal brain development (102) or demyelination with disease related processes have found less diffusion anisotropy when axons are less myelinated (22, 103, 104). During early brain development, all three eigenvalues decrease with increasing age, with most substation decline in diffusivity in the radial orientations ($\lambda_2 + \lambda_3$) and is consistent with the development of myelination (105).

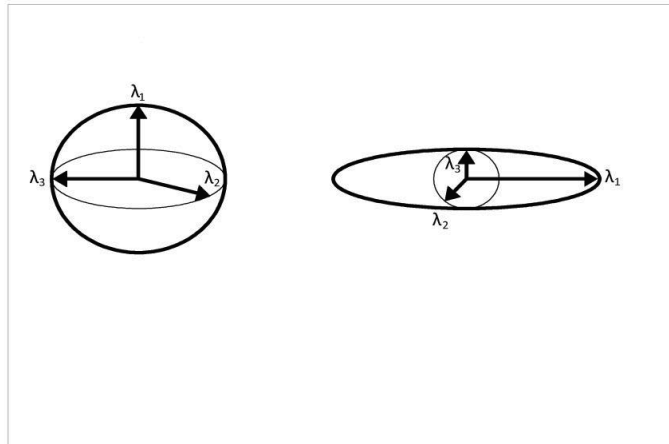


Figure 1.

Figure shows the measure of diffusivity in three directions is called eigenvalues (λ_1 , λ_2 , λ_3). The long axis pointing along the axon direction is λ_1 and the two small axes are λ_2 and λ_3 . The eigenvectors represent the major, medium, and minor principle axes of the ellipsoid and the eigenvalues represent the diffusivities in these three directions, respectively. In an isotropic tissue the ellipsoid is spherical, and water can diffuse equally in all directions. The mean diffusivity depends on the tissue water content through the density of hindering structures. In white matter, fibers are oriented in bundles (characterized by an ellipsoid), diffusion is anisotropic (restricted) where the anisotropy increases with fiber density and decreasing membrane permeability.

FreeSurfer has a novel fiber-tracking tool where DTI-derived metrics can be examined by using a tractography reconstruction tool named TRActs Constrained by Underlying Anatomy (TRACULA). TRACULA uses probabilistic tractography and assessment of diffusion properties in 18 major white matter tracts to assess fibertract integrity by measuring fractional anisotropy (FA), radial diffusivity (RD) and mean diffusivity (MD). This tractography tool enables modeling of fiber tract anatomy within each person's native diffusion space by using each person's own structural anatomy as estimation as priors and therefore does not rely on perfect alignment between the study subjects and training subjects.

Cerebral MRI findings in VLBW children

Cortex

Preterm born VLBW children have an increased risk of perinatal brain injuries, which may cause permanent brain lesions and subsequently alter the normal maturation of the brain.

Abnormalities in cortical and subcortical gray matter have been demonstrated in preterm born

children with VLBW as reduced brain cortical surface area at term-equivalent age; (56, 57), in toddlers at 18 to 22 months old (106), in children at the age of 10 years (107), and in adolescents and young adults (108, 109). Both regional thinning and thickening of the cerebral cortex have been reported in VLBW children 7 to 12 years of age (107, 110) and in young adults at the age of 19 (62). Deviant cortical development may impact cognitive abilities in this population, and several studies have shown an association with inferior IQ scores (86, 108, 111, 112). Reduced cognitive performance has also been related to reduction in cortical volume in 14 to 15 year old VLBW adolescents (113).

Subcortical structure volumes

Another robust finding in preterm born individuals is the reduction in volumes of subcortical gray matter nuclei, like thalamus and basal ganglia, in cerebellum, and in white matter like corpus callosum, as well as dilatation of the ventricular system (62, 113-117). Such volume reductions may have functional consequences. Reduced hippocampal volume has been associated with memory deficits and weakness in numeracy (70), and with deficits in working memory, particularly visuospatial working memory (118). Furthermore, a relationship between reduction in cerebellar volume and poorer cognitive performance has been reported in preterm born adolescents (62, 114).

White matter

Abnormal cerebral white matter in VLBW infants is one of the most common pathological findings in the premature population and the wide age range in the different studies may therefore indicate that white matter deviations do not improve or disappear with age, but seem to be permanent changes. Reduced fractional anisotropy on diffusion tensor images have been reported at 27 to 46 weeks of gestation (119), in adolescents (86) and in young adults aged 18 to 22 years (120), even in white matter that looks normal on conventional MRI. Fiber tracts like the corpus callosum and long-range association tracts appear to be especially sensitive to preterm birth and very low birth weight (86, 121-124). Diffusion measures of white matter tracts, especially reduced FA correlate with cognitive deficits, like language skills (125), IQ scores (10, 120), learning and memory (78), and visual-motor function (79).

Earlier findings in our study population of VLBW young adults

The participants from paper 1 and 2 are part of a longitudinal follow-up study. Our group has followed a population of about 200 children born in between 1986 and 88 including preterm born VLBW (birth weight ≤ 1500 g), term born SGA (BW $< 10^{\text{th}}$ percentile adjusted for gender and parity), and term born controls (BW $> 10^{\text{th}}$ percentile), living in the same region in Central Norway. The children have participated in a series of clinical and MRI studies from birth to young adulthood. This study was the first to combine multidisciplinary clinical assessments with cerebral MRI in a year cohort of VLBW children and found that $\sim 50\%$ of the children had signs of perinatal brain injury on conventional MRI at age 1 and 6 years and that brain pathology correlated with neuroimpairments (86, 126). Part of the VLBW cohort (those born in 1989) has been assessed at age 1 and 6 years, but the most comprehensive assessment was performed at ages 14-15 and 19-20 years. One of the main findings from the earliest studies is that early MRI pathology persisted into adolescence and motor, perceptual, cognitive and behavioral problems were seen in children with MRI findings consistent with perinatal PVL. In subsequent studies at 14 to 15 years of age, volumetric MRI and diffusion tensor imaging (DTI) revealed regional cortical thinning, decreased volume of basal ganglia and reduced FA values of white matter were associated with motor, perceptual, cognitive and behavioral impairments (86, 127-130). Furthermore, at age 19, tract-based morphology showed that all major central and posterior white matter tracts had significantly reduced FA compared with controls, and that reduced FA was associated with reduction of IQ in the VLBW group, indicating that the VLBW young adults have permanent changes in white matter microstructure (120). Cortical morphometry analysis has further revealed that VLBW young adults have regional parietal and temporal cortical surface area reduction and that surface area reduction was associated with deficits in various IQ indices, especially working memory and processing speed indices (131). Altered cerebral cortex with both regional thinning and thickening (112) and reduced brain volumes (62) in young adults at the age of 19 have been reported. A study using both cortical morphometry and DTI report that visual-motor integration was found to relate to reduced surface area of motor and visual cortices and disturbed connectivity in long association tracts containing visual and motor information in a study using both cortical morphometry and DTI (79).

Aims of the thesis

Aims of paper 1

In paper 1 the aims were to examine if VLBW young adults had more self-reported attention/executive problems and lower neuropsychological test results than term born controls. Further, we investigated whether there was a relationship between self-reported attention/executive problems, general cognitive ability (IQ) and neuropsychological test results. We hypothesized that the preterm group as young adults would obtain lower scores on executive function tests and report more problems on BRIEF-A, and that there would be a relationship between self-report subscales/composite scores and the results from the Delis-Kaplan tapping attention/executive function neuropsychological battery.

Aims of paper 2

In paper 2, our aims were to evaluate attention and executive functions and to relate the clinical findings to cortical surface area and cortical thickness in VLBW late teenagers compared with term born controls. We hypothesized that VLBW subjects would obtain inferior scores on the individual neuropsychological tests and on the domain scores compared with controls, and that there would be structure-function relationships between attention and executive domain scores and surface area and cortical thickness in higher order brain regions in the frontal, parietal and temporal lobes.

Aims of paper 3

The main aim of paper 3 was to compare cortical thickness and cortical surface area in 5–10 year old VLBW children and term born controls by using continuous maps of cortical thickness and surface area. In addition, we wanted to explore any relationship between regional measures of cortical morphology and Full IQ as an overall measure of cognitive functioning. We hypothesized that the cognitive abilities would be reduced in the VLBW population and reduced cognitive performance has been related to altered cortical morphometry.

Aims of paper 4

In paper 4 we wanted to investigate any group differences in subcortical brain structure volumes and white matter integrity, and their relationships to cortical thickness in VLBW children and controls at 5 to 10 years of age. Furthermore, we aimed to explore possible associations between brain structures, IQ scores and perinatal variables. We hypothesized that

white matter properties, cortical changes and subcortical brain structure volumes would be associated with and IQ scores and perinatal variables.

Materials and methods

Study design

Long term follow-up-study (paper 1 & 2)

The first study is based on a long term follow-up study with cross sectional data from age 19-20 years. All participants, both VLBW and controls, were enrolled at birth in a multi-center long-term follow-up study at St Olav's University Hospital in Trondheim, Norway, between 1986 and 88. The present study was carried out between September 2006 and December 2008, and IQ assessment and neuropsychological testing and evaluation were conducted by neuropsychologist Gro Løhaugen, PhD. Cerebral MRI images were obtained at the same time as the cognitive assessment.

MoBa-study (Mother-Child cohort) (paper 3 & 4)

This is a longitudinal follow-up study of children, with two assessments with a 12 to 18 month interval between testing. Present study was carried out between January 2012 and June 2014. The cognitive and MRI imaging data material used in paper 3 and 4 is cross-sectional data from the first data collection conducted between January 2012 and February 2013.

Study population

Participants in paper 1 and 2

The participants in paper 1 and paper 2 were enrolled in a long-term follow-up study at St Olav's University Hospital in Trondheim, Norway, between 1986 and 88. The mothers were of Caucasian origin, spoke a Scandinavian language, and lived in the Mid-Norway region in the period they were invited to participate.

VLBW group

A total of 121 children born preterm with VLBW were admitted to the neonatal intensive care unit (NICU) at St Olav's University Hospital in 1986 to 88. Thirty-three (27%) of these children died during the neonatal period and 9 had moved away at follow-up. Two subjects with severe cerebral palsy (CP) and one with Down syndrome were excluded from follow-up because of inability to perform the neuropsychological tests. VLBW participants included both singletons and twins and one participant had spastic diplegic CP. Of the 76 young adults

eligible for participation at age 19-20 years, 55 (72%) agreed to participate and completed cognitive assessment, and 42 participants completed the BRIEF-A self-report form. A total of 50 VLBW subjects were examined with cerebral MRI at age 19-20. The scans of four subjects had to be rejected due to motion artifacts, leaving 46 VLBW subjects for inclusion in the MRI analysis. See Figure 2 for flow chart for participants in paper 1 and 2.

Comparison group

The participants in the comparison group were born to mothers recruited in a multi-center study including 1200 pregnant women from the Trondheim region who had a singleton pregnancy and expected their second or third child. The women were enrolled before week 20 of pregnancy. The initial study's main aim was to investigate repeated small for gestational age (SGA) births in a group of high-risk mothers compared to SGA births of mothers who had previously delivered non-SGA infants (132). Children with birth weight greater than the 10th percentile adjusted for gestational age, born at term from a 10% random sample of the mothers, were included for long term follow-up. At 19 years of age, 10 subjects in the comparison group had moved and 2 were excluded because of congenital malformations. Of the 110 young adults eligible for participation, 81 (74%) consented to participate during 2006-2008 and met for cognitive assessment, 63 completed the BRIEF-A self-report form and 66 had cerebral MRI. Five scans were excluded due to motion artifacts caused by dental braces, poor image quality or lack of concomitant cognitive assessment and the analysis consists of a total of 61 control participants. See Figure 2 for flow chart for participants in paper 1 and 2.

Non-participants

Reasons for non-participation were not specifically asked for, but some reported shortness of time and lack of motivation. The VLBW and control groups were not significantly different in terms of gestational age and weight at birth, maternal age at child birth and parental socio-economic status from those who did not consent to participate at 19 years within each group. There was no significant difference in terms of clinical data within the different subgroup of participants in either group.

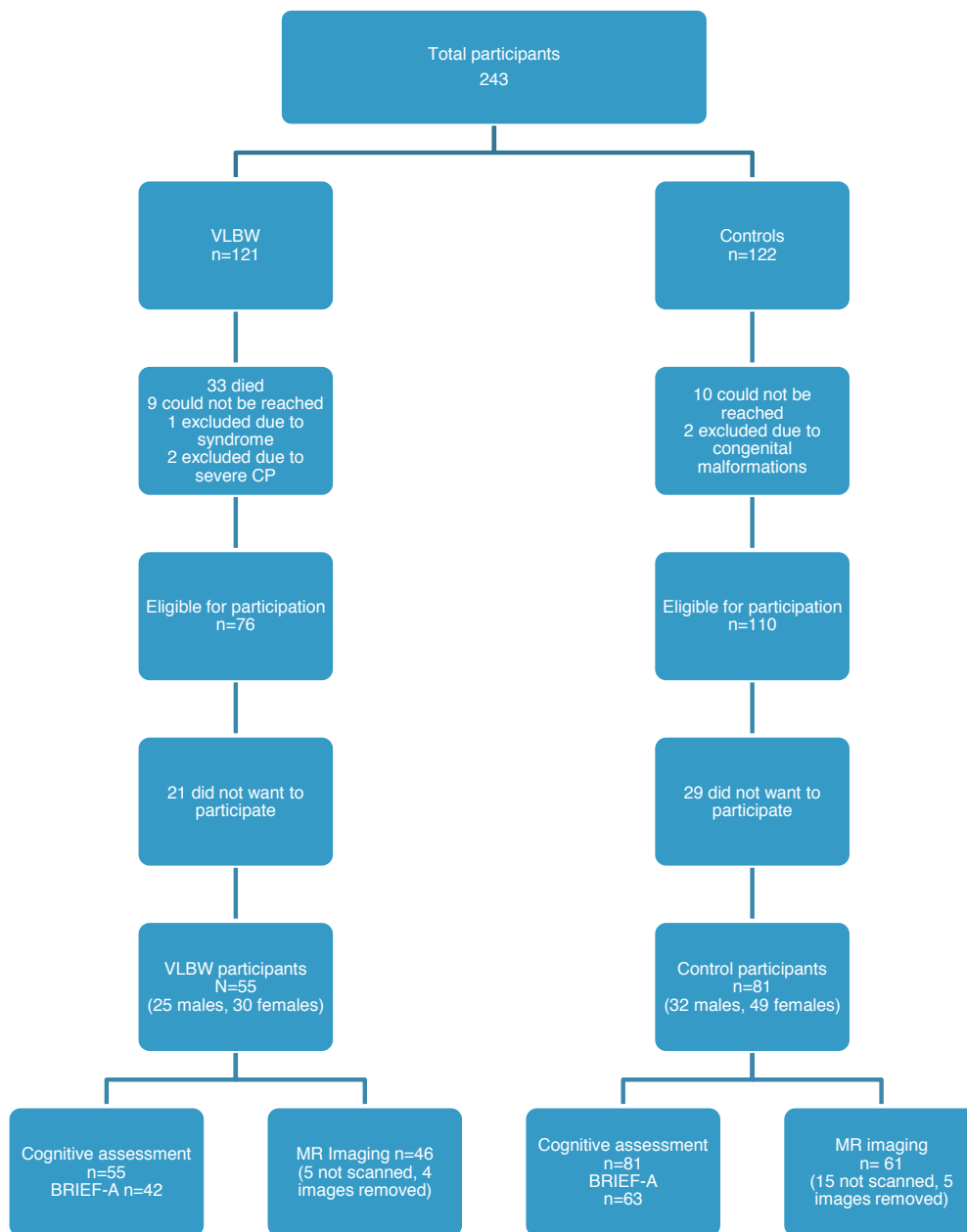


Figure 2.
Flow chart for participants in each step of the analysis in paper 1 and 2

Participants in paper 3 and 4

VLBW group

The children born prematurely with VLBW (birth weight \leq 1500 grams) were recruited based on admittance to the NICU at St. Olav's University Hospital in Trondheim, Norway, from 2003 to 2007. Sixty-three non-CP children between 5 and 11 years of age were invited and 57 (90%) agreed to participate in the study (31 females – 54%). Two children (twins of VLBW children) with birth weights of 1784 and 2090 grams were also included in the data analysis. In the VLBW group, analyses were conducted based on MR-images from 37 children (21 females). Of the 57 who were eligible for MR-scanning, 9 children did not want to be scanned and had cognitive assessment only. The youngest participants (4.5–6 years of age) were most likely to decline MRI scanning or be excluded due to movement artifacts. 11 images were excluded due to movement artifacts or disrupted scanning, resulting in MR images from 37 children (21 females). For the cortical morphometry analysis in paper 3 one child (a twin sibling to a VLBW child) with birth weight at 2090 grams was included in the data analysis, and post-hoc analysis showed similar brain morphology and IQ scores for this child as the VLBW cohort. In the TRACULA analysis one additional child with birth weight at 1784 grams was included. See Figure 3 for flow chart for participants in paper 3 and 4.

Control subjects

The control group, involving preschool and school aged children, was recruited from the Norwegian Mother and Child Cohort study (MoBa). MoBa was planned in the 1990s in collaboration between researchers at the Medical Birth Registry of Norway and the National Institute of Public Health. The objective of MoBa is to test specific etiological hypotheses by estimating the association between exposures, genetic factors and diseases. However, the study is not made on a specific set of hypothesis but aims to include data material on as many relevant exposures and health outcomes as feasible. The target population of the MoBa study is all women who give birth in Norway with no exclusion criteria. All hospitals and maternity units with more than 100 births annually, altogether 52 units, are to be included, and by January 2006, 50 of the 52 units participated in the study (133). Pregnant women were invited to participate by receiving a written informed consent form for both the mother and the father, a questionnaire and information about the study together with the appointment for ultrasound scanning in week 17-18 of pregnancy.

The control subjects had an age range between 4.5 and 11 years of age (n=143, 70 females). Participants included in the current study were living in the same geographical area as the VLBW participants (Nord- and Sør-Trøndelag) and had normal vision and hearing. Exclusion criteria were history of injury or disease known to affect the central nervous system (CNS), including neurological or psychiatric illness or serious head trauma. Furthermore, if the child was under psychiatric treatment, used psychoactive drugs known to affect CNS functioning, had a birth weight below 2500grams or had any known MRI contraindications they were excluded from participation in the current study. We were able to attain 104 MPRAGE images of good quality (54 females). A total of 143 children were invited to MR imaging, 22 children did not want to participate and 17 of the images had to be excluded due to movement artifacts or disrupted scanning. The youngest participants (4.5–6 years of age) were most likely to decline MRI scanning or be excluded due to movement artifacts. See Figure 3 for flow chart for participants in paper 3 and 4.

Non-participants

Reasons for non-participation were not specifically asked for, but some reported shortness of time and/or lack of motivation.

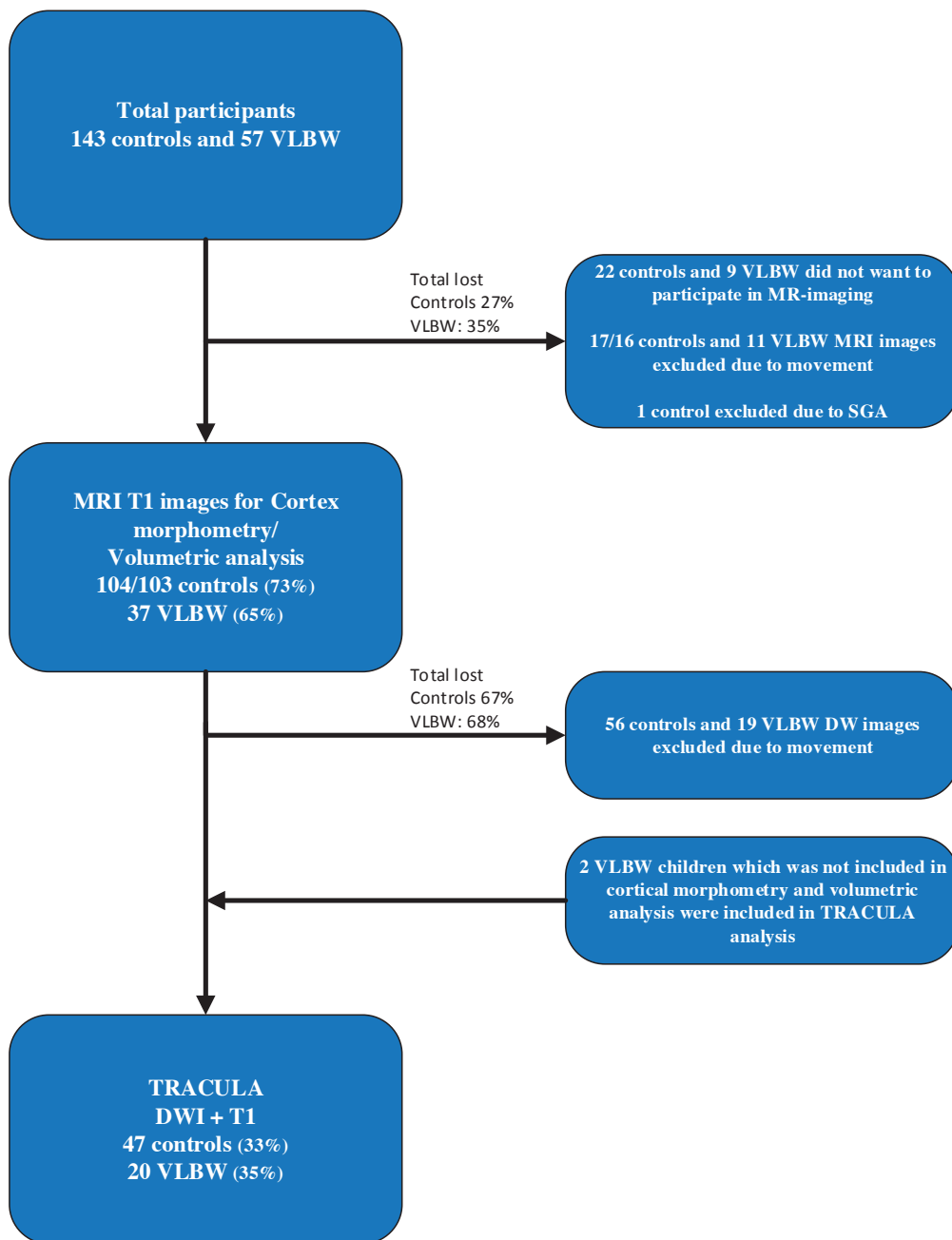


Figure 3.
Flow chart for participants in each step of the analysis in paper 3 and 4

Assessments

General cognitive assessment (IQ)

Long term follow up study

Wechsler Adult Intelligence Scale-III (WAIS-III)

The full-scale IQ (FSIQ) is based on results from 11 subtests. The WAIS-III (134) assesses specified domains of cognitive functions that are divided into four indices based on factor analysis: Perceptual organization, verbal comprehension, working memory and processing speed.

MoBa

Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III)

VLBW children under 6 years of age completed a full WPPSI-III. WPPSI-III provides three IQ indices: Full Scale IQ, Verbal IQ and Performance IQ (135). The controls younger than 6.5 years of age completed a short form of the (WPPSI-III) including similar subtests: vocabulary, similarities, block design and matrices, and Verbal IQ, Performance IQ and Full-scale IQ were calculated.

Wechsler Intelligence Scale for Children, 4th edition (WISC- IV)

Children ≥ 6 years of age were assessed with WISC- IV (136). WISC-IV comprises four indices: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index, and Full Scale IQ. WISC-IV is designed for testing children at 6 years and 0 months up to 16 years and 11 months.

Wechsler Abbreviated Scale of Intelligence (WASI)

Wechsler Abbreviated Scale of Intelligence (WASI) (137). The children in the control group older than 6.5 years of age were administered the WASI. The WASI is a validated screening test that is used to assess the following aspects of intelligence: verbal knowledge, visual information processing, spatial and nonverbal reasoning, and general intelligence. Three IQ scores can be extracted using the WASI: a Verbal IQ score (subtests: vocabulary and similarities) and a Performance IQ score (subtests: block design and matrices), which when combined provide an estimated Full-scale IQ score. The WASI consists of four subtests, two measuring verbal (Vocabulary and Similarities) and two measuring nonverbal/performance

(Block Design and Matrix Reasoning) abilities. Raw scores for each subtest are then converted into age-corrected T-scores. The sum of the T-scores for all four subscales can be used to obtain age-corrected Full Scale IQ. Similarly, Verbal IQ is obtained by summing the T-scores from the two verbal subtests, and Performance IQ can be obtained by summing the T-scores from the two performance subtests.

Neuropsychological testing

Attention and executive functions

For short description of each test used in study 1 (paper 1 and 2), see Supplemental Material in paper 2. For description of tests used in study 2 (paper 3 and 4) and which is not described in paper 2, see Supplemental Material 1.

The complete sample of test used in the two different study groups is presented in Table 1. It is important to note that not all test results and collected data has been used in the published papers and manuscripts.

Table 1.
Table shows all neuropsychological tests conducted in study 1 and study 2, with indications of which tests have been used on both VLBW and controls and which test results has been published in the papers in this thesis.

Test	Measure	Study	paper 1	paper 2	paper 3	paper 4
Paced Auditorial Serial Addition Test	Cognitive function that assesses auditory information processing speed and flexibility, as well as calculation ability	1		X		
Conners' Continuous Performance Test	Sustained and selective attention	1		X		
Wechsler Memory Scale 3rd edition	Memory for verbal and figural stimuli, memory for meaningful and abstract material, and delayed and immediate recall	1		X		
Wisconsin Card Sorting Test	Abstract thinking and flexibility in problem solving	1		X		
The Design and Verbal Fluency	Problem-solving behavior, fluency in generating visual patterns, creativity, task letter fluency, category fluency, and category switching.	1	X	X		
The Tower Test	Measures planning and organizing in problem solving	1	X	X		
Wechsler Adult Intelligence Scale-III	General IQ	1	X	X		
Stroop - The Color-Word Interference Test	Selective attention, inhibition	1,2	X	X		
Trail Making Test (TMT) I-5*	Attention and focused attention	1,2	X			
Spatial span	Visual working memory	2				
Visual attention	Focus selectively on and maintain attention to visual targets	2				
Statue	Inhibition and motor persistence	2				
Narrative memory	Narrative memory	2				
Digit Span	Verbal working memory	2				
Taylor Modified Figure Test	Visuospatial perception and visual memory	2				
Visual-Motor Integration	Visual perceptual and constructional abilities	2				
California Verbal Learning Test (CVLT)	Verbal learning ability and verbal memory	2				
Attention Network Test	Attention, alerting, orienting and executive control	2				
Wechsler Abbreviated Scale of Intelligence	Abbreviated Scale General IQ	2			X	X
Wechsler Intelligence Scale for Children, 4th edition	General IQ	2			X	X
Wechsler Preschool and Primary Scale of Intelligence, 3rd edition	Short form for controls. Full WPPSI for VLBW	2			X	X

Both VLBW and Controls Only VLBW Only controls X=data presented in paper *TMT 5 motor not included in analysis

Questionnaires

Brief-A

In study 1, the participants completed the Behavior Rating Inventory of Executive Function - Adult version (BRIEF-A) (138). The BRIEF-A is a self-report assessment of executive functioning in everyday activities over the past 30 days. For the 75 items included in the BRIEF-A, the participants answered the following question: "During the past month, how often has each of the following behaviors been a problem?" The answers are rated by a three-point scale, scored as follows: never=1, sometimes=2, often=3. T-scores from the BRIEF-A have a mean of 50 (SD=10), and scores ≥ 65 are considered clinically significant. Poorer executive functions are indicated by higher scores. The responses are summarized into an overall composite score; Global Executive Composite (GEC) and two index scores: Behavioral Regulation Index (BRI) and Metacognition Index (MI). The BRI is composed of the following sub-scales: Inhibit, Shift, Emotional Control and Self-Monitor, and MI is composed of the sub-scales Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials.

Brief children

In study 2, the BRIEF (139) used was a standardized questionnaire for assessing the performance of executive functions in children and adolescents, which consists of two forms; a parent form and a teacher form, where only the parent form was handed out in this study. The questionnaire is designed to assess executive functions in the home and school environment. BRIEF is appropriate for investigation of children and youth with a wide range of both development-related and acquired neurological damage, learning disabilities, attention deficit disorder, traumatic brain injury, developmental disorders, depression and other developmental, neurological, psychiatric and medical conditions.

Each BRIEF-form consists of 86 questions within eight overlapping clinical scales: Impulse Inhibition, Flexibility, Emotional control, Initiation, Working memory, Planning / Organization, Organization of materials, Monitoring, and two validity scales; Negativity Scale and Inconsistency scale, which make two broader index: Behavioral regulating index (AI) and Meta cognition index (MI), and an overall index; Global executive function (GEF).

ADHD rating scale

The Adult ADHD Self-Report Scale (140) is an 18-item scale corresponding to the 18 items in the DSM criteria that is divided into 2 subscales: hyperactivity/impulsivity and inattentiveness. It contains 18 questions with answers ranging from “never” to “very often.”

Vineland-II

Vineland-II is one of the most widely used instruments used for mapping of adaptive behavior. It provides both a measure of overall adaptive skills and skills in more specific functional areas (141). There is an interview form and a parent form, with Scandinavian norms for age range of 2.0-21.11 years. Vineland-II defines adaptive behavior as “implementation of the daily activities required to manage on their own, both on a personal and a social plan.”

Socio-economic status

The Hollingshead’s Two Factor Index of Social Position was used to calculate the Socio-economic status (SES) based on the education and occupation of one parent, or the mean index from both parents (142). This information was gained through interview at the day of assessment. For study 1, this information was mainly collected during the 14-15-year follow-up.

Cerebral Magnetic Resonance Imaging

MRI acquisition

Study 1 (paper 2)

Cerebral MRI was performed on a 1.5 Tesla Siemens Magnetom Symphony Sonata System with Quantum gradients (30 mT/m) and a quadrature head coil.

A structural T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with: TR= 7100 ms, TE= 3.45 ms, TI= 1000 ms, 128 sagittal partitions, 1.33 mm slice thickness, square FOV of 256 mm, and acquisition duration of 8.5 min.

The FreeSurfer 5.1.0 software package was used to create a three-dimensional model of the cortical surface for measurement of cerebral and cerebellar gray and white matter volume, cortical thickness and surface area (143, 144). The surfaces were smoothed with a full-width-half-maximum Gaussian kernel of 30 mm (662 iterations) and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns (145).

Study 2 (paper 3 and 4)

MRI data were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions). The pulse sequence used for morphometric analyses was a T1-weighted MPRAGE scan with the following parameters: repetition time (TR), 2400 ms; echo time (TE), 3.61 ms; inversion time (TI), 1000 ms; flip angle, 8°, FoV 240 × 240 and acquisition duration of 4 min and 18 s. Each volume consisted of 160 sagittal slices with voxel sizes of 1.25 × 1.25 × 1.20 mm. The total scan time was on average 30 min.

Diffusion Weighted Imaging (DWI) was acquired using a conventional 2D single shot balanced-echo EPI sequence. The series included 30 images acquired with diffusion weighting along non-collinear directions ($b = 700 \text{ s/mm}^2$), and 6 images acquired without diffusion weighting ($b = 0$). The acquisition parameters were: matrix size 128 X 128, FOV 256 x 256 mm², slice thickness 2mm, giving isotropic voxels of 2 x 2 x 2 mm³, number of slices= 64 (no gap), TE= 70ms, TR=7700ms, TA=4:22, BW= 1396 Hz/px, and GRAPPA acceleration factor 2.

Raw datasets were de-identified and transferred to Linux work-stations for processing. Each MPRAGE was visually inspected and only scans with no or minimal movement artifacts were included in the analyses. T1 and DWI raw data were visually inspected to remove subjects with significant movement or other artifacts.

Image analysis

General

Cortical reconstruction was performed with the software package FreeSurfer 5.3.0, which is well documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>).

Image analysis includes motion correction and averaging (146) of multiple volumetric T1 weighted images and removal of non-brain tissue using a hybrid watershed/surface deformation procedure (147). An automated Talairach transformation, intensity normalization (148), tessellation of the gray and white matter boundary and automated topology correction (149, 150) are then applied before 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 (144, 151). Once the cortical models are

complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (152), registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects (153), parcellation of the cerebral cortex into units with respect to gyral and sulcal structures (154, 155), and creation of a variety of surface based data (see Figure 4). FreeSurfer 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 (151). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity.

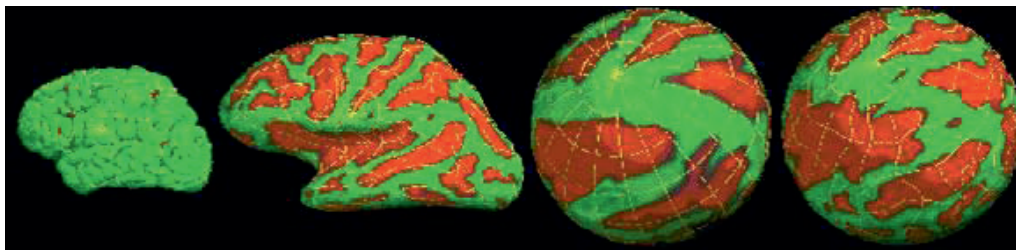


Figure 4.

Figure shows pial surface (left figure) and inflated surface (second figure from left) and the spherical registration (two figures to the right) and illustrates the sulcal map to the spherical inflation with a high-dimensional, non-linear registration to spherical template.

Volumetrics

We used FreeSurfer software version 5.3 to extract volumes of subcortical structures. Analyses were carried out on 26 brain structures as defined by FreeSurfer parcellations: cerebral white matter, cerebral gray matter, brain stem, left and right accumbens area, left and right amygdala, left and right caudate, left and right cerebellum cortex, left and right cerebellum white matter, left and right hippocampus, left and right pallidum, left and right putamen, left and right thalamus, left and right ventral DC, lateral and inferior lateral ventricle (merged into single volumes) for left and right hemispheres, fourth and third ventricle. This is an automated method that assigns a neuroanatomical label to every voxel in the brain by using both global and local spatial information. The automatic labeling procedure can also be used to automatically define regions of interest (ROIs), and this method has been shown to be comparable in terms of accuracy to a previously validated method of manual segmentation (156).

Cortical morphometry

FreeSurfer software version 5.3 was used for analyzing the cortical morphometry, and the two cerebral hemispheres were processed separately. In this method the surfaces is smoothed with a full-width-half-maximum Gaussian kernel of 30 mm (662 iterations) and averaged across participants. Each surface consist of approximately 160,000 vertices arranged in a triangular grid, and estimates of cortical area is obtained by computing the area of each triangle in the standardized, spherical atlas space surface tessellation when mapped into the individual subject space. Next, a vertex-wise estimate of relative areal expansion for each individual subject in atlas space is computed by assigning one-third of the area of each triangle to each of its vertices (157). The cortical surface in each subject is then automatically parcellated using defined gyri and sulci as landmarks, and the surface is further divided into 34 anatomical regions for each brain hemisphere defined in FreeSurfer (154, 158). These defined anatomical regions are used to anatomically identify affected regions after significance testing.

Tracula

TRACULA (TRActs Constrained by UnderLying Anatomy) was used for DTI analysis and tractography (for detailed description of the method see Yendiki et al. (159)). Briefly, TRACULA applies probabilistic tractography to DTI data based on a set of anatomical atlas information. This is an algorithm for automated global probabilistic tractography that estimates the posterior probability of 18 pathways, based on a “ball-and-stick” (160) as well as a pathway prior term, which incorporates prior anatomical knowledge on the pathways from a set of training subjects. The “ball-and-stick” model assumes that water molecules belongs to one of two populations; a restricted population of water molecules in and around fibers and a free population that does not interact with fibers. The probability is calculated separately for every point along each pathway that is passing through anatomical segmentation labels along the trajectory of the pathway. These anatomical segmentation labels are obtained from the T1-weighted images analyzed for obtaining cortical morphology and subcortical volumes. The 18 reconstructed white matter pathways are presented in Figure 5.

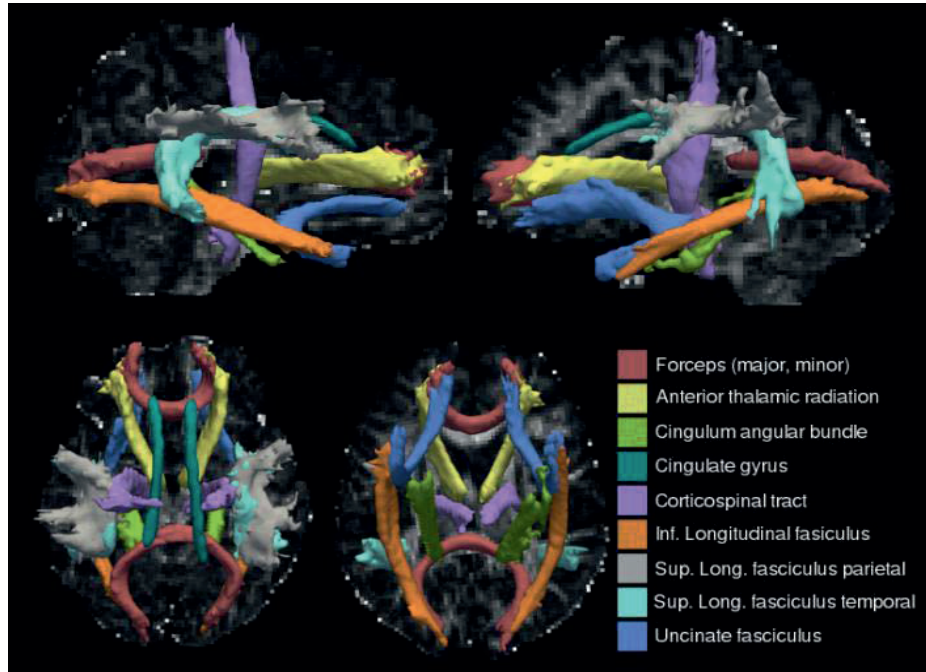


Figure 5.
 Probabilistic reconstruction of 18 white matter tracts generated by TRACULA visualized based on data from one subject.

Statistics

Paper 1

All statistical analyses in paper 1 were conducted with the IBM SPSS Statistics version 20.0 for Macintosh. The comparison of the clinical variables and BRIEF-A scores between groups had to be analyzed with the non-parametric Mann-Whitney U test due to the data failing to be normally distributed and/or not having equal variances. Mean values of neuropsychological test scores were computed using a univariate general linear model with group as fixed factor and gender and SES as covariates. The analysis was repeated including the Processing Speed Index from WISC-IV as co-variate. Effect size was measured as Cohen's *d*, which indicates the standardized difference between the means of the two study groups. Correlations between the neuropsychological test results and self-reported BRIEF-A sum and index scores within both groups were analyzed with the Pearson bivariate correlations. We conducted Fisher's *z* Transformation to test if the correlations between the two groups were different. To correct for multiple comparisons, we considered an alpha level of 0.01 as significant for all analyses.

Paper 2

The IBM SPSS statistics (Statistical Package for Social Sciences) version 19 (IBM, Armonk, New York) was used for statistical analyses. Clinical data were analyzed using the non-parametric tests; Mann-Whitney U test for ordinal and interval data, and the χ^2 test for nominal data. The same analyses were used to look at differences between participants and non-participants.

Missing data (SES and neuropsychological test data) were dealt with by multiple imputations.

Log transformations were used to deal with variables with non-normally distributed data.

To correct for multiple comparisons, we considered an alpha level of 0.01 as significant for all analyses involving subtests. Tests were first categorized into five domains: attention, executive functions, language, visual-spatial/motor and memory and a confirmatory factor analysis (CFA) was then applied to examine the fit of our five-domain model using MPlus version 7 (161, 162). Data from this CFA have previously been published in Østgård et al. (163). In this paper, only the results of the attention / executive function tests and the domain scores for attention and executive function will be presented, since visual-motor integration and memory test results have already been published (79, 164).

A general linear model was applied to analyze the relationship between groups (VLBW vs controls) and neuropsychological test scores and domain scores, with SES, sex and age at assessment as covariates. All analyzes were performed both with and without participants with CP. Domain scores were calculated by averaging Z-scores from the individual tests within each domain. Correlation analyses (Spearman's rho and Pearson's r) were used to examine the relationship between clinical variables and domain scores in the VLBW group.

Secondary analyses were also performed to look at correlations between clinical variables and tests where the VLBW group performed significantly more poorly than controls. All effect sizes (ES) were calculated by the Glass' Delta (Δ). Odds ratios (ORs) were calculated to study the association between group adherence and having an impairment (score $<-2SD$) in any of the neuropsychological domains. To look at the association between neuropsychological domain scores and cortical surface area and thickness, we used partial correlations controlling for sex, age at assessment and SES.

Paper 3

IBM SPSS Statistics 19 edition was used for the analysis of the clinical and cognitive measurements by independent samples t-tests and non-parametric tests. Data with non-equal variances were analyzed with non-parametric testing. Matlab 2011b was used for statistical analyses of morphometry data. To examine group differences, a general linear model was fitted with cortical surface area or cortical thickness as dependent variable and group, sex and age at MRI scan as independent variables. The regression of IQ on cortical morphology was tested with the same general linear model with Full IQ as an added continuous predictor. Appropriate contrast vectors were set in order to perform the various significance tests. The hemispheres were analyzed separately, and effect size and p-maps were generated. Effect size is reported as Cohen's d for group comparisons and $r = F / (F + df)$ for continuous predictors (IQ and birth weight). The p-maps were thresholded, and multiple comparisons were corrected for with a 5% false discovery rate (FDR) that was applied co-jointly across the hemispheres. Differences in cortical morphology between the groups were tested. For the clinical variables, 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 scan.

Missing data in the independent variables (full IQ and birth weight) were dealt with by multiple imputations. Pattern analysis was performed, showing that we had below 5% missing data and that we could assume data was missing at random. Seven full-scale IQ data and two birth weights were imputed and pooled imputations were used in further analyses.

Paper 4

Matlab software suite 2011b (MATLAB and Statistics Toolbox Release 2011b. The MathWorks, Inc., Natick, Massachusetts, US) was used for statistical analyses of subcortical and cortical morphometry and DTI data. The software package IBM SPSS 21 (Chicago, USA) was used to generate group differences and correlations between morphometric, DTI, IQ, and clinical measures. General linear models were fitted for group comparisons of subcortical brain structure volumes, controlled for age at scan, sex, and estimated total intracranial volume from FreeSurfer. Partial correlation tests, controlled for age at scan and sex, were used to investigate the relationships between morphometry and DTI 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 by using Fisher's exact test. Holm-Bonferroni step-down (165) was used to correct for multiple comparisons.

Ethics

Study 1

The Regional Committee for Medical Research Ethics approved the study protocol (project number 4.2005.2605). Written informed consent was obtained from each participant. If individual test results indicated learning disorders, or if there was a concern about the mental health, the participants were offered a referral to an appropriate public institution for further assessment and diagnostic evaluation.

Study 2

The Regional Committee for Medical Research Ethics approved the study protocol (project number: 2010/2359), and written informed consent was obtained from the parent/guardian of all participants. If individual test results indicated learning disorders, or if there was a concern about the mental health, the participants were offered a referral to an appropriate public institution for further assessment and diagnostic evaluation.

Main results

This thesis consists of four papers based on two different cohorts. The two first studies examine executive and attention functions as well as brain morphometry in young adults, while paper 3 and 4 are based on Full IQ and brain morphometry from preschool- and school-aged children. First an overview of the group characteristics will be presented, and then the main results will be presented for each paper separately.

Paper 1

The clinical characteristics for participants in paper 1 are presented in Table 2 (the table was published in paper 1).

Table 2.

Clinical characteristics and WAIS-III scaled-scores in the VLBW and the control group

	VLBW n=42	Controls n=63	
	Mean/median, (SD/min.-max/%)	Mean/median, (SD/ min.-max/%)	p value
Clinical characteristics			
Birth weight(grams)	1237 (219)	3676 (495)	0.000
Gestational age, (weeks)	30 (24-35)	40 (2)	0.000
Days on mechanical ventilator ^a	1 (0-44)	-	-
Days in the NICU ^b	59 (25-386)	7 (4)	0.002
Days to regain birth weight ^c	16 (3-39)	-	-
Apgar score 1 minute ^d	7 (1-9)	9 (0)	0.000
Apgar score 5 minute ^e	9 (1-10)	10 (0)	0.000
Socio-economic status ^f	3.4 (1.3)	3.8 (1.0)	0.176
Received special education at school	7 (17%)	3 (5%)	0.013
Currently employed	12 (29%)	18 (21%)	0.979
Currently unemployed	6 (14%)	1 (2%)	0.011
Currently at school	23 (54%)	41 (65%)	0.259
Age at assessment (years)	19.5 (0.8)	19.6 (2.4)	0.495
WAIS-III scaled scores			
Full-scale IQ	89 (13.1)	101 (12.5)	0.000
Verbal IQ	87 (11.3)	98 (12.8)	0.000
Performance IQ	93 (14.8)	104 (12.4)	0.000
Verbal comprehension	90 (12.9)	99 (13.6)	0.005
Working memory	83 (12.8)	93 (12.8)	0.001
Perceptual organization	98 (17.2)	109 (13.5)	0.001
Processing speed	93 (15.2)	100 (12.4)	0.003

Mann-Whitney U test

Abbreviations: WAIS-III: Wechsler Adult Intelligence Scale third edition; VLBW: very low birth weight; SD: standard deviation; NICU: neonatal intensive care unit

^a VLBW n= 40, ^b Controls n=29; ^c VLBW n= 32; ^d Controls n= 58; ^e Controls n= 59; ^f Controls n=62

Table 3.
Clinical characteristics and WAIS-III scaled-scores in the VLBW and the control group

	VLBW (n=55)		Non-CP VLBW (n=51)		Controls (n=81)	
	mean (SD)	(vs controls)	mean (SD)	(vs controls)	mean (SD)	(vs controls)
Birth weight (grams)	1217 (233.3)	<0.001	1234 (215.8)	<0.001	3707 (473.2)	
Gestational age (weeks)	29.1 (2.5)	<0.001	29.4 (2.3)	<0.001	39.7 (1.2)	
Apgar score 1 min*	7 (1-9)	<0.001	7 (1-9)	<0.001	9 (7-9)	
Apgar score 5 min*	9 (1-10)	<0.001	9 (1-10)	<0.001	10 (9-10)	
Days in the NICU	74 (54.0)	<0.001	75 (61.7)	0.002	7 (2.8)	
Days on mechanical ventilator	5 (11.2)	-	3 (8.0)	-	-	
Days to regain birth weight	17 (8.4)	-	16 (8.5)	-	-	
Gender (F/M)	30/25	0.601	28/23	0.718	48/33	
Maternal age at birth (years)	28.4 (4.8)	0.045	28.6 (4.7)	0.064	30.3 (4.4)	
Socio-economic status	3.3 (1.3)	0.110	3.3 (1.3)	0.091	3.7 (1.0)	
Special education in school: Yes/no	12/43	<0.001	10/41	<0.001	2/79	
Unemployed or sick leave at time of assessment: yes/no	8/46	0.011	7/43	0.013	2/77	
Age at assessment	19.2 (0.9)	0.875	19.2 (0.9)	0.800	19.2 (0.7)	
Full IQ score (WAIS-III) at age 19-20 years**	88.2 (1.6)	<0.001	89.3 (1.6)	<0.001	100.3 (1.3)	

Mann-Whitney U-test for two independent samples; Chi Square analysis for categorical data
Abbreviations: VLBW: Very Low Birth Weight; CP: Cerebral Palsy; SD: Standard Deviation; WAIS-III: Wechsler Adult Intelligence Scale 3rd edition* Apgar score 1 and 5 minutes presented as median and range. **Calculated by a general linear model, univariate analysis of variance, estimated marginal means with gender and SES as covariates.

Paper 2

The characteristics for the participants in paper 2 are presented in Table 3 (the table was published in paper 2).

Paper 3

The clinical and perinatal characteristics for the participants in paper 3 are presented in Table 4.

Table 4.

Clinical and perinatal characteristics for the VLBW and the control group

	VLBW/ Control number	VLBW Mean (SD/median)	Controls Mean (SD)	<i>p</i> value
Age (years)	37/104	7.8 (1.73)	8.2 (1.02)	0.352 ^a
Gender (boys/girls)	37/104	16/21	50/54	0.616
Birth weight (grams)	37/104	1050 (358)	3657 (484)	< 0.001
Gestational age (weeks)	37	28.5 (28)	na	
SES	34/85	3.9 (0.9)	4.3 (0.8)	0.021
Full IQ	37/104	98 (10)	108 (14)	< 0.001 ^b
Special education, n (%)	37/104	10 (27%)	2 (1.9%)	< 0.001 ^c
Apgar score 1 min	37	7.4 (8)	na	
Apgar score 5 min	37	8.4 (9)	na	
Antenatal steroids, n (%)	37	22 (59.5)	na	
Mechanical ventilation, days	37	5.4 (0-47)	na	
Intraventricular hemorrhage				
Grade 1, n (%)	37	2 (5.4)	na	
Grade 3, n (%)	37	1 (2.7)	na	
Days in NICU	37	45.2 (44)	na	
SGA, n (%)	37	3 (8)	na	

Abbreviations: VLBW: very low birth weight; SES: socio-economic status; SD: standard deviation; na: not available; NICU: Neonatal Intensive Care Unit; SGA: Small for gestational age (birth weight below the 10th percentile).

^aNon-parametric due to not equal variance, ^bAdjusted for socio-economic status, ^cFisher's exact test

Paper 4

Paper 4 is based on the same population as in paper 3. However, some changes to the number of participants were needed due to the different demands for image quality in the two image analysis. The data is presented below divided into the two different analyses.

Volumetric data

One male participant in the control group from paper 3 was not included in paper 4 due to poor image quality. This changed the mean birth weight in the control group to 3661 grams (SD=485), and age at MR from 8.2 to 8.3 years. No other characteristics changed.

Diffusion tensor data

For the TRACULA analysis we were able to include images from 20 VLBW (9 boys, 11 girls) and 47 controls (22 boys/25 girls). The participants in the VLBW group had a mean birth weight at 1103 grams (SD=364), mean age=8.6 years (SD=1.22), SES= 4 (SD=0.84) and mean Full IQ=96 (SD=12). For controls the mean birth weight was 3691grams (SD=531), mean age=8.7 years (SD=0.7), SES= 4.3 (SD=0.76) and mean Full IQ=112 (SD=14).

Main results Paper 1

The VLBW participants obtained lower scores on 8 of the 18 neuropsychological subtests assessing different aspects of attention and executive functions and scored lower on full IQ as well as on all IQ indices compared with controls. When including processing speed index as a covariate for the attention and executive neuropsychological subtests, VLBW subjects still scored poorer on Design Fluency 1, TMT1, TMT2, TMT3 and TMT4 compared with controls. There were no significant group differences in self-reported BRIEF-A mean scores. However, on the Behavioral Regulation Index, 31% of the VLBW participants reported scores higher than +1 SD from mean value in the comparison group, while this was true for 16% of the controls (not significant). The BRI scores did not reach the level of clinical significance in either of the groups. Further, higher scores on BRIEF-A sum-indices correlated to poorer scores on the Trail Making Tests (based on scores on Shift and Working Memory) and Stroop tests (explained by scores from Working Memory and Plan/Organize), but with no correlation to Design Fluency in the VLBW group. In comparison, all of the BRIEF-A sum indices correlated negatively to one or several of the D-Kefs test scores in the control group.

Main results Paper 2

Our main finding was that young adults born preterm with VLBW obtained inferior scores on all neuropsychological tests and within both attention and executive function domains, as compared with the term born control group, with the VLBW group having lower raw scores than controls on 28 of the 29 subtests, after adjustment for SES, sex and age at assessment. Differences reached significance ($p < 0.01$) for 15 of the 29 measures. After exclusion of the four subjects with CP, significant groups differences was still reached in the Stroop-tests, the TMT tests, the WMS-III-tests, Design Fluency, and the WCST Failure to maintain set. In the VLBW group there was an increased risk of having an impairment in the attention domain (OR=2.16, 95% CI [1.46, 3.15]) and the executive functions domain (OR=2.76, 95%CI [2.19, 3.48]). None of the clinical risk factors that were investigated correlated with the domain scores, but the domain scores correlated with special education in school (Attention: $r=0.559$, $p < 0.001$; Executive functions: $r=0.691$, $p < 0.001$). The executive function domain scores correlated positively with different cortical surface areas, i.e., better scores correlated with larger regional surface area. The relationship between the executive function domain score and surface area is presented in Figure 6 (published in paper 2). No domain score correlated significantly with cortical thickness measures.

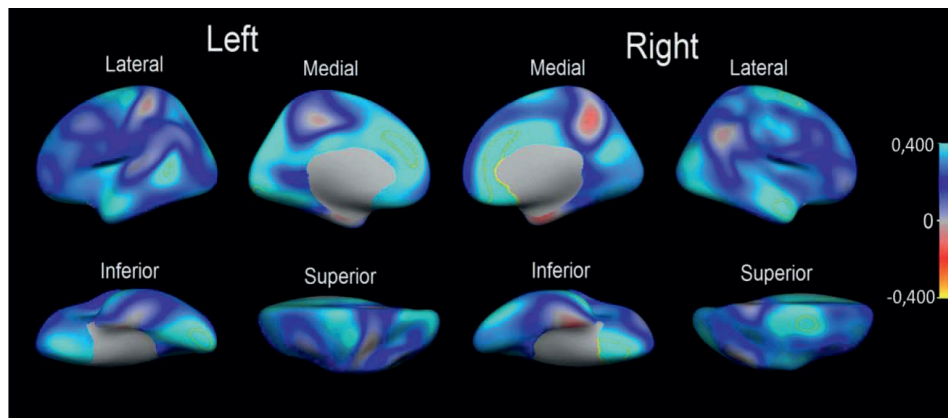


Figure 6.

Effect size maps (correlation coefficient r) for cortical surface area and executive functions domain score in the VLBW young adults. The color scale shows the dynamic range of correlation coefficient (r), where dark blue to light blue color represents an increasing positive correlation, i.e., more surface area with higher executive function score. Red to yellow indicates an increasing negative correlation. Areas where correlations were significant after FDR-correction are marked with a yellow outline. Significant positive correlations between cortical surface area and executive functions were observed in the posterior superior temporal sulcus, lingual gyrus, lateral occipital gyrus in the left hemisphere, and the caudal and rostral anterior cingulate, medial orbitofrontal gyrus extending into lateral orbitofrontal gyrus, anterior medial temporal gyrus and superior temporal gyrus, as well as posteriorly in lateral superior frontal gyrus in the right hemisphere. The effect size is based on a GLM with cortical surface area as dependent variable, group and sex as categorical predictors, and age and executive function domain score as continuous predictors.

Abbreviations: FDR: false discovery rate; GLM: general linear model; VLBW: very low birth weight

Main results Paper 3

In paper 3 we reported significant reduction of cortical surface area in 5- to 10-year old VLBW children relative to an age-matched term born control group. The VLBW group showed bilateral reduction in cortical surface area in the frontal, temporal, and parietal lobes (see Figure 8 in Discussion). The effect size of the group difference ranged from $d = 0.4$ to 0.8 in most cortical regions. The VLBW group also presented significantly thicker cortex in the frontal (medial orbitofrontal gyrus, rostral anterior cingulate, frontal pole) and occipital regions (pericalcarine sulcus) bilaterally, and a thinner cortex in the right posterior parietal lobe compared with controls (Figure 7, published in paper 3). Moderate to large effect sizes ($d = 0.6$ – 0.8) were observed in the frontal and occipital regions. There were medium- to large-sized correlations between reduced surface area and thicker cortex and poorer IQ scores, in both the VLBW and the control group. There were no significant associations between birth weight or gestational age and cortical area or thickness in the VLBW group. There was, however, a positive correlation of days on ventilator and surface area bilaterally in the dorsal frontal regions, including the superior and medial frontal gyrus, precentral gyrus, and orbitofrontal cortex, as well as the left supramarginal and posterior superior temporal gyrus, and the right precuneus and superior parietal gyrus.

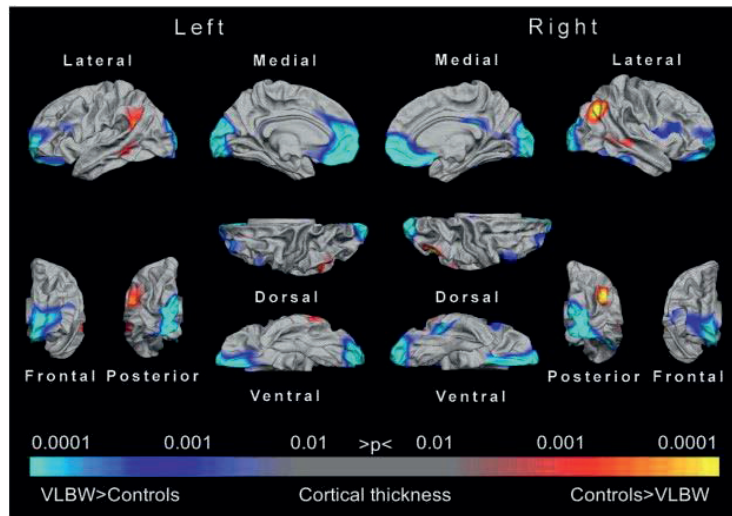


Figure 7.

Statistical p-maps showing regions with significant differences in cortical thickness between the VLBW group and the control group. The maps were produced from GLMs fitted at each location (vertex) across the cortical surface, with cortical thickness as the dependent variable and group as the independent variable, co-varying for sex and age. The maps were thresholded to yield an expected 5% FDR. The FDR threshold was obtained for the left and right hemispheres conjointly. Red to yellow denotes regions with cortical thinning in the VLBW group, and blue to light blue denotes regions with cortical thickening in the VLBW group.

Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight.

Main results Paper 4

This follow-up study of a preterm born VLBW and term born cohorts found significant reductions in the VLBW group in volumes of thalamus, right globus pallidus, right ventral DC, right hippocampus, cerebral white matter, brain stem and corpus callosum. Only the corpus callosum posterior subsegmentation volume correlated significantly to gestational age among VLBW subjects ($R=0.58, p<0.0001$). In controls, birth weight correlated significantly to volumes of cerebellar white matter ($R=0.50, p<0.0001$), cerebellar gray matter ($R=0.36, p<0.0001$) 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 controls. On diffusion tensor imaging (DTI), only group differences in axial diffusivity (AD) in the posterior part of the left superior longitudinal fasciculus parietal bundle (SLFP) and in the temporal bundle (SLFT) were significant after correction for multiple comparisons. We found significant correlations in AD in left CAB in the VLBW group with gestational age ($R=0.87, p<0.0001$) and AD in left uncinate fasciculus in the control group with birth weight ($R=0.52, p<0.001$). 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 in need for assisted ventilation driving the correlations. No other correlations survived Holm-Bonferroni correction. In an exploratory analysis projecting tract endpoints onto the inflated cortical surface to assess cortical thickness in the subjects' native space, none of the correlations between DTI measures and cortical thickness reached significance after correction for multiple comparisons.

Discussion

Summary of results

In paper 1 we found that VLBW young adults do not report more problems regarding attention/executive function in daily life than controls in spite of lower results on several neuropsychological tests assessing attention and executive function. In addition, in paper 2 we showed that the VLBW young adults display cognitive problems across executive function and attention domains, compared with controls. These problems may be related to reduction in cortical surface area, especially in the medial frontal lobe of the brain.

In paper 3 we reported that cortical deviations are evident in childhood even in VLBW children born in 2003-2007 who have received state-of-the-art medical treatment in the perinatal period and who did not present with focal brain injuries on neonatal ultrasonography. The cortical deviations were associated with reduced cognitive functioning. In paper 4 we further reported that compared to controls, the VLBW group had reduced volumes in several subcortical structures, however, only small differences regarding white matter integrity was observed between the VLBW group and controls.

Strengths and limitations

Strengths

Study 1

Young adults:

Strength of this study includes the use of a well-defined study sample with a longitudinal design where the participants have been followed throughout their childhood and adolescence with repeated examinations that, in addition to the comprehensive assessment, covering several aspects of neuropsychological functioning, were combined with structural MRI. Another strength is that one experienced neuropsychologist who was blinded to group affiliation and earlier medical history performed all neuropsychological testing. The follow-up rate was similar to what reported in other long-term follow-up studies (166), and there was no difference between participants and non-participants in terms of SES, gestational age, birth weight or maternal age at child birth. Furthermore, the combination of use of the BRIEF-A self-report instrument (138) and comprehensive standardized neuropsychological test battery intended to measure equivalent cognitive functions is a novel approach that has not been examined before within a population of VLBW young adults.

Study 2

Young children:

The strengths in this study are the large cohort of healthy term born children between 5-10.5 years of age and the comprehensive clinical assessment, covering several aspects of neuropsychological functioning combined with multimodal MRI. All neuropsychological testing was performed by trained testers under supervision of an experienced neuropsychologist, a major benefit to the study. As in study 1 we analyzed the cerebral MR imaging using an automatized segmentation technique (FreeSurfer) for quantitative measures of cortical morphometry. In addition we obtained white matter and deep nuclei brain structures and used a novel method (TRACULA) for diffusion MR imaging with tractography, which was performed and analyzed in collaboration and with guidance from the main developer of the method.

Limitations

Study 1

Young adults:

A possible limitation of the current study is the lack of a BRIEF-A informant report form, which might have given additional valuable information about the participants' executive functioning in daily life activities. Furthermore, since our study population was born during the late 1980s and neonatal intensive care has improved considerably since then, we must be careful not to overgeneralize our results to preterm born populations born in the 1990s and later. Another limitation may be our relatively small sample size with power to detect only major group differences and correlations. Non-significant results should therefore be interpreted with caution.

Study 2

Young children:

Limitations of this study were the relative small sample size in the VLBW group, and the fact that due to long duration of the MRI (about 30 minutes), many of the images of the youngest children had to be excluded due to movement artifacts. Because the term born children were part of a larger collaboration study with researchers at the University of Oslo these children received a less comprehensive standardized test battery to be used in this multicenter study. The test battery was therefore slightly different from that in the VLBW group. In addition, full corpus callosum segmentation is not available in the current version of TRACULA.

Corpus callosum has been associated with deficits in diverse cognitive skills in previous VLBW studies and would have been an interesting complement to the 18 tracts investigated with TRACULA. Furthermore, the pointwise statistics in TRACULA are based on probabilistic reconstruction of tracts and may therefore understate diffusion measures in tract extremities, including those closer to their cortical endpoints.

Bias and confounders

A possible limitation in both studies is selection bias regarding the preterm and control groups. However, the participation rate was acceptable and comparable to and even better than many other studies that have followed VLBW subjects into adulthood, with a participation rate of 72% in the VLBW group and 74% in the controls at our 19 years follow-up. It has been proposed that the participants lost during follow-up studies are the ones with most problems and the worst prognosis (167), but the background information about the participants in our study does not support this notion. Parents that experience problems or have expectations of disabilities in their children might be more interested and motivated in participating in clinical studies (168), whereas healthy controls and the parents may have more altruistic reasons for participating.

The term born children in study 2 are part of the large multicenter MoBa study, in which they and their parents have been participating since the mother was pregnant with the child. Strains due to participation in multiple spin-off studies (like our neurocognitive imaging study) and repeated requests to answer different comprehensive questionnaires, one may argue that the parents in these types of studies most probably need to be highly motivated. This could lead to a selection bias in the control group. The socio-economic status was slightly different in the two groups; parents of the MoBa children had higher education level than the parents in the VLBW group. This could confound the results; hence most statistical analysis was corrected for SES. One possible bias in study two was the fact that the VLBW children and the controls received slightly different cognitive test batteries and consequently the testers were not blinded to group affiliation. The long duration of the MRI may be a confounder as the youngest children and the children with reduced ability to maintain still had to be excluded due to movement artifacts. However, an approximately equal percentage of the VLBW group and controls were excluded due to poor image quality. There was no difference in mean IQ score in the group who had to be excluded and the ones included in the MRI analysis within each study group. The majority of excluded images due to excess movement were obtained

from the youngest children in both groups. We did choose to control for age at MRI and sex, since larger studies have shown associations between certain subcortical volumes and age and sex (169). However, in this cross-sectional study it was not the intention to identify specific developmental changes within this age range, nor specific gender differences. In general, VLBW children are often smaller than their term born peers and consequently have reduced head circumference compared to controls. We therefore adjusted for estimated total intracranial volume in the brain volumetric group analyses.

IQ, neuropsychology and executive functions

Cognition correlating to brain morphometry will be discussed in each of the sections covering the morphometry and diffusion data acquired by MRI.

In both study cohorts, poorer cognitive scores were reported in the preterm group compared to controls. This is in line with what is commonly found in other follow-up studies where up to 50% of very preterm children develop neurodevelopmental impairments and deficits, including low IQ, specific cognitive impairments, as well as behavior and socialization problems (170-173).

The VLBW group in paper 1 had lower scores than controls on 8 of the 18 neuropsychological subtests assessing different aspects of attention and executive functions where effect size for the tests with significant group differences varied between 0.54-0.88. In addition they had significantly poorer full-scale IQ than controls. This is in line with results from several other studies in VLBW adolescents and young adults (76, 77, 93). Individuals from the same study cohort were included in paper 2, and here we further report lower scores on all neuropsychological tests and within both executive function and attention domains, as compared with the term born control group. This may indicate that young adults born preterm with VLBW continue to be at disadvantage into young adulthood and that they seem to have multiple cognitive problems.

Previous reports of general executive function problems (76, 174) as well as reduced processing speed and attention deficit (89) in VLBW adults are in accordance with our findings. In accordance with our results in paper 2, Nosarti et al. (76) and Allin et al. (175) found that VLBW subjects had problems with verbal fluency, and Tanskanen, Valkama (176)

showed problems with verbal learning among VLBW adults compared with term born controls.

In several studies, processing speed has been reported as being poorer among VLBW children and adults than term born controls (76, 89, 177, 178). Processing speed plays an important role in working memory and general intelligence together with other functions (179). Gnigler, Neubauer (177) found that complications of prematurity, such as corticosteroid treatment, retinopathy of prematurity grades three and four, as well as intracranial hemorrhage, predicted reduced processing speed in VLBW children at age five. In accordance with this, Murray, Scratch (178) found significant associations between brain abnormality on MRI at term equivalent age and poor processing speed and attention scores in VLBW children at age seven. When correcting for Processing Speed Index in the statistical model in paper 1, group differences in the tests Design fluency 2, 3 and Stroop 3 disappeared and the significance levels were also reduced from $p \leq 0.001$ to $p \leq 0.01$ on all other tests except for TMT2. Mulder et al. claimed that slow processing speed and reduced working memory explain inferior academic attainment in preterm children (180) and that processing speed seems to be an important determinant underpinning many neuropsychological deficits seen in VPT children in middle childhood (180). This is in line with our results where we found fewer group differences after co-varying for processing speed index. We have also reported reduced Processing Speed and Working Memory Indices compared with controls in the same group of VLBW young adults (75).

IQ-difference between the two cohorts

In both study cohorts inferior full-scale IQ score was found within the VLBW group when compared to controls. The VLBW young adults had a mean Full IQ at 88 (SD =13) compared to 98 (SD = 10) in the VLBW school aged children. A student thesis from our research group investigated the mean IQ score for ELBW and VLBW children from 3 study cohorts born in the late 80s, the 90s and the 2000s, respectively, and found that the mean IQ score for the children born after 2002 was significantly higher than for children born in the late 80s, even though survival rates had increased markedly (181). The difference in IQ scores between ELBW children and term born controls has decreased with time; in contrast the difference between VLBW and controls did not change significantly from the cohort born on the 80s and the cohort born in the 2000s. The VLBW children born in the late 80s and the children born in the 2000s had a mean IQ score of 90 (SD = 12) and 95 (SD = 11) respectively (181). This

could indicate that improved prenatal care and medical treatment in the NICU result in better cognitive outcome, especially for the most immature and vulnerable infants. However, the effect of prematurity per se does still negatively affect the cognitive abilities in survivors. In a study by Taylor, Minich (182) neuropsychological outcomes were worse for individuals with a higher risk of brain injury, i.e., those with the lowest birth weight, gestational age and longer periods of extra oxygen requirement. In accordance with Taylor et al. the higher full-scale IQ scores reported in school-aged VLBW children compared to the VLBW young adults could therefore possibly be accounted for by less perinatal morbidity. However, the perinatal variables in our two cohorts only vary to a limited extent with the cohort of VLBW children having reduced birth weight (1217 grams in VLBW young adults compared to 1050 grams in VLBW children) and gestational age (29.1 weeks in VLBW young adults compared to 28.5 weeks in VLBW children) compared to the VLBW young adults. Apgar scores after 1 and 5 minutes and days on mechanical ventilator were almost identical in the two cohorts. We report in paper 2 that none of the clinical variables investigated stood out as substantial indicator of neuropsychological performance in adulthood within the VLBW group. These results are somewhat in agreement with Nosarti et al. (76) who found no association between perinatal variables and executive function in their VLBW group of young adults. These rather inconsistent results indicate that the relationship between perinatal variables and later cognitive abilities are complex and more research is needed.

BRIEF-A Self-report

Even though the VLBW participants obtained lower scores on several of the neuropsychological tests, we found no significant group differences in self-reported BRIEF-A mean scores. Within the VLBW group, there was a correlation between some BRIEF-A indices and a limited number of D-Kefs test scores. Higher scores on BRIEF-A sum-indices correlated to poorer scores on the TMT (based on scores on Shift and Working Memory) and Stroop tests (explained by scores from Working Memory and Plan/Organize), but with no correlation to Design Fluency in the VLBW group. In the control group all BRIEF-A sum indices correlated negatively to one or several of the D-Kefs test scores. However, it is important to note that the correlation was not significantly different for the two groups when conducting Fisher's z transformation statistics.

One possible explanation for the limited correlation between BRIEF-A and test scores within the VLBW group could be that the reduced test scores may reflect other cognitive core

deficits than executive functions per se. All but one of the tests did have a strict time limit and the inferior results in the VLBW group may therefore be partially related to a reduced processing speed. This is in line with our results where we found less group differences after co-varying for PSI; however, since some group differences in tests scores persisted after correcting for PSI, reduced processing speed could not fully explain the inferior test results in the VLBW group.

In a study by Rabin et al (183), that included persons with mild cognitive impairment, the BRIEF-A seemed to be sensitive to executive function changes in everyday aspects that are not necessarily assessed by standard neuropsychological tests and BRIEF-A may therefore provide more ecologically valid information than performance-based tests administered in strict controlled testing environments. Our results in the VLBW group are in agreement with a review of ecological validity of neuropsychological tests where it was argued that self-reported executive functions have no or low correlation to executive tests (184).

In paper 1, we further suggested that there may be an underreporting of problems among the preterm born young adults, caused either by lack of insight or as a result of environmental compensation. Underreporting due to reduced insight regarding own functioning has been reported by others (185), and Burgess et al. found that an adult population of neurological patients reported fewer problems than controls and their significant other, although they had poorer performance on the executive tests (186). The authors suggested that people with deficient executive functions are not good informants on their own abilities due to reduced self-awareness (186).

Hack et al. found that the VLBW young adults did not distinguish themselves from the controls even though test results indicated an increase in psychopathology in this group (88). Parents and teachers' BRIEF reports showed increased symptoms in VLBW adolescents (87, 187-190) and Indredavik et al. assessed mental health in VLBW adolescents from the same study population as ours, and reported no difference between the VLBW and control adolescents in self-reporting of behavioral problems, even though the parents of the VLBW subjects reported that their teens had more problems (189). It is therefore likely that the VLBW young adults underreport their own struggles in this study using BRIEF-A self-report. There are indeed concerns regarding the reliability of self-report, as the ability to rate one's own cognitive control has been shown to be difficult not only for patients with different neurological deficits, but also for healthy adults (191).

Cortical surface area and cortical thickness

In paper 3 we reported a significant reduction in cortical surface area in 5-10 years old VLBW children born between 2003 and 2007, in comparison to a term born control group, with widespread reductions of cortical area in frontal, temporal, parietal, and occipital regions. The VLBW group also presented significantly thicker cortex in the frontal (medial orbitofrontal gyrus, rostral anterior cingulate, frontal pole) and occipital regions (pericalcarine sulcus) bilaterally, and a thinner cortex in the right posterior parietal lobe compared with controls.

Reduced cortical surface area has previously been reported in ELBW children at the age of 10 years (107), in VLBW adolescents at 15-16 years of age (109), and in VLBW late adolescents at 19 years of age (108). The surface area map from the study of Skranes et al. (108) is displayed together with the surface area map from paper 3 in Figure 8. The MRI findings of the VLBW young adults presented in Skranes et al. (108) are from the same population as in paper 1 and 2, and the reductions seen in cortical surface areas are remarkably similar to the reductions observed in the preterm children in our study (paper 3), both in terms of magnitude and localization of the affected regions. Several similar cortical regions are affected in the two cohorts at ages 5-10 and 18-20 years, respectively, especially in the temporal, posterior parietal/occipital and ventral frontal regions. Figure 8 clearly demonstrates that similar cortical changes are found in VLBW survivors born in the late 80s and after the year 2000, in spite of the advances in perinatal medicine. One interpretation of this finding may be that the morphological abnormalities observed in the preterm children are not only reflecting delayed maturation but rather aberrant development leading to permanently altered cortical architecture.

The explanations for the altered cortical surface area may be due to prenatal factors, such as fetal growth restriction and/or that immature birth exposes the neonate to environmental factors such as inflammation and stress that may exert an epigenetic influence on the genes controlling normal cortical development. Cortical area and cortical thickness reflect at least two distinct sources of genetic effects (192), consistent with the developmental origin of cortical architecture as described in the radial unit hypothesis (193), and other studies have suggested independent and divergent developmental trajectories for area and thickness (194-196). A recent study demonstrated that cortical surface area is more related to genetic factors than cortical thickness (197). In addition we found in a post-hoc analysis in paper 4 that cerebral white matter volume correlates to surface area and not to cortical thickness in both the premature and the controls. The deviations seen in cortical surface area in the VLBW

group may therefore be both primary changes due to abnormal cortical development and secondary to altered white matter microstructure and connectivity.

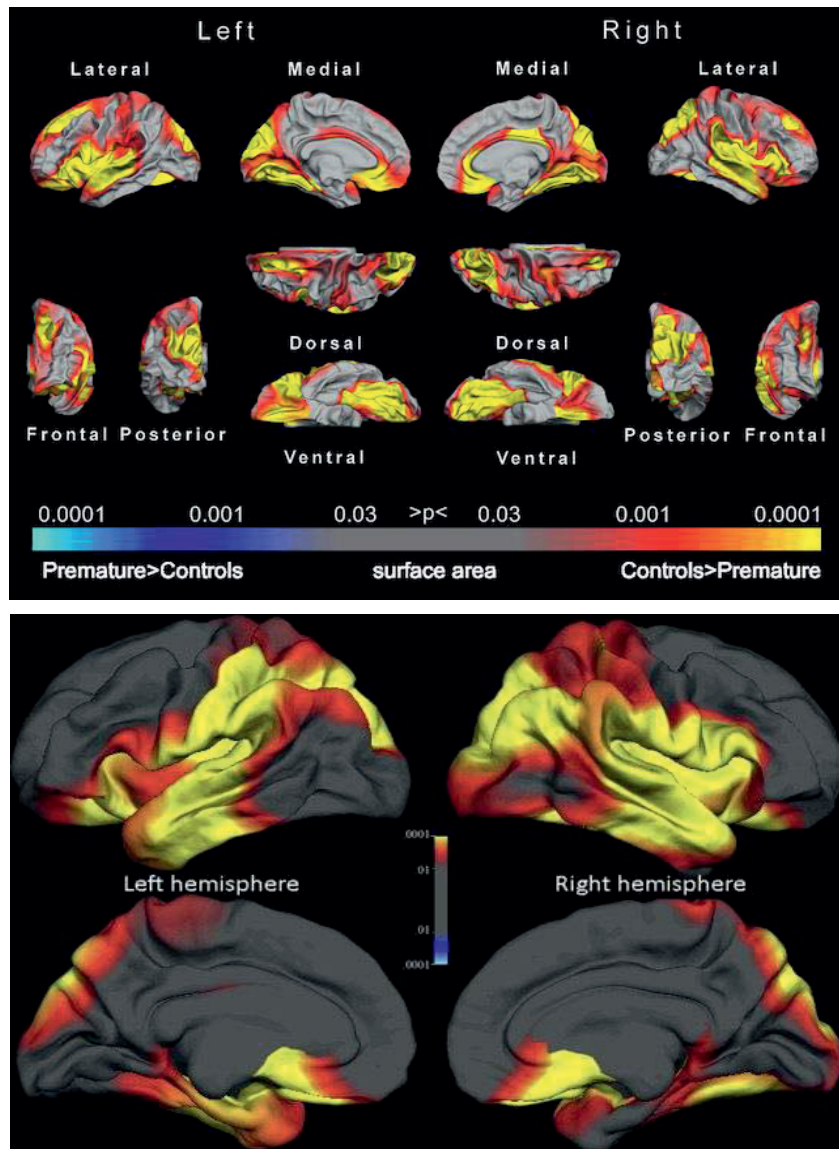


Figure 8.

The figure shows group differences in cortical surface area between VLBW and control children with mean age of 8 years (the 6 figures at the top), and in VLBW and control young adults at age 19 (the 4 figures at the bottom). The mapping of cortical surface area is shown on the reconstructed cortical surface. Cortical areas with statistically significant difference between groups are shown in color, and the color scale shows the dynamic range of the statistically significant changes (in p-values), red to yellow represents an increasing reduction of the cortex in the VLBW group compared with controls.

The VLBW children had thicker cortex in the frontal and occipital lobes bilaterally. These results are consistent with previous studies reporting increased cortical thickness in both children and adolescents born prematurely (106, 107, 110-112). In normal development cortical thickness increases during early infancy due to late arriving interneurons, and decreases with age starting at age 4 years (23) due to pruning as neural connectivity improves (194-196). Since children develop at varying paces, one possibility could be that the group differences in cortical thickness in our study reflect delayed maturation in the VLBW group, as suggested by Mürner-Lavancy (110). In a study of VLBW and term born control children at 7-12 years of age, Mürner-Lavancy (110), reported thicker frontal and parietal cortex in the youngest VLBW children compared to controls but no such group differences in the oldest children. Results from previous studies are somewhat inconsistent. Grunewald et al. (107) found cortical thickening only in the occipital lobe at 10 years of age in a cohort of ELBW children, whereas Bjuland et al. (112) found increased cortical thickness in frontal and occipital regions but also thinner cortex in parietal and temporal regions in 19-year old VLBW adolescents.

The VLBW children in the present study were born between 23 and 35 weeks of gestation, which is a particularly sensitive period of cortical development, and preterm birth may therefore affect processes like neuronal migration, synaptogenesis and apoptosis in late second and early third trimester (10), resulting in the deviant cortical thickness and reduced surface area observed in our cohort. In addition, the exposure to the harsh extra-uterine environment in the NICU is also believed to increase the risk of disrupted brain development in very preterm born survivors. Repeated procedures inducing pain-related stress place very preterm infants at particular risk due to the very rapid brain development and programming of stress systems while they are in the NICU (17, 187). The consequences of such developmental disruptions in an extremely sensitive period of brain growth may be profound alterations of subcortical and cortical morphology that might affect brain functioning. Ranger et al. (198) reported that more neonatal pain-related stress was associated with lower cortical thickness in frontal, parietal, and temporal regions at school age in children born very preterm, independent of other neonatal confounding factors. Furthermore, greater exposure to neonatal pain-related stress has been shown to be associated with altered development of the subcortical gray matter and white matter microstructure from birth to term equivalent age (199).

Cortical morphology and cognitive measures

We found that the executive function domain scores correlated positively with cortical surface area, i.e., better scores correlated with larger regional surface area in the 19 years old VLBW young adults in paper 2. Significant positive correlations between cortical surface area and executive functions were observed in the posterior superior temporal sulcus, lingual gyrus, lateral occipital gyrus in the left hemisphere, and the caudal and rostral anterior cingulate, medial orbitofrontal gyrus extending into lateral orbitofrontal gyrus, anterior medial temporal gyrus and superior temporal gyrus, as well as posteriorly in lateral superior frontal gyrus in the right hemisphere. In the school-aged children in paper 3, we reported a relationship between full-scale IQ and surface area in the caudal middle frontal gyrus, lateral orbitofrontal gyrus, medial orbitofrontal gyrus, pars orbitalis, rostral anterior cingulate, frontal pole and insula in both groups, albeit as a non-significant trend in the VLBW group. However, larger effect sizes were noted in frontal, temporal and medial parietal regions in the VLBW children than for the controls. The frontal regions in which surface area was related with IQ were regions where the VLBW children had significantly reduced surface area in comparison with controls, and these areas are believed to be important for cognitive functions such as decision making, executive functions, semantics, attention, and working memory. We speculate that the reduced cognitive function in the VLBW group may therefore at least partly be caused by the observed reduction in surface area. A study from the same cohort as the individuals in paper 2 revealed reductions in cortical surface area in the VLBW group compared with controls, where IQ correlated with surface area reductions in some areas of the brain (108). Figure 8 shows a clear overlap between our findings of group difference in cortical surface area in the VLBW children and the findings in the young adult study by Skranes et al. (108). Furthermore, there was also some overlap between their results showing significant correlations between surface area reduction and IQ and our results in the VLBW children. This overlap was especially pronounced for the Working Memory Index in their study and the executive function domain in our study, with correlations to surface area in the medial frontal lobe, indicating affected structure-function relationship in the preterm brain.

Other cross-sectional studies have reported significant associations between smaller cortical thickness in parahippocampal regions and lower IQ (130) and entorhinal cortical thinning and reduced executive function scores (127) in VLBW adolescents. We did not find any significant correlations between neuropsychological test scores and cortical thickness in paper 2 or between Full IQ and cortical thickness in paper 3. However, a trend-level negative

relationship was found in paper 3 between cortical thickness and Full IQ in both groups in widespread cortical regions, i.e., the thinner the cortex, the higher the IQ scores in the school-aged children. In the VLBW group, the regions with the strongest negative associations between IQ and cortical thickness were also the regions where the VLBW children displayed thicker cortex than controls. Moreover, some temporal and parietal regions showed a positive relationship to Full IQ in the VLBW group, i.e., thinner cortex was related to lower IQ scores. This is consistent with previous studies of the relationship between cortical thickness and cognitive functions in normally-developing 5- to 11-year old children, where cortical thinning in left dorsal frontal and parietal lobes was correlated with improved verbal performance (30) and as shown in the VLBW adolescents with low IQ in cohort 1, where Full IQ and cortical thickness correlated negatively in frontal (thicker in the VLBW group) and positively in parietal (thinner in the VLBW group) areas (112).

Our findings suggest that altered cortical development in the VLBW children seem to affect their cognitive abilities. We suggest a need for more longitudinal studies starting at birth to determine when these cortical deviations appear, how they progress and whether these deviations persist during further brain maturation throughout school age, adolescence and into early adulthood also for these recent year cohorts of VLBW children.

Subcortical volume

Several neuroimaging studies have revealed a variety of region-specific volumetric abnormalities in preterm infants and children, including reductions in gray matter volume and abnormalities of white matter (58, 200-203). In paper 4 we examined structural brain volumes in the VLBW children and controls and found reduced volumes of several subcortical structures: cerebral white matter, thalamus, globus pallidus, hippocampus, ventral diencephalon (DC), and brain stem in the VLBW children compared to controls. In addition, the volumes of the corpus callosum posterior, mid-posterior, central, and mid-anterior segmentations also showed significantly reduced volume ($p < 0.0001$) as well as increased volume in lateral and third ventricles in the VLBW group.

Our findings of reduced brain structure volumes in the VLBW children in paper 4 are consistent with several other studies who have reported reduced corpus callosum volumes in 7- to 8-year old children (115); reduced white matter volume in preterm children between 5 and 12 years of age (204); smaller globus pallidus and thalamic volumes in 8- and 10-year old children born very preterm (63, 107) as well as reduced volumes of putamen and cerebellar

cortex (107). Taylor et al. (205) found smaller brain stem and thalamic volumes in VLBW adolescents compared to controls, with additional reduction in cerebral white matter and hippocampal volumes also evident comparing controls to adolescents born preterm with birth weight < 750 grams. These reductions in the brain structure volumes appear to persist with age as they have also been documented into adolescence and adulthood in preterm born groups (62, 113, 130, 206-212).

Bjuland et al. (62) published a paper on cortical brain volumes and cognition in the VLBW young adult population studied in paper 1 and 2 in this thesis. They reported that the VLBW group displayed smaller brain volumes, especially thalamus, globus pallidus and parts of corpus callosum as well as larger lateral ventricles. A negative correlation was found between number of days in NICU and volumes of globus pallidus, nucleus accumbens and posterior part of corpus callosum, but with no correlation to gestational age. Nosarti et al. (113) found reduced gray matter volume in thalamus, caudate nucleus and putamen, and smaller subcortical white matter volume where the volume alterations were correlated to gestational age and birth weight. In the cohort of young school aged children in paper 4 there was a positive correlation between the volumes of corpus callosum posterior and gestational age among VLBW subjects. In addition positive correlations were observed in cerebral white matter, left accumbens area, right cerebellar white volume and gestational age as well as a positive correlation between birth weight and, cerebellum white matter and left accumbens area ($p \leq 0.05$). However, only the correlation in corpus callosum survived correction for multiple comparisons ($p \leq 0.001$).

We further reported a negative correlation between days on mechanical ventilation and volumes of thalamus, brain stem, left accumbens area, left ventral DC, right caudate and right cerebellar white matter, however only thalamic volume survived correction for multiple comparisons. In contrast, Bjuland and colleagues did not find any volumetric correlation to the number of days on ventilation (62).

Subcortical volumes seem to be negatively affected by increased perinatal risk factors and prematurity and are manifested even in premature children born after 2000.

White matter volume seems to be particularly sensitive to many of the clinical variables in the premature group. We found reduced surface area in the VLBW children presented in paper 3 and in paper 4 we report significantly reduced white matter volume in the same children. Post-hoc analysis showed that white matter volume correlated significantly with cortical

surface area in both groups. By applying the novel DTI method, TRACULA, we investigated the endpoints for the white matter tracts in cortical regions and were able to extract data on cortical thickness from these regions. We did not find any significant correlations that survived correction for multiple correlations between tract diffusion measure and endpoint cortical thickness. However, when examining in which of these cortical parcellations the white matter tracts with deviations in diffusion measures ended, we found that these cortical regions had group differences in cortical surface area and cortical thickness. This may indicate an anatomical relationship between abnormal connectivity and appurtenant cortical areas. A connection between white matter volume and cortical surface area has also been shown in a population of healthy adults (213), and white matter connectivity has been shown to have the potential to partly determine gyrification in the developing brain (214). Ortinau and Neil (215) identified global reductions in brain volume and cortical surface area of very preterm children at school age compared to term born children which was accompanied by specific regional patterns of cortical morphological changes, including shallower sulcal depth in the superior temporal sulcus, more convoluted medial fronto-parietal cortex and abbreviated cingulate sulci in premature children. A recent study showed that cortical surface area is related phenotypically and genetically to general cognitive ability (197).

The third trimester is a period of massive expansion of subcortical white matter, formation of long-distance connections, and extensive cortical folding. It has been proposed that mechanical tension generated by axons within the white matter may be a major factor that contributes to cortical folding during normal brain maturation (214). Furthermore, white matter injury may impact the development of basal ganglia and thalamus and it has been suggested that this disturbance to the connectivity of developing neural systems may have important functional consequences (67). Decreased volumes of the basal ganglia and thalamus have been frequently reported (55, 59, 68, 202, 216) and such reductions have been associated with concomitant white matter injury (55, 59, 202, 216). Ortinau and Neil (215) suggest that the volume of the thalamus could be associated with injury to cortex and white matter where widespread white matter injury can reduce input to the thalamus, and subsequently reduce the number of thalamic neurons. Pathology that involves injury to the developing white matter and disturbances of axonal/neuronal development may involve cell types like pre-oligodendrocytes (OLs), white matter axons, subplate neurons, and late-migrating GABAergic neurons (17).

Subcortical volumes and Cognitive abilities

Structural brain abnormalities have been associated with cognitive and behavioral defects during childhood and adolescence (113, 200, 202, 203, 217). Cognitive abilities have been seen to correlate with white matter volume in 8- to 12-year old preterm children (204), and a positive linear regression has been documented between cerebellar volume and Full IQ in 8-year old preterm children (218). In contrast to these previous reports, we did not find any relationship between subcortical volumes and Full IQ in either of our groups. This may be due to a limited sample size in the VLBW group, but also cognitively well-functioning children where the majority of the children in both groups displayed Full IQ scores within the normal range. In the study by Bjuland et al. (62) of 20 years old VLBW young adults the authors reported several correlations between brain structure volumes and Full IQ scores, also for some of the brain structures with reduced volume in our VLBW children. One explanation to this discrepancy can be the difference regarding Full IQ scores. The mean IQ in the 19-20 year old VLBW group was 89 (range = 85-93) whereas our children had a mean IQ of 98 (range = 82-132).

In the MoBa neurocognitive study (paper 3 and 4), we collected a large amount of neuropsychological test results and included parent based questionnaires. Several of the subcortical structures that were smaller in the VLBW children are involved in working memory networks, where McNab and Klingberg (69) identified the globus pallidus as essential for controlling access to working memory, while functional and structural imaging of basal ganglia and thalamus predicted healthy children's visuospatial working memory two years later (219). A relationship between smaller hippocampal volumes and inferior memory function in our cohort of VLBW young adults have been reported by our group (164). In addition, reduced volumes of putamen, cerebellar white matter and corpus callosum were found to correlate with higher ADHD rating scale score and higher BRIEF main indices reflecting more attention deficit, hyperactivity and executive function problems in 10 years old ELBW children (107). Such results indicate the need to run further analysis on our data material to see whether there are associations between brain volumes and the results on neuropsychological tests as well as parent reports.

Most of the previous studies include preterm children, adolescents and young adults born before the year 2000 who have not received the same state of the art medical treatment as our population born after the millennium. Since our VLBW group consists of relatively healthy

children, most of them with a rather uncomplicated neonatal period, these overlapping findings of reduced subcortical volumes in the preterm groups could imply that these volume reductions may be more influenced by prematurity per se causing reduced growth and development than brain injury in the perinatal period. In future research, the relationship between early trajectories of cortical morphology and neurodevelopmental outcomes will be important to elucidate.

Diffusion tensor imaging - DTI

Our DTI results with only minor group differences in diffusion measures were somewhat surprising based on previous literature where widespread reductions of FA in white matter tracts have been reported in young children (13, 220, 221), school aged children (204, 222, 223), adolescents and young adults (120, 125, 218, 224, 225). A DTI study at near-term age in preterm infants reported no group differences in FA between preterm and term born participants and concluded that FA was more associated with complications of preterm birth than with preterm birth per se (226). Respiratory disease during the perinatal period has proven to be critical for white matter lesions in preterm infants (227). Acute episodes of hypoxia–ischaemia and chronic hypoxia can cause acute degeneration of late oligodendroglial precursors followed by a regenerative response of the surviving pre-oligodendroglia (123). However, the surviving cells may display altered and incomplete maturation leading to a failure to produce myelin (228).

In our population of premature children, only 5 children were in need of assisted ventilation during the NICU period, ranging from 8 to 35 days on mechanical ventilation. The white matter integrity in the VLBW group was different from the controls in several tracts, however only forceps minor displayed significantly reduced FA ($p \leq 0.05$). A post-hoc analysis using partial correlation, corrected for age and sex, displayed a robust negative correlation between days on ventilator and FA in forceps minor ($r = -0.88$, $n = 17$) where the reduction of FA was driven by an increased radial diffusivity (RD) in these five children. Further analysis showed that FA in the right inferior longitudinal fasciculus, the uncinate fasciculi and cingulum also correlated negatively with days on ventilator with a p-value between $p = 0.016 - 0.048$. However, none of these correlations survived correction for multiple comparisons. Nevertheless, our findings may indicate that only the limited number of preterm children with neonatal respiratory complications seemed to have deviations in white matter microstructure,

possibly explaining why we did not find a widespread reduction in mean FA in the entire VLBW group.

Furthermore, a significant increase in RD in left cingulum was observed in the VLBW children compared to controls, which may indicate reduced myelination. Cingulum is thought to connect the entorhinal cortex and the anterior cingulate cortex, with the anterior cingulate cortex is involved in motor functioning of the hands, among other functions. Furthermore this area is thought to be involved in visual-spatial and tactile analysis as well as motor output and memory. Sripada et al. (79) reported that visual-motor integration (VMI) problems persist into adulthood for very low birth weight individuals, and found a correlation between VMI results and FA especially in the corpus callosum, inferior fronto-occipital fascicles, and anterior thalamic radiation bilaterally with reduced FA primarily driven by an increase in radial diffusivity.

We also report an increased FA in the left cortico-spinal tract in addition to increased axonal diffusivity (AD) in the posterior part of the left superior longitudinal fasciculus and in the arcuate fasciculus in the VLBW children. Superior longitudinal fasciculus connects the rostral inferior parietal cortex and the ventral precentral gyrus, and it is suggested that this tract is involved in transferring somatosensory information to and between the ventral premotor cortex, the supramarginal gyrus and the lateral inferior prefrontal cortex. The arcuate fasciculus is part of the superior longitudinal fasciculus and connects the superior temporal gyrus with the dorsal prefrontal cortex, suggesting an involvement of transmitting auditory information. Furthermore, there is a common understanding that the arcuate fasciculus connects two important areas for language use, Broca's area and Wernicke's areas. One possible interpretation of the increased FA and AD in these regions in VLBW children can be that these tracts are involved in processing sensory information like auditory, tactile and visual processing, and studies have shown increased FA values in various motor and sensory tracts in premature infants possible due to increased stimuli and early exposure with more rapid maturation of these tracts (22, 221).

Another possible explanation of increased AD and FA values in white matter could be that the VLBW children often display ventricular dilatation. In a case study of preterm born adolescents with ventricular dilatation, Myall et al. (229) describe possible axonal straightening and increased axonal density in the superior longitudinal/arcuate fasciculus, among other tracts, leading to increased AD measures. Additionally, a study on diffusion

measurements on myelin-deficient and demyelinated fibers suggested that fractional anisotropy and mean diffusivity could arise predominantly from axonal density rather than from myelin content (221). However, in our study post-hoc analysis showed no correlation between ventricular volume and white matter integrity in the VLBW children. Even though many studies report reduced FA in several tracts in the VLBW population, a DTI study including 58 preterm born children with normal functioning at 9 to 16 years of age did not find any significant FA reductions compared with age-matched controls, but actually showed widespread increases in FA in the preterm group (224). One suggestion was that this may represent a relative increase due to reduction in white matter volume, crossing fibers and/or dendritic branching (224), or that this increase in FA could be due to compensatory mechanisms in order to maintain normal neurological functions (125). Other studies have also reported no difference in FA in preterm born adolescents (109) and adults (230) compared to controls. Interestingly, in a study of adults born preterm, FA was lower in some clusters and higher in other clusters of white matter tracts (218). The increased FA was actually associated with more severe neonatal brain injury in the very preterm group. Furthermore, the reduced FA was associated with lower birth weight and perinatal hypoxia and with reduced adult cognitive performance in the very preterm group only (218).

We speculate that high cognitive functioning in our VLBW children may explain the minor differences in white matter diffusion measures between the two groups in this study. One possible explanation for our rather surprisingly normal diffusion findings is that the preterm children scored within the average range on the test of intelligence and most had no apparent white matter injury on structural MRI. Additionally, 31.6% of the preterm children received follow-up with special education in preschool and school, and white matter is known to respond to experiences such as training (231). This could possibly have improved the white matter integrity over time in the VLBW children with highest risk of white matter pathology. Fractional anisotropy has been reported as significantly associated with IQ and other functional outcomes within several preterm groups (86, 125, 224, 225), but most of these studies include preterm children from older year cohorts. We did not find any correlation between FA and Full IQ in study 2, while this has been reported for the VLBW young adults in study 1 (86, 120).

Finally, FA in white matter tracts does seem to increase with increasing age in normally-developing children as reported in a study with children from age 6 to 19 years (232). We

found no correlation between FA and age in our children population in study 2. However, this may be explained by a narrow age span in our study groups, where the mean age was between 8 to 9 years of age in 61 of 67 participating children. Due to the use of different DTI sequences and methods of analysis, we have not compared the diffusion measures in our VLBW young adults with the findings in the VLBW children.

Clinical implications and Future directions

Based on our results in paper 1 and previous studies we would argue that young adults born preterm with VLBW do have executive function deficits, but these deficits does not seem to represent a great challenge in their daily life functioning, at least according to themselves. In general, studies including reports of executive functioning from relatives have shown stronger correlates to results on executive function tests, than from self-reports. We recommend that a combination of behavioral ratings and neuropsychological tests should be applied to obtain a more complete picture of executive functioning in a clinical group like preterm born VLBW individuals. Løhaugen et al. found that the need for special education was higher in the VLBW young adult group included in the present study, and they were more often unemployed compared with controls (75). To explore the effect poorer executive functions can have in adulthood, more ecologically valid tests of executive functions may be called for, and future follow-up assessing cognition, mental health and quality of life are therefore planned for this cohort of VLBW adults. These studies should incorporate other known variables that can impact preterm children's long-term outcome, such as parents' mental health and family functioning in early childhood and adolescence, as this could add valuable information regarding the young adults' mental health.

Altered brain morphometry was reported in both the VLBW study groups where we showed reduced cortical surface area, regionally increased cortical thickness and reduced subcortical volumes. Previous structural MRI studies have similarly found that the amount of gray matter continue to decrease in the early adulthood with almost linear volume reductions hereafter (233-235). Reduction in gray matter in temporal cortices has been associated with early-life psychosocial adversities in individuals without a current psychiatric diagnosis (236). Altered patterns of cortical development following very preterm birth observed in this thesis is similar to cortical brain regions related to psychiatric disorders known to be more prevalent in preterm samples than controls (237, 238). Reductions in white matter and smaller total cortical surface area could be central anatomical abnormalities and drive, at least partially, the

reduced regional gray matter volumes observed in illnesses like schizophrenia (239). Furthermore, Shaw et al. (240) observed neurodevelopmental changes in cortical thickness resembling those found in ADHD in typically developing youth exhibiting hyperactive/impulsive signs. This indicates that the premature children with deviant brain volumes and morphometry should be followed more closely than term born peers due to their possibly increased risk for behavioral and psychiatric disorders.

Age-related white matter volume changes are characterized by a nonlinear trend with an increase continuing into the fifth decade of life followed by an accelerating white matter shrinkage with advancing age (233-235).

The VLBW subjects have decreased brain volumes and altered cortical morphometry in addition to poorer outcome on cognitive measures, and it is not known whether these deviances will have a negative impact on the aging brain in this population, constituting an increased risk of pathological aging with dementia. We found reduced surface area in the VLBW children in our study population in paper 3, and in paper 4 we report significantly reduced white matter volume in the same children. Post-hoc analysis showed that the white matter volume correlated positively to cortical surface area in both groups. In normally aging adults a decrease in white matter tissue components including demyelination has been reported (241, 242), and a decrease in cortical surface area seems to co-occur with accelerating changes in white matter volume (in the elderly) (243, 244).

In normal aging both cross-sectional and longitudinal studies find robust declines in abilities such as encoding new memories of episodes or facts, working memory and processing speed (245, 246). Poorer working memory and processing speed has also been seen in the VLBW cohort. The white matter abnormalities in normal aging are associated with poor performance on tasks of processing speed, executive function and immediate and delayed memory, but not with declines in general intelligence measures (247). Early results from longitudinal MRI research show that in normally aging adults, volume loss in the striatum throughout adulthood, as well as age-related alterations in white matter in the prefrontal cortex and the anterior corpus callosum (248); however, all regions also show some age-related decline in white matter integrity (248, 249). Several hypotheses for the anatomical volume loss seen in normal aging have been proposed in a review by Hedden and Gabrieli (250), including loss of synaptic density, decreased activation caused by activity in smaller neuronal populations due to greater variance or less synchrony in population firing, decreased neurotransmitter binding,

decreased neuronal metabolic activity or failures in afferent excitatory connections. Consequently, we would argue that a close follow-up of the very preterm born population beyond childhood age is important as studies suggest that an increased risk of developing psychiatric disorder following very preterm birth may be reinforced by region-specific altered cortical development (251), in addition we fear an increased risk of pathological aging among those born preterm due to less brain reserves.

Possible clinical interventions

Low IQ may have a pervasive impact on educational attainment. Since both VLBW groups in study 1 and study 2 display reduced Full IQ scores and poorer outcome on several neuropsychological tests, this may indicate the need for increased awareness of possible learning problems in this population during preschool and school age. Our experience is that an assessment of Full IQ is a good screening and prognostic tool with regard to different cognitive deficits. It may be important to implement IQ testing for the children in risk at preschool age with a follow-up IQ assessment at age 10 years. By doing so, we would be able to identify the children in need of special education at an early age and thereby provide extra resources and help during preschool and at school and hopefully prevent them from lagging behind their fellow students in educational progress. Possible interventions may be individualized special education or more help at school. An adaptive learning environment which gives the child more time and leaving more time for repetition could improve the consolidation of knowledge. Poorer executive functions may indicate that they could benefit from help with planning, organizing and initiating different tasks during sessions. Several studies, including our results from study 1, show that the VLBW population often struggle with reduced processing speed, and may therefore benefit from longer time limits on exams and by being able to use computers in school since fine motor function is also often reduced.

We have further shown that the VLBW population has more problems with working memory. An intervention study using computer-based working memory training has shown promising results where VLBW preschoolers had positive short- and long-term effects on trained and non-trained working memory tasks with transferred effects seen as improved auditory attention, phonological awareness, and visual as well as verbal memory (107, 252). This intervention might be valuable in preterm children before they start school, and such interventions may prevent or at least reduce cognitive problems that impact educational achievement and social functioning. More studies are needed before computerized working

memory training can be recommended as prophylactic treatment of cognitive deficits in preterm born children.

Diffusion properties in white matter tracts among VLBW individuals have been shown to correlate with diverse cognitive deficits, and it is possible that VLBW individuals exhibit plasticity to develop different neural network trajectories and compensatory connections related to certain cognitive functions (110, 253, 254). Brain morphometry, especially of white matter microstructure and cortical surface area, may reveal biomarkers for early detection of children with developmental delay and increased risk of poorer cognitive functions. Coupled with emerging techniques in diagnostic imaging and analysis (PET MRI, quantitative EEG, fMRI), our increased understanding of connectivity in the developing brain may inspire the implementation of use of multimodal MRI in early childhood to predict later cognitive outcomes and improve targeted early interventions.

Future research plans

The cohort in the longitudinal study (paper 1 and 2) have further been invited to follow-up studies at 23 and 26 years of age with emphasis on motor outcomes, mental health, cognition and multimodal MRI. The study group managing the longitudinal study is member of the Adults Born Preterm International Collaboration (APIC) for multicenter studies where the goals of this collaboration are to advance the knowledge on the long-term outcomes of premature infants in adulthood and middle age. Several papers are currently being produced or have already been published based on the longitudinal studies and the multicenter collaboration.

The second study (paper 3 and 4) in this thesis is part of a collaboration with Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology at the University of Oslo (UiO), headed by Professors Kristine Walhovd (principal investigator of the project) and Anders Fjell. All data material collected from the term born children at both study sites will be merged into the larger MoBa database owned by the Norwegian Institute of Public Health to be used by other researchers in further research. The research group in Oslo has already implemented data from the term born children from our site with their data, and two papers by the research leaders in Oslo are currently under review in high-impact international scientific journals. A PhD student at UiO is also working with the data from this collaboration study.

In our research group, the Center for Early Brain Development (CEBRA), an article based on the school aged VLBW children and controls from the NTNU material examining the relationship between hippocampal volumes and memory test scores, is currently in preparation. Several other studies will be published on this data material in the near future. We have a large amount of results from neuropsychological tests that are more specific to specialized cognitive abilities and plan to combine these results with brain volumetric and cortical morphometric data. The participants in study 2 also came to a second appointment with repeated testing and MR imaging 12 to 18 months after their first session. In addition, some control children had supplementary neuropsychological testing at their second visit with tests identical to the VLBW test battery. Longitudinal clinical and neuroimaging data are therefore available for the cohort in study 2, and these data will be used in another ongoing PhD project.

Conclusions

In spite of being born about 20 years later than our first cohort of VLBW young adults, and despite major improvements in perinatal medical treatment and care, the VLBW children in study 2 still have altered brain morphometry and reduced IQ compared to term born peers. Our results from paper 4 indicate an improvement in white matter integrity in VLBW born children compared with earlier year cohorts. Closer inspection of the data material in study 2 indicated that the VLBW children on mechanical ventilation had the most adverse white matter alterations, and we speculate that white matter injury seen in preterm is related to perinatal morbidity more than gestational age and birth weight. In paper 3 and 4 we report deviant cortical surface area and cortical thickness as well as smaller subcortical gray and white matter volumes in the VLBW children. The gray matter regions affected are strikingly similar in the VLBW children as in the population of VLBW young adults born about 20 years earlier. Reduced cortical surface area was strongly related to poorer cognitive outcome in both our two VLBW cohorts, and we recommend further research to investigate whether cortical surface area may serve as an early biomarker for later cognitive problems when screening preterm born infants and children in the clinics in order to start early intervention programs.

To conclude, the main results from this thesis give a strong indication that prematurity per se does influence brain maturation and morphometry even in quite healthy preterm born children born in the 2000s who have received state-of-the-art neonatal medical treatment and care. White matter integrity in particular seems to have improved in the young VLBW children

compared to the older cohort; however the altered brain development still seems to have negative consequences for higher order cognitive functioning like attention and executive functions.

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Supplemental Material

Supplemental Material

Visual attention

This test is part of NEPSY and assesses the speed and accuracy with which a child is able to focus selectively on and maintain attention to visual targets within an array. The test consists of two different tasks; Cats - the child is presented with a response booklet with drawings of rabbits, cats, faces, cars etc. The child must find and mark all the cats presented in the booklet as fast as possible. Faces – the child is presented with a booklet of drawings of different faces. The child must identify two fixed faces correctly and as fast as possible.

Statue

This test is part of NEPSY and assesses a child's inhibition and motor persistence. The child is told to stand completely still for a time period of 75 seconds and if the child responds to distractions from the administrator the child is supposed to inhibit giving a response to the distraction (e.g, eye opening, body movement, vocalization).

Visual-Motor Integration

This test consists of 3 different tasks.

The VMI copy requires the subject to copy 30 different geometrical shapes of increasing complexity without a time limit; VMI visual task requires that the subject finds the shape identical to the target figure among several others through 30 task with increasing difficulties; VMI motor requires that the subject places a line between the double lines that makes up 30 different geometrical figures without crossing the lines.

Narrative memory

The test in part of NEPSY and assesses narrative memory. The child listens to a story and must recall it (free recall). Then the child must answer questions to the story.

Digit Span

This test is part of WASI and is used to assess verbal working memory. Administrator reads numbers and the test subject must repeat the numbers in same order. The test subject is required to remember an increasing number of digits. In the second part; the test must repeat the digits backwards.

Taylor Modified Figure Test

TMFT is designed as a retest for RCFT by Taylor (1969, 1979) and is administered identical to RCFT, described in the RCFT paragraph above. In this study, only copy and recollection after 30 minutes was conducted.

California Verbal Learning Test (CVLT)

This test is used to assess strategies and processes when learning new verbal material and verbal memory. The subject listens to a list of words being read out loud and is asked to repeat the words in the list. The word list is presented orally five times to the subject, who is asked to recall as many words as possible after each trial, as well as after a 30 minute delay. The task also includes an interference list that is only presented once, after which the subject is asked to recall it and then to recall the first list (rehearsed five times). Free recall and recognition of initial lists are assessed after a delay. Scores are the total number of correctly recited words after the rehearsal of the first list, as well as number of words remembered after the delay.

Attention network task (ANT)

The ANT is a task designed to test three attentional networks in children and adults: alerting, orienting, and executive control. Efficiency of the alerting network is examined by changes in reaction time resulting from a warning signal. Efficiency of orienting is examined by changes in the reaction time that accompany cues indicating where the target will occur. The efficiency of the executive network is examined by requiring the participant to respond by pressing two keys indicating the direction (left or right) of a central arrow surrounded by congruent, incongruent or neutral flankers.

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PAPER 1 - 4

PAPER 1

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PAPER 2

Executive function relates to surface area of frontal and temporal cortex in very-low-birth-weight late teenagers

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Short title: Executive function and brain findings in VLBW adults

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Abstract

Background: Being born with very low birth weight (VLBW: bw<1500 g) is associated with increased risk of maldevelopment of the immature brain which may affect neurological functioning. Deficits in attention and executive function problems have been reported in VLBW survivors compared with healthy subjects.

Aims: The aim of this study was to evaluate attention and executive functions and to relate the clinical test results to cortical morphometry findings in VLBW late teenagers compared with term-born controls.

Study design: Prospective follow-up study of three year cohorts of VLBW and control children from birth to adulthood.

Outcome measures: A comprehensive neuropsychological test battery was administered to 55 VLBW subjects born preterm (mean birth weight: 1217 g) and 81 term-born controls (mean birth weight: 3707 g) at age 19-20. Cerebral MRI was successfully obtained in 46 VLBW subjects and 61 controls. The FreeSurfer software package was applied for the cortical analyses based on T1-weighted MRI images.

Results: The VLBW group obtained inferior scores on 15 of the 29 neuropsychological measures assessing attention and executive function and on both the attention and executive function domain scores. We found positive correlations between the executive function domain score and cortical surface area, especially in the antero-medial frontal and the temporal lobes of the brain in the VLBW group.

Conclusion: Late teenagers born with VLBW show deficits in attention and executive function compared with controls. The executive problems were related to smaller cortical surface area in brain regions known to be involved in higher order cognitive functioning.

Key words: Very-low-birth-weight, preterm birth, executive function, attention, cerebral MRI, cortical surface area

Abbreviations: VLBW: Very Low Birth Weight, IQ: Intelligence Quotient, WAIS-III: Wechsler Adult Intelligence Scale – III, GA: gestational age, SES: Socioeconomic status, WMS-III: Wechsler Memory Scale-III, ES: Effect Size, MRI: Magnetic Resonance Imaging, CP: Cerebral Palsy

1. Introduction

Approximately 1.5% of all live births are infants born preterm with very low birth weight (VLBW; birth weight <1500g) [1]. Cognitive deficits without major motor problems affect up to 50% of VLBW survivors, and are considered the most prevalent neurologic sequelae in this population [1]. Very low birth weight has been associated with lower IQ scores compared with term born controls in childhood [2, 3] and lasting into adulthood [4, 5]. This may in turn lead to deficits in academic and professional achievement [5, 6]. The increased survival rate and persistent cognitive, psychological and general health problems also imply that clinicians will meet this high risk group in increasing numbers in adulthood [7].

Studies published on VLBW adults have reported poorer scores on general intelligence and executive functions [4, 5, 8, 9]. Nosarti et al. [8] reported executive function impairments, including slower processing speed, in adults (age 22) born very preterm (<33 weeks of gestation). Pyhälä et al. [9] found lower scores on general IQ and tests assessing executive functions, attention and visual memory among 25 year old VLBW subjects compared with term born controls. These findings were confirmed by Eryigit Madzwamuse et al. [4] who showed that also their cohort of VLBW adults (age 26) obtained lower IQ scores and poorer scores on executive functions tests than term born controls. This suggests persisting cognitive deficits in VLBW survivors.

Perinatal brain injuries are common in preterm born children and may have consequences for normal maturation and growth of the immature brain [1]. Aberrant cortical findings include less complex cortical folding [10], smaller cortical surface area [11] and deviations in cortical thickness [12, 13]. Recent studies have started to explore possible cortical structure-function relationships in the preterm brain in adolescence and early adulthood. Lower IQ scores in the VLBW group have been related to cortical thinning and reduced surface area in adolescents [12] and young adulthood [11, 13]. In the present study population, poorer scores on visual-motor integration has been shown to correlate to altered white matter integrity [14], while memory deficits were associated with reduced hippocampal volume [15].

To our knowledge, no study has looked at the relationship between attention and executive functions and cortical measures in brain areas known to take part in higher order cognitive functions in VLBW survivors reaching early adulthood. This study therefore aimed to assess attention and executive function and to relate clinical test results to cortical morphometry findings in VLBW late teenagers compared with term-born controls.

We hypothesized that VLBW late teenagers would obtain inferior results scores on the individual neuropsychological tests and on the domain scores compared with controls, and that there would be structure-function relationships between attention and executive domain scores and surface area and cortical thickness in higher order brain regions in the frontal,

parietal and temporal lobes.

2. Material and methods

This study is a hospital-based follow-up study of the long term clinical consequences of being born preterm with very low birth weight (VLBW: BW<1500 g). Three year cohorts (born in 1986-88) of VLBW children and controls born at term appropriate for gestational age (bw > 10th percentile) were evaluated at the age of 19 to 20 years.

2.1. VLBW group

A total of 121 children with VLBW (birth weight \leq 1500g) were admitted to the neonatal intensive care unit (NICU) at the University Hospital in Trondheim. Of these, 33 children died and nine were not contactable at follow-up. One child with Down syndrome and two young adults with severe cerebral palsy (CP) classified at Gross Motor Function Classification System (GMFCS) level V were excluded because they were unable to perform the neuropsychological tests. Of the remaining 76 young adults, a total of 55 (72%) agreed to participate at 19-20 years of age. These participants were also assessed at one and six years of age (one year cohort of VLBW only) and also at 14 years of age (VLBW and controls) [16-18]. A total of 50 VLBW subjects were examined with cerebral MRI at age 19-20. The scans of four subjects had to be rejected due to motion artifacts, leaving 46 VLBW subjects for inclusion in the MRI analysis. Neurological examinations at 14 years of age showed that four of those participating at 19-20 years of age had CP: two had spastic diplegia and were classified at GMFCS level II, and two had combined spastic diplegia and hemiplegia, of whom one was classified at GMFCS level I and one at GMFCS level IV [19]. No participant was visually impaired (according to the World Health Organization definition) based on the 14 year follow-up visual examination [18].

2.2. Controls

The term born controls was recruited from the same year cohorts and living in the Trondheim region. The group originally consisted of 122 children, but two subjects with congenital malformations were excluded and 10 were not contactable at follow-up. The recruitment of the control group has been reported previously [5]. From the 110 eligible subjects, 81 (74%) met for cognitive assessment and 66 had cerebral MRI. Due to motion artifacts caused by dental braces, poor image quality or lack of concomitant cognitive assessment five MRI scans were excluded.

2.3. Non-participants

There were no significant differences between participants and non-participants in any of the groups regarding maternal age at child birth, gestational age and birth weight.

2.4. Ethics

The Regional Committee for Medical Research Ethics approved the study protocol (project number 4.2005.2605). Written informed consent was obtained from each participant. All participants were offered a follow-up session about their test results with the clinical neuropsychologist.

2.5. Socio-economic status

Socio-economic status (SES) was calculated according to Hollingshead's Two Factor index of Social Position, based on the education and occupation of both parents [20]. Information regarding occupational and educational attainment in the young adults was obtained through a short interview. SES data was missing in four VLBW subjects and seven control participant and for those SES values were imputed by the multiple imputation method. Sex, age at assessment and SES were included as covariates in all analyses on group differences.

2.6. Cognitive assessment

The neuropsychological testing was performed by a trained neuropsychologist who was blind to group affiliation and medical history. Testing took place during one session with a fixed order of tasks. A comprehensive neuropsychological test battery assessing IQ, attention, executive function, language, visual/motor and memory function was administered. A detailed description of the neuropsychological tests performed in the present study is given in Supplemental Material (S1). A Confirmatory Factor Analysis was applied to extract domain scores based on the individual tests, as reported before [21]. Full IQ was assessed by the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III), and results have been published earlier [5].

2.7. Neonatal variables

The following clinical variables were considered: birth weight, gestational age, head circumference at birth, birth length, Apgar scores at 1 and 5 min, days in the NICU, days on mechanical ventilator, days to regain birth weight, SES, the participant's age at assessment and maternal age at child birth.

2.8. MR imaging

2.8.1. Image acquisition

Cerebral MRI was performed on a 1.5 T Siemens Magnetom Symphony Sonata System with Quantum gradients (30 mT/m) and a quadrature head coil. We used a structural T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with: TR= 7100 ms, TE=

3.45 ms, TI= 1000 ms, 128 sagittal partitions, 1.33 mm slice thickness, square FOV of 256 mm, and acquisition duration of 8.5 min.

2.8.2. Image analysis

The freely available FreeSurfer 5.1.0 software suite, version 5.1. (<http://surfer.nmr.mgh.harvard.edu/>) was used to create a three-dimensional model of the cortical surface for measurement of cortical thickness and surface area [22-24]. The surfaces were smoothed with a full-width-half-maximum Gaussian kernel of 30 mm (662 iterations) and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns [25]. Group differences in brain morphometry from this study sample at age 19-20 have been published previously [11, 13, 26].

2.8.3. Statistical analyses

The IBM SPSS statistics (Statistical Package for Social Sciences) version 19 (IBM, Armonk, New York) was used for statistical analyses. Clinical data were analyzed using the non-parametric tests; Mann-Whitney *U* test for ordinal and interval data, and the chi-squared test for categorical data. Log transformations were used to deal with variables with non-normally distributed data. Analyses on non-normally distributed data were initially performed on the original scales to ease interpretability. Missing data (SES and neuropsychological test data) were dealt with by multiple imputations.

To correct for multiple comparisons, we considered an alpha level of 0.01 as significant for all analyses involving subtests. The neuropsychological tests were first categorized into five domains based on literature: [27-29] attention, executive functions, language, visual-spatial/motor and memory and then a Confirmatory Factor Analyses (CFA) was applied to examine the fit of our five-domain model using MPlus version 7 [30]. More detailed description about the performance and results of the CFA have been published earlier (see [21]). In summary, the final model after CFA still consisted of the same five domains. However, the visual-spatial/motor domain was excluded from further analyses as only two subtests loaded on this domain. In this paper, only the results of the attention / executive function tests and the domain scores for attention and executive function will be presented, since visual /visual-motor and memory test results have already been published [14, 15].

A General Linear Model was applied to analyze the relationship between group (VLBW versus controls) and neuropsychological test scores and domain scores, with SES, sex and age at assessment as covariates. We compared raw scores on all tests and all analyzes were performed both with and without participants with CP. Tests with a higher score representing poorer performance (i.e. errors or time) were transformed to negative scores. Z-scores were calculated in the VLBW group, based on mean score and SD in the control group, for each

neuropsychological test, and all scores were converted so that lower values were to be interpreted as negative. Domain scores were calculated by averaging Z- scores from the individual tests within each domain. Correlation analyses (Spearman's rho and Pearson's r) were used to examine the relationship between clinical variables and domain scores in the VLBW group. All effect sizes (ES) were calculated by the Glass' Delta (Δ). Odds ratios (ORs) were calculated to study the association between group adherence and having an impairment (score < -2SD) in any of the neuropsychological domains.

To look at the association between the attention and executive function domain scores and cortical surface area and thickness, we used partial correlations controlling for sex, age at assessment and SES. Correlation maps were made in FreeSurfer with a 5% false discovery rate (FDR) to correct for multiple comparisons. Brain cortical morphometry data were analyzed within the Matlab software suit. 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 neuropsychology domain scores as continuous predictor. The appropriate contrast vectors were set to test for a relationship between each of the domain scores for attention and executive function and cortical surface area and thickness. 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, p-maps were thresholded to yield an expected false discovery rate (FDR) of 5%, which was applied co-jointly across the hemispheres.

3. Results

Table 1 shows the clinical characteristics of the VLBW (with and without CP), and the control groups. The mean gestational age and birth weight in the VLBW group was 29.1 weeks and 1217 g respectively. Apgar scores at 1 and 5 minutes were lower in the VLBW group, and the mothers of VLBW subjects were slightly younger than control mothers. There were no group differences regarding SES, sex or age at assessment. A total of 22% in the VLBW reported receiving special education in school, compared with only 2.5% in the control group, and 15% reported being unemployed or on sick leave at the time of assessment in the VLBW group, compared with 2.5% in the control group. The VLBW group obtained lower full IQ scores than controls at age 19 [5]. There was no difference in clinical characteristics between VLBW subjects with and without MRI-scans (data not shown).

3.1. Neuropsychological test scores

The VLBW group had inferior raw scores than controls on most of the subtests for attention and executive function, after adjustment for SES, sex and age at assessment (**Table 2**). Differences reached statistical significance ($p < 0.01$) for 15 of the 29 measures with effect sizes ranging from 0.54 – 2.07. After exclusion of the four VLBW subjects with CP, significant

group differences were still reached for the Stroop tests, the TMT tests, the WMS-III-tests, Design Fluency, and the WCST failure to maintain set (data not shown).

3.2. Domain scores

The VLBW group obtained significantly lower scores than controls on both the attention and the executive function domain after adjusting for SES, sex and age at assessment, and results were still highly significant after exclusion of the four VLBW subjects with CP (**Table 3**). There was an increased risk of having an impairment in the attention domain (OR=2.16, 95% CI [1.46, 3.15]) and the executive functions domain (OR=2.76, 95%CI [2.19, 3.48]) in the VLBW group.

3.3. Associations of clinical variables with neuropsychological outcome in the VLBW group

None of the neonatal risk factors that were investigated correlated with any of the neuropsychological domain scores and the only correlation found between such risk factors and individual tests was between the PASAT Correct and 5-minute Apgar score ($r=0.438$, $p=0.001$). However, the neuropsychological domain scores correlated with special education in school (Attention: $r=0.559$, $p<0.001$; Executive functions: $r=0.691$, $p<0.001$).

3.4. Associations of neuropsychological domain scores with cortical findings in the VLBW group

The executive function domain score correlated positively with cortical surface of frontal and temporal areas in the right hemisphere and to a lesser extent with frontal, temporal and occipital areas. Specific gyri affected included the medial orbitofrontal gyrus extending into lateral orbitofrontal gyrus, the rostral and caudal anterior cingulate, posterior parts of the superior frontal gyrus, as well as in the anterior part of the medial and superior temporal gyri in the right hemisphere. In the left hemisphere, correlations were found in the anterior cingulum and superior frontal gyrus, and in the posterior superior temporal sulcus, the lingual gyrus, and lateral occipital gyrus (**Figure 1**). No correlation was found between the attention domain score and surface area, and none of the domain scores correlated significantly with cortical thickness measures.

4. Discussion

Our main finding was that young adults born preterm with VLBW obtained significantly inferior scores on about half of the attention and executive functions tests and on both the domain scores compared with the term born controls. Most results remained significant after exclusion of four subjects with CP in the VLBW group. We found a positive correlation between the executive function domain score and cortical surface area, especially in anterior medial and superior frontal and lateral and inferior temporal areas of the brain in the VLBW group.

4.1. Methodological consideration

The strength of this study is the comprehensive clinical assessment using standardized tests, combined with morphometric MRI. Furthermore, all neuropsychological testing was performed by one experienced neuropsychologist blinded to group affiliation and earlier medical history. The FreeSurfer package is used extensively and has been validated against both a post mortem brain material [31] and manual measurements [32, 33]. Algorithms have shown satisfactory test–retest reliability for different MRI scanners and field strengths [34, 35]. However, any automated method for surface reconstruction may be vulnerable to inaccuracies in the normalization process and registration errors may be introduced. In our study, we inspected the reconstructed cortical models for errors and minimal manual editing was performed by one single person. Strength was also the well-defined study cohort that has been followed prospectively since birth. The follow-up rate was acceptable and comparable to other long-term follow-up studies [36]. No differences were found between study participants and non-participants regarding SES, gestational age, birth weight and maternal age at child birth. This makes selection bias less likely. One limitation may be our relatively small sample size and non-significant results should therefore be interpreted with caution. However, our findings express moderate to large effect sizes, making chance less likely.

4.2. Deficits in attention and executive function in VLBW young adults

The VLBW group had significantly lower scores than controls on 5 of 9 attention tests and 10 of 20 executive function tests. This result indicates that subjects born preterm with VLBW continue to be at a cognitive disadvantage when entering into young adulthood. These findings are in accordance with other studies of VLBW adults, showing various executive function problems [8, 37] as well as problems with attention and processing speed [38]. Similar to our findings, Nosarti et al. [8] and Allin et al. [39] also found that VLBW subjects had problems with verbal fluency, and Tanskanen et al. [40] also showed problems with verbal learning among VLBW adults compared with term born controls. Taylor, Minich, Bangert, Filipek, and Hack [41] confirmed executive function deficits in their preterm born adolescents (mean age 16.6 years) with very low (birth weight between 750g-1499g) and extremely low birth weight (<750g). None of the neonatal risk factors in our VLBW group came forth as significant predictors of attention and executive function in early adulthood, which is in accordance with the results of Nosarti et al. [8] who found no association between perinatal variables and executive function in their VLBW group. Since many of the tests assessing attention and executive function with inferior results in the VLBW group have time demand, reduced processing speed may be a contributing factor. Both in the present study cohort and in several other studies processing speed has been reported as being poorer among VLBW children and adults than term born controls [5, 8, 38, 42, 43]. This is a function that plays an important role in working memory and intelligence together with other functions [44]. Gnigler et al. [42] found that complications of prematurity, such as corticosteroid treatment, severe retinopathy of prematurity (ROP), and intraventricular hemorrhage predicted reduced processing speed in

VLBW children at age five. Murray et al. [43] found significant associations between brain abnormality on MRI at term equivalent age and poor processing speed and attention scores in VLBW children at age seven.

4.3. Executive function and cortical surface area

In the VLBW group, we found that the executive function domain score correlated positively with cortical surface area in anterior medial and superior frontal and lateral and inferior temporal regions. These results are partly in accordance with a study that investigated the neural substrates of executive function in 182 patients with focal brain damage using voxel-based lesion–symptom mapping and derived measures of executive functions from the Delis–Kaplan Executive Function System. Impaired executive functions was especially associated with damage to frontal lobe (e.g. anterior and dorsolateral prefrontal cortex, anterior cingulate/medial prefrontal cortex) and superior and inferior parietal cortex [45]. A previous report from the present cohort revealed reduction in cortical surface area in ventrolateral prefrontal, temporal and parietal regions in the VLBW late teenagers group compared with controls. Inferior WAIS full IQ and the working memory index scores correlated with surface area reduction in superior, dorsolateral and inferior antero-medial frontal areas, and in medial temporal and occipital regions in the VLBW group [11]. When comparing these findings with the executive function – surface area relationship reported in the present study there was some overlap concerning affected brain areas, which included: Right medial orbitofrontal and rostral anterior cingulate in the frontal lobe and the superior temporal gyri. These areas showed reduction of surface area in the VLBW group, in addition to the correlation between surface area and executive function / working memory. All the involved regions participate in cognitive tasks based on the classification by Brodmann. Brodmann areas (BA) related to our surface area findings included: BA 10 (medial orbitofrontal area), BA 11, 12 (orbitofrontal and superior frontal areas), BA 22 (superior temporal gyrus), and BA 30, 32, 33 (rostral and caudal anterior cingulate). These regions are thought to be involved in executive functions like decision making, reward, planning, encoding new information into long term working memory and are active during executive function tasks (BA 10, 11 and 12), important for language (BA 22) and rational thought processes, especially during Stroop tasks (BA 30,32,33). Surface area reduction in frontal areas may interfere with normal cognitive functioning and influence networks to and from the prefrontal cortex.

The executive function domain score consists of tasks like WCST, verbal fluency and Stroop, and working memory tasks. WCST have been seen to be sensitive to lesions in frontal areas including DLPFC and superior medial, with inferior task performance in patients with lesions in these regions [46]. Increased activation during a verbal fluency task has been reported in the left dorsolateral prefrontal cortex [47, 48], anterior cingulate [47, 49], and left inferior frontal gyrus [49, 50] in addition to activation of a number of non-frontal brain areas, including the thalamus [47, 50], parietal lobes and temporal lobes [51]. Functional studies using PET and fMRI found that Stroop test activates the middle frontal

gyrus [52-55], parietal lobe regions [53, 54, 56], motor areas [53, 56], and temporal lobe regions [53, 54]. We have already pointed to the concurrence of correlations between reduced surface area and executive functions and working memory, respectively in our study population of VLBW late teenagers. The lateral prefrontal cortex extending from BA 10 through mid-dorsolateral prefrontal cortex and anterior cingulate and frontal operculum has been reported to be involved during maintaining a task goal [57-60], whereas more posterior regions of dorsolateral prefrontal cortex (e.g., inferior frontal junction) as well as parietal regions has been observed during changes in the focus of attention [60, 61]. Increased activation in the anterior cingulate cortex during executive tasks suggests that this is a critical brain region for selective attention, task-oriented sensory, alerting, and working memory [56, 62].

In addition to the frontal areas we found a correlation between poorer executive domain scores and reduced surface area in temporal and occipital regions. Executive functions are most likely recruited from a wide range of functional abilities partly being orchestrated by the frontal lobes. However, high-level cognitive tasks most likely require participation of both cortical and subcortical regions with connections to and from the frontal lobes [63]. In fact, studies have shown that attention and executive function are relying on an extensive connectivity to other parts of the brain. Damage to any link in the complex system underlying executive functions can result in functional deficits [64]. Reduced surface area in frontal, temporal and occipital regions combined with previously reported deviations in white matter microstructure, especially in long association tracts [65] may suggest that the necessary communication between these regions for attention/executive functioning is suboptimal and may in part account for the deficits in executive functions observed in the VLBW group.

Smaller brain volumes and areas with thinner cortex (left parietal and temporal lobes) and thicker cortex (frontal areas bilaterally) has been reported previously in the same VLBW group compared with controls [13, 26]; however we found no significant correlations between neuropsychological domains and cortical thickness in our study.

4.4. Clinical implications

The observed problems related to attention and executive functions are in accordance with the higher incidence of Attention Deficit/Hyperactivity Disorder (AD/HD) symptoms reported in VLBW adolescents [17] and adults [66]. A much higher proportion of subjects received special education in school in the VLBW group than in the control group, and there were more VLBW subjects that were unemployed or on sick-leave at the time of assessment than control subjects. This suggests a functional implication of the observed cognitive impairments in this group of young adults. Future studies should also look into the long term cognitive effects of early intervention programs in order to suggest prevention and treatment plans for these high-risk infants before higher order cognitive deficits manifest.

5. Conclusions

Late teenagers born with VLBW show deficits in attention and executive function compared with controls. The executive problems were related to smaller cortical surface area especially in frontal and temporal brain regions known to be involved in higher order cognitive functioning.

Conflict of interest statement

None of the authors have any financial and personal relationships to disclose that could inappropriately influence (bias) this work.

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Table 1. Clinical characteristics in the VLBW and control group

	VLBW (n=55) mean (SD)	p-value (vs controls)	VLBW non-CP (n=51) mean (SD)	p-value (vs controls)	Controls (n=81) mean (SD)
Birth weight (grams)	1217 (233.3)	<0.001	1234 (215.8)	<0.001	3707 (473.2)
Gestational age (weeks)	29.1 (2.5)	<0.001	29.4 (2.3)	<0.001	39.7 (1.2)
Apgar score 1 min*	7 (1-9)	<0.001	7 (1-9)	<0.001	9 (7-9)
Apgar score 5 min*	9 (1-10)	<0.001	9 (1-10)	<0.001	10 (9-10)
Days in the NICU	74 (54.0)	<0.001	75 (61.7)	0.002	7 (2.8)
Days on mechanical ventilator	5 (11.2)	-	3 (8.0)	-	-
Days to regain birth weight	17 (8.4)	-	16 (8.5)	-	-
Gender (F/M)	30/25	0.601	28/23	0.718	48/33
Maternal age at birth (years)	28.4 (4.8)	0.045	28.6 (4.7)	0.064	30.3 (4.4)
Socio-economic status	3.3 (1.3)	0.110	3.3 (1.3)	0.091	3.7 (1.0)
Special education in school: Yes/no	12/43	<0.001	10/41	<0.001	2/79
Unemployed or sickleave at time of assessment: yes/no	8/46	0.011	7/43	0.013	2/77
Age at assessment	19.2 (0.9)	0.875	19.2 (0.9)	0.800	19.2 (0.7)
Full IQ score	88.2 (1.6)	<0.001	89.3 (1.6)	<0.001	100.3 (1.3)

Mann-Whitney U-test for two independent samples; Chi Square analysis for categorical data

Abbreviations: VLBW: very low birth weight; CP: cerebral palsy; SD: standard deviation;

*Apgar score 1 and 5 minutes presented as median and range

Table 2. Neuropsychological test results (raw scores) in the VLBW (n=55) and the control group (n=81)

Domain	Individual test	VLBW		Controls		Effect-size	p-value
		mean	95% CI	mean	95% CI		
Attention	Pasat Correct*	35.9	30.5, 41.2	45.6	42.6, 48.6	-0.73	0.001
	Stroop 1 Naming colours	34.1	30.7, 37.4	28.8	27.6, 29.9	-1.03	0.001
	Stroop 2 Reading colour names	24.4	22.3, 26.4	22.5	21.7, 23.4	-0.48	0.142
	TMT 1 Visual scanning*	26.7	21.1, 32.3	18.1	17.0, 19.1	-1.87	<0.001
	TMT 2 Numbers*	53.2	39.0, 67.3	30.9	28.5, 33.3	-2.07	<0.001
	TMT 3 Letters	41.8	36.6, 46.9	28.7	26.7, 30.8	-1.40	<0.001
	CPT Omissions*	9.2	4.1, 14.4	2.7	1.8, 3.6	-1.61	0.012
	CPT Commissions*	18.5	16.3, 20.7	17.9	16.4, 19.5	-0.08	0.602
	CPT reaction time*	339.1	318.3, 359.9	317.7	309.9, 325.4	-0.61	0.075
Executive	WMS-III Mental Control	22.7	20.8, 24.5	26.7	25.7, 27.8	-0.85	<0.001
	WMS-III Spatial Span	14.9	13.8, 15.9	17.6	16.9, 18.3	-0.89	<0.001
	Design Fluency Total Score	24.7	22.1, 27.2	32.6	31.1, 34.1	-1.16	<0.001
	Stroop 3 Inhibition	65.4	56.9, 73.9	49.6	47.3, 51.9	-1.49	<0.001
	Stroop 4 Inhibition and Switching	75.4	63.8, 87.1	58.1	55.5, 60.7	-1.48	<0.001
	TMT 4 Numbers and Letters	97.9	83.9, 111.8	65.6	60.5, 70.6	-1.42	<0.001
	Verbal Fluency Total Correct	31.42	28.2, 34.7	37.9	35.4, 40.5	-0.57	0.004
	WCST Number of categories*	5.1	4.7, 5.6	5.7	5.5, 5.9	-0.59	0.008
	WCST Trials to complete first*	20.2	13.1, 27.3	15.6	12.8, 18.5	-0.35	0.315
	WCST Failure to maintain set*	0.9	0.7, 1.2	0.5	0.3, 0.7	-0.54	0.006
	WCST Total correct*	71.0	68.1, 73.9	70.1	68.4, 71.7	0.13	0.958
	WCST % perseverative responses*	13.6	10.2, 17.0	10.3	9.1, 11.5	-0.59	0.076
	WCST % perseverative errors	12.4	9.7, 15.0	9.7	8.7, 10.7	-0.57	0.073
	WCST % non-perseverative errors*	13.3	10.8, 15.8	10.0	8.5, 11.6	-0.47	0.015
	Tower Time to first move*	45.6	37.9, 53.2	36.0	31.9, 40.0	-0.52	0.028
	Tower Number of moves*	144.1	130.4, 157.9	143.0	134.5, 151.4	-0.03	0.714
	Tower Rule breaking*	1.8	0.6, 3.0	0.43	0.2, 0.6	-1.51	0.009
	Tower Total time*	454.5	405.6, 503.3	416.7	388.5, 444.9	-0.30	0.201
	Tower Total Correct*	16.6	15.5, 17.8	17.7	17.0, 18.5	-0.32	0.075
	WAIS-III Letter-number sequencing	7.7	7.0, 8.6	8.9	8.4, 9.4	-0.51	0.029

*Not included in final extraction of attention and executive function domain scores (in the CFA).
A General Linear Model was used to compare scores in the two groups, with SES, age at assessment (except

for scaled scores) and gender as covariates. Log transformations were made for non-normally distributed data for some of the tests before group comparisons, but these tests are also presented as raw data in the table to simplify interpretation of scores. Multiple imputations were applied for missing data. Adjusted means are presented. Effect sizes were calculated by the Glass' delta (Δ).

Abbreviations: VLBW: very low birth weight; WMS-III: Wechsler Memory Scale-III; WAIS-III: Wechsler Adult Intelligence Scale-III; WCST: Wisconsin Card Sorting Test; TMT: Trail Making Test; CPT: Conner's Continuous Performance Test;

Table 3. Domain scores in the VLBW group with and without CP.

	VLBW incl CP (n=55)			VLBW excl CP (n=51)		
	Effect size	95% CI	<i>p</i> -value	Effect size	95% CI	<i>p</i> -value
Attention	-0.98	-1.35, -0.60	<0.001	-0.65	-0.97, -0.33	0.002
Executive	-0.98	-1.28, -0.68	<0.001	-0.74	-1.00, -0.48	<0.001

Domain scores were calculated by averaging z-scores from individual neuropsychological tests in each of the two categories attention and executive function. Categorization was based on theory and confirmatory factor analysis. A General Linear Model was used to compare groups with socio-economic status (SES), gender and age at testing as covariates. Effect sizes were calculated by the Glass' delta (mean and SD from the control group).

Abbreviations: VLBW: Very Low Birth Weight; CP: Cerebral palsy; incl: included; excl: excluded; CI: Confidence interval.

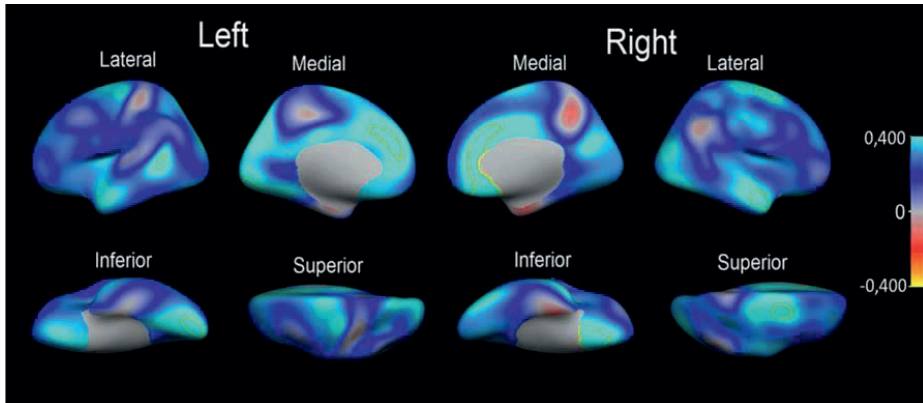


Figure 1: Effect size maps (correlation coefficient r) for cortical surface area and executive functions domain score in the VLBW young adults. The color scale shows the dynamic range of correlation coefficient (r), where dark blue to light blue color represents an increasing positive correlation, i.e., larger surface area with higher executive function score. Red to yellow indicates an increasing negative correlation. Areas where correlations were significant after FDR-correction are marked with a yellow outline. Significant positive correlations between cortical surface area and executive functions were observed in the medial orbitofrontal gyrus extending into lateral orbitofrontal gyrus, the rostral and caudal anterior cingulate, posterior parts of the superior frontal gyrus, as well as in the anterior part of the medial and superior temporal gyri in the right hemisphere. In the left hemisphere correlations were found in the anterior cingulum and superior frontal gyrus, and in the posterior superior temporal sulcus, the lingual gyrus, and lateral occipital gyrus. The effect size is based on a GLM with cortical surface area as dependent variable, group and sex as categorical predictors, and age and executive function domain score as continuous predictors.

Abbreviations: FDR: False Discovery Rate; GLM: General Linear Model; VLBW: Very Low Birth Weight

Supplemental material

S1: Neuropsychological tests

Attention tests

Paced Auditory Serial Addition Test (PASAT)

Numbers are read to the participant that is to summarize the last two numbers that were presented ($1+2=3$). Then the examiner gives another number (i.e. 5), and the subjects need to summarize this number with the last number given in the first round ($5+2=7$). There are totally 60 responses required. Scores are number of correct answers. This is a task assessing several functions, and is considered a strong measure of working memory, divided attention (switching between two tasks: adding digits and encoding the next digit) and sustained attention.

Processing speed is also involved.

Stroop - The color-word interference test

This Stroop-version is the Color-word interference test from the D-KEFS battery, and consists of four subtests. *Stroop 1* is a sheet with squares in three different colors: red, blue and green. The subject is then required to name these colors as fast as he/she can. *Stroop 2* is a sheet with color-words (red, blue, green) printed in black. The subject is required to read these words as fast as he/she can. *Stroop 3* is a sheet with the same color-names as in Stroop 2, only these are printed in color. The color on the word and the color-word is mismatching, and the task is to name the color the word is written in, and not reading the word. The *Stroop 4* is a sheet of color words, where some of the words are printed inside a black square. The task is to say the color of the words that are not in a square, and read the words that are inside a square. Score is time to complete each sheet. The Stroop test is considered a test of executive function: cognitive control, and the ability to hold a goal in mind and inhibiting an overlearned response to perform a less familiar response. Mental speed, working memory and semantic activation also seem to play a part in the performance of the Stroop. *Stroop 1 and 2* (word-reading and color-naming) are the simpler component processes of this task. *Stroop 3*: This task puts demands on inhibition of the impulse to read the color-word. *Stroop 4*: This task puts demands on inhibition and switching. Goal maintenance and inhibition of a more pre-potent response are both important aspects assessed by the *Stroop 3 and 4*, which both are classified as executive function tests in the present classification.

Trail Making Test (TMT)

This test is part of the Delis-Kaplan battery and consists of five subtests. The *TMT 1 (visual scanning & attention)* is a page with lots of numbers on it, where the task is to mark all the number “3’s” as fast as possible. The *TMT2 (number sequencing)* is a page with numbers, where the task is to connect numbers from lowest to highest, as fast as possible. The *TMT3 (letter sequencing)* is a page with letters, where the test subject is to connect letters alphabetically as fast as possible. The *TMT4 (number-letter switching)* is a page with both letters and numbers, where the task is to connect letters and numbers interchanging. This test is classified as a. executive function test in the present study. The *TMT5 (testing motor speed and not included in the present study)* is a set of circles with dotted lines in between. The task is to go as fast as possible from the first circle to the last. Score is time to complete each task. The TMT is a complex test assessing several functions, including attention, speed and mental flexibility. All TMT subtests also put some demands on eye-hand coordination/fine motor functioning. The first three TMT tests are basically assessing attention and processing speed. The TMT4 requires switching and inhibition. The TMT5 puts more demands on eye-hand coordination and motor speed.

Conners’ Continuous Performance Test (CPT)

This is a computer-based test, where the subject is required to press the space bar as fast as possible whenever a letter is presented on the screen. The subject is told not to press when the letter “X” appears. There are several outcome measures of this test; we have only chosen to include: omissions, commissions and reaction time. Omission is when the subject does not press space bar to the letters given, and reflects inattention. Commission is when the subject presses space bar when an “X” appears, and reflects inattention and lack of inhibition. Reaction time is given in milliseconds. The CPT is a widely used attention test, which tests sustained attention and response inhibition. The omission score is considered a measure of inattention, while the commission score assesses inattention and impulsivity. However, it has been discussed whether this test is mainly an attention or an executive function test, as perseveration and delayed responses can affect the outcome.

Executive function tests

WMS-III Mental Control

This task is a part of the Wechsler Memory Scale 3rd edition. The subject is to repeat different

sequences; counting backwards from 20 to 1, saying the alphabet, stating the days of the week forward and backward, and stating months of the year forward and backward. In addition the subject is to state the days of the week and at the same time add the number 7 (Monday-7, Tuesday-14, and so on). This is an optional subtest of the WMS-III, and assesses the ability to retrieve and mentally manipulate overlearned information. It is considered to assess executive control and auditory working memory.

WMS-III Spatial Span

This task is also a part of the Wechsler Memory Scale 3rd edition. The Spatial Span is a white board with 10 blue blocks. The examiner points on different blocks, and the test subject is to point on the same blocks in the same order. An increasing number of blocks are given. The second part of the task is the same, only now the subject has to point in backwards order, also here increasing the amount of blocks pointed at in a row. In our study, the outcome score is the total score. The spatial span puts demands on visual working memory.

Design Fluency (DF)

The DF is a test where the subject creates different figures within a time limit according to a set of rules. The test subject is not allowed to make the same figure several times. The score is number of different correct designs within the time limit. The DF is considered a measure of executive functioning. Working memory, shifting set and inhibition of reproducing designs are also parts of the test.

Verbal Fluency (VF)

The VF is a test where the subject produces as many words as possibly with given letters and categories, and also a task where they have to switch between two categories. Score is number of correct answers in each subtest. We have used total correct responses as outcome in this study. Verbal fluency is considered a measure of executive functioning that demands active attention, especially the suppression of a previous response and monitoring for repetitions. The test also has a verbal component, and there are some studies showing the importance of episodic verbal memory to the verbal fluency score.

Wisconsin Card Sorting Test (WCST)

This is a test where the subject is to sort different cards by trial and error according to a rule set by the examiner. There are several outcomes of this test, where we have looked at the following: “*total number of categories achieved*” (how many times they figure out and follow a new rule for 10 consecutive trails), “*trials to complete first category*”, “*failure to maintain set*” (not holding on to the rule before reaching 10 correct trails), “*total correct responses*”, “*perseverative responses*” (following an old rule after it has been switched), “*perseverative errors*” (if the subjects keep following a rule they know is incorrect) and “*non-perseverative errors*” (randomly responding). The WCST is independent of time. The WCST is considered a measure of executive functioning, as it assesses several aspects of problem solving behavior: the ability to form abstract concepts, switching and holding on to cognitive strategies while utilizing environmental feedback. The test requires the ability to use strategic planning, organized searching, goal-orienting and regulating impulsive reaction.

Tower Test

In this test the test subject is required to move five disks on to three pegs to build a target tower in as few moves as possible. There are several outcome measures of this task, and we have included the following in the current paper: “*time to first move*”, “*number of moves to complete the task*”, “*rule breaking*”, “*total time to complete the task*”, “*total correct on the task*”. This test puts demands on the ability to make plans, learn rules and to inhibit responses. Abstract thinking, creativity and problem solving are also aspects of this test, and the tower test is considered a measure of executive functioning.

Letter-Number Sequencing

This is a task which is shared in WAIS-III and the WMS-III. The examiner presents a list of mixed letters and numbers out loud and the test subject has to sort and then repeat the letters in alphabetical order, and then numbers in numerical order. Score is number of correct answers. This is a subtest considered to measure working memory.

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PAPER 3



Cortical morphometry and IQ in VLBW children without cerebral palsy born in 2003–2007



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ABSTRACT

Children born prematurely with very low birth weight (VLBW: bw \leq 1500 g) have an increased risk of preterm perinatal brain injury, which may subsequently alter the maturation of the brain, including the cerebral cortex. The aim of study was to assess cortical thickness and surface area in VLBW children compared with term-born controls, and to investigate possible relationships between cortical morphology and Full IQ. In this cross-sectional study, 37 VLBW and 104 term children born between the years 2003–2007 were assessed cognitively at 5–10 years of age, using age appropriate Wechsler tests. The FreeSurfer software was used to obtain estimates of cortical thickness and surface area based on T1-weighted MRI images at 1.5 Tesla. The VLBW children had smaller cortical surface area bilaterally in the frontal, temporal, and parietal lobes. A thicker cortex in the frontal and occipital regions and a thinner cortex in posterior parietal areas were observed in the VLBW group. There were significant differences in Full IQ between groups (VLBW $M = 98$, $SD = 9.71$; controls $M = 108$, $SD = 13.57$; $p < 0.001$). There was a positive relationship between IQ and surface area in both groups, albeit significant only in the larger control group. In the VLBW group, reduced IQ was associated with frontal cortical thickening and temporo-parietal thinning.

We conclude that cortical deviations are evident in childhood even in VLBW children born in 2003–2007 who have received state of the art medical treatment in the perinatal period and who did not present with focal brain injuries on neonatal ultrasonography. The cortical deviations were associated with reduced cognitive functioning.

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1. Introduction

Children born before week 32 with very-low-birth weight (VLBW: birth weight \leq 1500 g) are more likely to need medical treatment during the perinatal period, and their immature nervous and cardiovascular systems render these children prone to focal brain injuries such as intraventricular hemorrhages and periventricular leukomalacia (PVL) (Volpe, 2009). Volpe (2009) has suggested that the complex of encephalopathy of prematurity includes both destructive and developmental disturbances, and primary white matter injury could have secondary effects on cortical and gray matter nuclei development. Although perinatal care and medical treatment in the neonatal intensive care unit (NICU) have improved radically during the last decades with reduced incidence of focal brain injury, the immature brain and exposure to

the harsh extra-uterine environment in the NICU are still believed to increase the risk of disrupted brain development in very preterm born survivors. The consequences of such developmental disruptions in an extremely sensitive period of brain growth may be profound alterations of subcortical and cortical morphology that may affect brain function.

Previous studies have reported abnormal cerebral white matter in VLBW infants as the most common pathological finding, manifested as reduced fractional anisotropy on diffusion tensor images at 27–46 weeks of gestation (Ball et al., 2013), in adolescents (Skranes et al., 2007) and in young adults aged 18–22 years (Eikenes et al., 2011). However, changes in cortical and subcortical gray matter have also been demonstrated in children with VLBW as reduced brain cortical surface area at term-equivalent age; (Ajayi-Obe et al., 2000; Kapellou et al., 2006), in toddlers 18–22 months old (Phillips et al., 2011), in children at the age of 10 years (Grunewaldt et al., 2014), and in adolescents and young adults (Frye et al., 2010; Skranes et al., 2013). Both regional thinning and thickening of the cerebral cortex have been reported in children 7–12 years of age (Grunewaldt et al., 2014; Mürner-Lavanchy

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et al., 2014) and in adolescents at the age of 19 (Bjuland et al., 2014). Possible mechanisms underlying these cerebral changes in the VLBW population may include injuries that affect neuronal migration and thereby cortical development (Volpe, 2009).

The aim of the present study was to investigate cortical thickness and cortical surface area in 5–10 year old children born preterm with VLBW and term-born controls. To our knowledge, no previous study has explored regional cortical morphology using continuous cortical surface maps in VLBW children as young as 5–10 years of age. Using continuous maps of cortical thickness and surface area increases both sensitivity and specificity compared to volumetric methods (Rimol et al., 2012).

In addition, the present study explores the relationship between regional measures of cortical morphology and Full IQ as an overall measure of cognitive functioning. Cognitive abilities have been shown to be reduced in the VLBW population (Aarnoudse-Moens et al., 2009; Anderson et al., 2004; Lohaugen et al., 2010; Nosarti et al., 2007; Taylor et al., 2004), and reduced cognitive performance has been related to reduced cortical volume in 14–15 year old VLBW adolescents (Nosarti et al., 2014). Finally, previous studies of VLBW young adults have shown negative correlations between IQ and cortical thickness (Bjuland et al., 2013), and positive correlations with surface area (Skranes et al., 2013). However, these VLBW young adults were born in 1986–1988, and it is unclear whether the same relationships between cortical morphology and cognitive function exist for school aged VLBW children born after year 2000, who have received modern neonatal intensive care.

2. Material and methods

2.1. Participants

2.1.1. VLBW group

The children born prematurely with very low birth weight (VLBW) (birth weight ≤ 1500 g) were recruited based on admittance to the Neonatal Intensive Care Unit (NICU) at St. Olav University Hospital in Trondheim, Norway between 2003 and 2007. Sixty-three non-CP children were invited and 57 agreed to participate in the study (31 females). One child (a twin sibling to a VLBW child) with birth weight at 2090 g was included in the data analysis, and post-hoc analysis showed similar brain morphology and IQ scores for this child as for the VLBW cohort.

2.1.2. Control subjects

The control subjects were recruited from the national Norwegian Mother and Child Cohort Study (MoBa) managed by the Norwegian Institute of Public Health (Magnus et al., 2006), with ages ranging between 4 and 11 years ($n = 143$, 70 females). The participants included in the current analysis were living in the same geographical area as the VLBW participants (Nord- and Sør-Trøndelag) and had normal vision and hearing. The exclusion criteria were a history of injury or disease known to affect the central nervous system (CNS) function, including neurological or psychiatric illness and serious head trauma. Furthermore, if the child was under psychiatric treatment, used psychoactive drugs known to affect CNS functioning, had a birth weight below 2500 g, or had any known MRI contraindications, they were excluded from participation in the current study.

2.2. MR imaging

2.2.1. Image acquisition

MRI data were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions). The pulse sequence used for morphometric analyses was one 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) scan with the following parameters: repetition time (TR), 2400 ms; echo time (TE), 3.61 ms; inversion time (TI), 1000 ms; flip angle, 8°,

FOV 240×240 and acquisition duration of 4 min and 18 s. Each volume consisted of 160 sagittal slices with voxel sizes of $1.25 \times 1.25 \times 1.20$ mm. The total scan time was on average 30 min. Raw datasets were de-identified and transferred to Linux work-stations for processing. Each MPRAGE was visually inspected and only scans with no or minimal movement artifacts were included in the analyses.

2.2.2. Morphometric image analysis

Cortical reconstruction was performed with the FreeSurfer 5.3.0 image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in other publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl et al., 2004a; Fischl and Dale, 2000; Fischl et al., 2001). Briefly, this includes motion correction and averaging (Reuter et al., 2010) of multiple volumetric T1 weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, intensity normalization (Sled and Pike, 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., 1999), registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999), parcellation of the cerebral cortex into units with respect to the gyral and sulcal structures (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 the 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). Each surface consisted of approximately 160,000 vertices arranged in a triangular grid, and estimates of the 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 cortical area 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 of each subject 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 (Desikan et al., 2006; Fischl et al., 2004a), which were used to anatomically identify the affected regions after significance testing.

In the VLBW group, analyses were conducted based on MR-images from 37 children (21 females). Of the 57 who were eligible for MR-scanning, 10 children did not want to be scanned and had cognitive assessment only, and 10 images were excluded due to movement artifacts or disrupted scanning. In the control group we were able to attain 104 MPRAGE images of good quality (54 females). A total of 143 children were invited to MR imaging, 22 children did not want to participate and 17 of the images had to be excluded due to movement artifacts or disrupted scanning. The youngest participants (5–6 years of age) in both groups were most likely to decline MRI scanning or be excluded due to movement artifacts.

2.3. Cognitive measures

2.3.1. VLBW group

In the VLBW group, children <6 years of age were assessed with the age-appropriate, complete version of the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) (Wechsler, 2002), whereas children ≥ 6 years were assessed with Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler, 2003). WPPSI-III provides three IQ indices: Full Scale IQ, Verbal IQ and Performance IQ, while WISC-IV comprises four indices: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index, and Full Scale IQ.

2.3.2. Control group

Cognitive abilities in the controls who were ≥ 6.5 years of age were assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The WASI is a validated screening test that is used to assess the following aspects of intelligence: verbal knowledge, visual information processing, spatial and nonverbal reasoning, and general intelligence. Three IQ scores can be extracted using the WASI: a Verbal IQ (VIQ) score (subtests: vocabulary and similarities) and a Performance IQ (PIQ) score (subtests: block design and matrices), which when combined provide an estimated Full-scale IQ (FSIQ) score. The controls who were younger than 6.5 years of age completed a short form of the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) (Wechsler, 2003), including similar subtests: vocabulary, similarities, block design and matrices, and Verbal IQ (VIQ), Performance IQ (PIQ) and Full-scale IQ (FSIQ) were calculated.

2.3.3. Statistical analysis

IBM SPSS Statistics 19 edition was used for the analysis of the clinical and cognitive measurements by independent samples t-tests and non-parametric tests. Data with non-equal variances were analyzed with non-parametric testing. Matlab 2011b was used for statistical analyses of morphometry data. To examine group differences, a general linear model was fitted with cortical surface area or cortical thickness as dependent variable and group, sex and age at MRI scan as independent variables in each vertex across the cortical surface. The regression of IQ on cortical morphology was tested with the same GLM with Full IQ as an added continuous predictor. Appropriate contrast vectors were set in order to perform the various significance tests. The hemispheres were analyzed separately, and effect size and p-maps were generated. Effect size is reported as Cohen's *d* for group comparisons and $r = F / (F + df)$ for the continuous predictors (IQ and birth weight). The p-maps were thresholded and multiple comparisons were corrected for with a 5% false discovery rate (FDR) that was applied co-jointly across the hemispheres. Significance tests were performed to investigate differences in cortical morphology between the groups. For the clinical variables birth weight, gestational age, and days on ventilator general linear models were fitted in each vertex across the surface, with cortical surface area or cortical thickness as the dependent variable and one of the clinical variables as a covariate, and adjusted for sex and age at MRI scan. These analyses were performed in the VLBW group exclusively. Findings on any of these clinical variables were followed up with further exploratory analyses.

2.3.4. Imputation of missing data

Missing data in the independent variables (Full IQ and birth weight) were dealt with by multiple imputations. Pattern analysis was performed, showing that we had below 5% missing data and that we could assume that data were missing at random. Seven Full IQ data and two birth weights were imputed and pooled imputations were used in further analyses.

2.3.5. Socio-economic status

Hollingshead's (1975) two factor index of social position based on education and occupation of one parent or the mean index of both was used to calculate socio-economic status (SES).

2.3.6. Ethics

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

3. Results

3.1. Group characteristics

Demographic and clinical characteristics of the study groups are shown in Table 1. In the VLBW group, mean birth weight was 1048 g and mean gestational age was 28.5 weeks. Detailed perinatal data for the VLBW children are presented in Appendix Table A1. There was no significant group difference in age at examination; however, the controls had higher mean socioeconomic status (SES) than the VLBW group. The VLBW group had significantly lower scores than controls on Full IQ, also after adjusting for socioeconomic status ($n = 34/85$).

3.2. Structural MRI

3.2.1. Cortical surface area group differences

There were significant differences in cortical surface area between the VLBW and the control group. The VLBW group showed bilateral reduction in cortical surface area in the frontal, temporal, and parietal lobes (Fig. 1). The effect size of the group difference ranged from $d = 0.4$ to 0.8 in most cortical regions (see Appendix Fig. A1). Table 2 lists all cortical regions with significant group differences in surface area as determined by the GLM (after 5% FDR correction), where 20 out of 35 regions had ≥90% reduction of cortical surface area in the VLBW group compared with controls.

3.2.2. Cortical surface area and IQ

In the control group, there were widespread cortical regions in both hemispheres showing a significant relationship between Full IQ scores and cortical surface area (see Appendix Fig. A2 and Table A2). In the VLBW group, the relationship between Full IQ scores and cortical surface area did not reach statistical significance. However, the correlation coefficients were 0.2–0.4 in several cortical regions in both groups, and as high as 0.6 in some regions in the VLBW group (Fig. 2). The lack of statistical significance in these analyses is readily explained by loss of statistical power due to the smaller sample size.

3.2.3. Cortical thickness group differences

The VLBW group showed significantly thicker cortex in the frontal (medial orbitofrontal gyrus, rostral anterior cingulate, frontal pole)

Table 1
Demographic and clinical characteristics.

	VLBW/Control number	VLBW Mean (SD/median)	Controls Mean (SD)	<i>p</i> value
Age (years)	37/104	7.8 (1.73)	8.2 (1.02)	0.352 ^b
Gender (boys/girls)	37/104	16/21	50/54	0.616
Birth weight (grams)	37/104	1050 (358)	3657 (484)	<0.001
Gestational age (weeks)	37	28.5 (28)	na	
SES	34/85	3.9 (0.9)	4.3 (0.8)	0.021
Full IQ	37/104	98 (10)	108 (14)	<0.001 ^a

Abbreviations: VLBW: very low birth weight; SES: socio-economic status; SD: standard deviation; na: not available.

^a Adjusted for socio-economic status.

^b Non-parametric due to non-equal variance.

Table 2

Proportion (%) of cortical regions showing significant differences in cortical surface area between VLBW and controls.

Cortical region of interest	Proportion (%) of region	
	Left	Right
Banks of the superior temporal gyrus	68	91
Caudal anterior cingulate gyrus	80	99
Caudal middle frontal gyrus	85	63
Cuneus	100	100
Entorhinal cortex	4	4
Fusiform gyrus	79	75
Frontal pole	100	1
Inferior parietal gyrus	58	66
Inferior temporal gyrus	10	16
Isthmus cingulate	51	97
Insula	99	98
Lateral occipital gyrus	51	47
Lateral orbitofrontal gyrus	100	99
Lingual gyrus	100	100
Medial orbitofrontal gyrus	100	84
Middle temporal gyrus	50	63
Parahippocampal gyrus	97	97
Paracentral gyrus	1	0
Pars opercularis	99	100
Pars orbitalis	100	79
Pars triangularis	96	95
Pericalcarine sulcus	100	100
Postcentral gyrus	90	54
Posterior cingulate	64	92
Precentral gyrus	62	79
Precuneus	62	58
Rostral anterior cingulate	99	100
Rostral middle frontal gyrus	37	21
Superior frontal gyrus	58	51
Superior parietal gyrus	75	86
Superior temporal gyrus	99	100
Supramarginal gyrus	71	91
Temporal pole	33	37
Transverse temporal gyrus	100	100

The table presents the percentage of surface area in each of the cortical parcellations (defined by the Desikan–Killiany parcellation scheme implemented in FreeSurfer) that showed a significant result in the GLM (after 5% FDR correction). The calculations of proportion of surface area were based on the fsaverage surface (-h.white.avg.area.mgh).

Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight.

and occipital regions (pericalcarine sulcus) bilaterally, and a thinner cortex in the right posterior parietal lobe compared with controls (Fig. 3). Moderate to large effect sizes ($d = 0.6–0.8$) were observed in the frontal and occipital regions (Appendix Fig. A3).

Proportion (%) of cortical regions with significant differences in thickness between the VLBW and the control groups is displayed in Table A3 (Appendix) with >90% involvement of the frontal poles, medial orbitofrontal gyri, left rostral anterior cingulate and right pericalcarine sulcus. Fig. A4 (Appendix) demonstrates the degree of spatial overlap between the observed between-group differences in cortical surface area and cortical thickness.

3.2.4. Cortical thickness and IQ

There were no significant correlations between cortical thickness and Full IQ in either group. However, the effect size maps in Fig. 4 demonstrate a trend-level negative relationship between cortical thickness and Full IQ in both groups in widespread cortical regions, i.e. the thinner the cortex, the higher the IQ scores (Fig. 4, blue regions). Some temporal and parietal regions showed a positive relationship to Full IQ in the VLBW group, i.e. thinner cortex was related to lower IQ scores (Fig. 4, red regions).

3.2.5. Clinical variables: birth weight, gestational age and number of days on ventilator

There were no significant associations between birth weight or gestational age and cortical area or cortical thickness in the VLBW group.

There was, however, a significant effect of days on ventilator on surface area bilaterally in the dorsal frontal regions, including the superior and medial frontal gyrus, precentral gyrus, and orbitofrontal cortex, as well as the left supramarginal and posterior superior temporal gyrus, and the right precuneus and superior parietal gyrus. There were two subjects with extreme scores on days on ventilator, i.e. more than 3 weeks on ventilator (35 and 47 days), and these subjects also had low gestational age (23.5, 26 weeks). Region-of-interest based examination of cortical surface area and cortical thickness showed that the child with 47 days on ventilator was an outlier on 5 of 36 cortical parcellations (>2 SD from the mean in the control group), and the child with 35 days on ventilator was an outlier in one parcellation. Excluding these two subjects from the analysis of group differences between VLBW and controls did not affect the results. Finally, in order to check the effect of prolonged exposure to the ventilator, we excluded children who had spent more than 10 days on ventilator. Since this reduces the statistical power to detect, because the sample is smaller than that in the full analysis, we compared maps of effect size (Cohen's d). The maps from the analyses with the reduced sample are presented in Appendix Fig. A5.

4. Discussion

We report significant reduction of cortical surface area in 5–10 year old VLBW children, relative to a term-born control group. Cortical area was reduced in frontal, temporal, parietal, and occipital regions, and cortical thickness was increased in the medial frontal and occipital lobes, in the VLBW group. Moreover, there were medium sized to large correlations between reduced surface area and thicker cortex and poorer IQ scores, in both the VLBW and the control group. However, only in the control group did correlations between reduced surface area and IQ reach statistical significance.

4.1. Widespread cortical surface area differences between the groups

The VLBW children showed significantly reduced cortical surface area in frontal, temporal, posterior parietal and medial occipital regions, as well as the right anterior cingulate (see Fig. 1). Cortical surface area expands significantly during preschool years and into adolescence in normally developing children, with the greatest changes occurring in higher order regions such as the prefrontal cortex and temporal association cortex (Brown and Jernigan, 2012). However, by the age of 10, the occipital and superior parietal lobes start to show a decrease in surface area, most probably due to pruning (Brown and Jernigan, 2012). Hence, the reduced surface area observed in the VLBW children could reflect altered maturation of cortical surface area.

Reduced cortical surface area has previously been reported in extremely low birth weight (ELBW) children at the age of 10 (Grunewaldt et al., 2014), VLBW adolescents at 15–16 years of age (Frye et al., 2010), and VLBW late adolescents at 19 years of age (Skranes et al., 2013). The magnitudes of reduction, and precisely which gyri/sulci are affected, differ somewhat between these studies. However, Skranes et al. (2013) reported reductions in cortical surface area similar to the reductions observed in the present study, both in terms of magnitude and localization of the affected regions. The fact that similar cortical regions are affected in cohorts aged 5–10 and 18–20, suggests that the morphological abnormalities observed in the present study may not simply reflect delayed maturation but rather aberrant development leading to permanently altered cortical architecture. These results also demonstrate that similar cortical changes are found both in VLBW survivors born in the late 80s and after year 2000, in spite of the advances in perinatal medicine. We speculate whether the explanation for this has to do with prenatal factors, such as fetal growth restriction, or that immature birth exposes the neonate to environmental

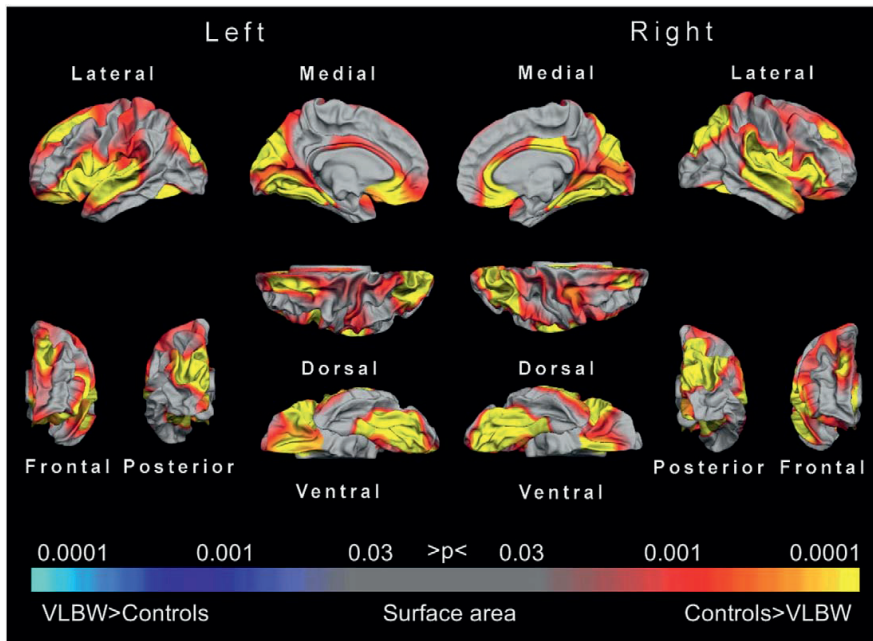


Fig. 1. Statistical p-maps showing cortical regions with significant differences in surface area between the VLBW and the control groups. The maps were produced from GLM models fitted at each location (vertex) across the cortical surface, with cortical area as the dependent variable and group as the independent variable, co-varying for sex and age at scan. The maps were thresholded to yield an expected 5% FDR across both hemispheres. The red to yellow regions are those where the VLBW group showed reduced surface area, whereas blue regions would reflect areas with increased surface area in the VLBW group compared to controls. *Abbreviations:* FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight.

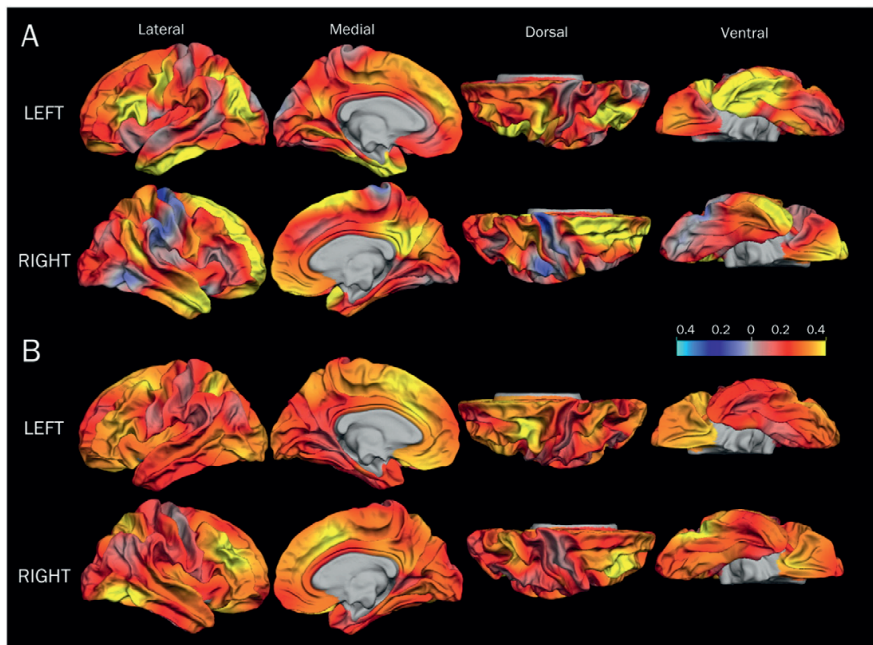


Fig. 2. Effect size maps (r) for cortical surface area and Full IQ scores in the VLBW (A) and the control (B) groups. The effect sizes are based on GLMs with cortical surface area as the dependent variable, group and sex as categorical predictors, and age and Full IQ index score as continuous predictors. Red to yellow indicate a positive correlation and blue to light blue indicate a negative correlation. Only the results for the control group reached statistical significance (see Fig. A2). *Abbreviations:* GLM: general linear model; VLBW: very low birth weight.

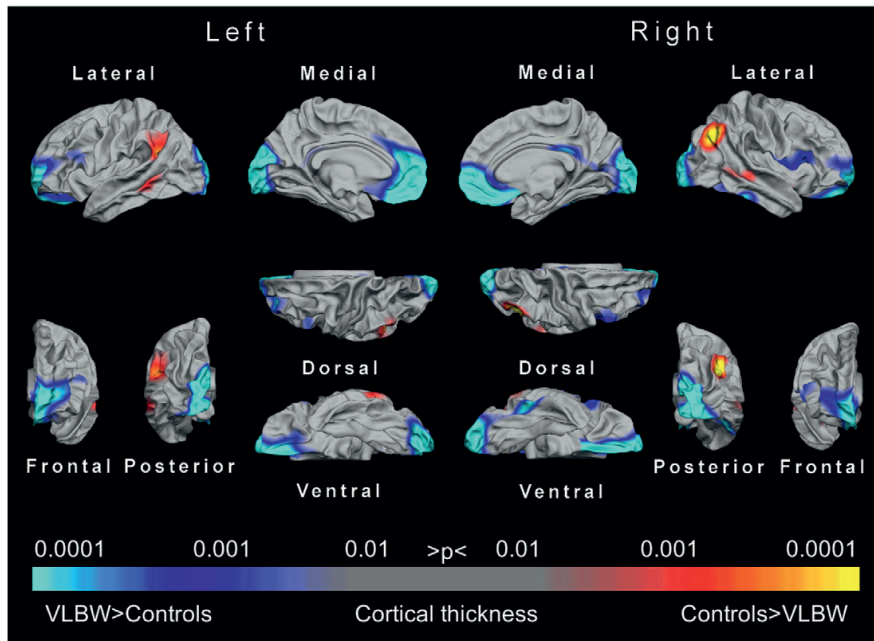


Fig. 3. Statistical p-maps showing cortical regions with significant differences in cortical thickness between the VLBW group and the control group. The maps were produced from GLMs fitted at each location (vertex) across the cortical surface, with cortical thickness as the dependent variable and group as the independent variable, co-varying for sex and age. The maps were thresholded to yield an expected 5% FDR. The FDR threshold was obtained for the left and right hemispheres conjointly. Red to yellow denote regions with cortical thinning in the VLBW group, and blue to light blue denote regions with cortical thickening in the VLBW group. *Abbreviations:* FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight.

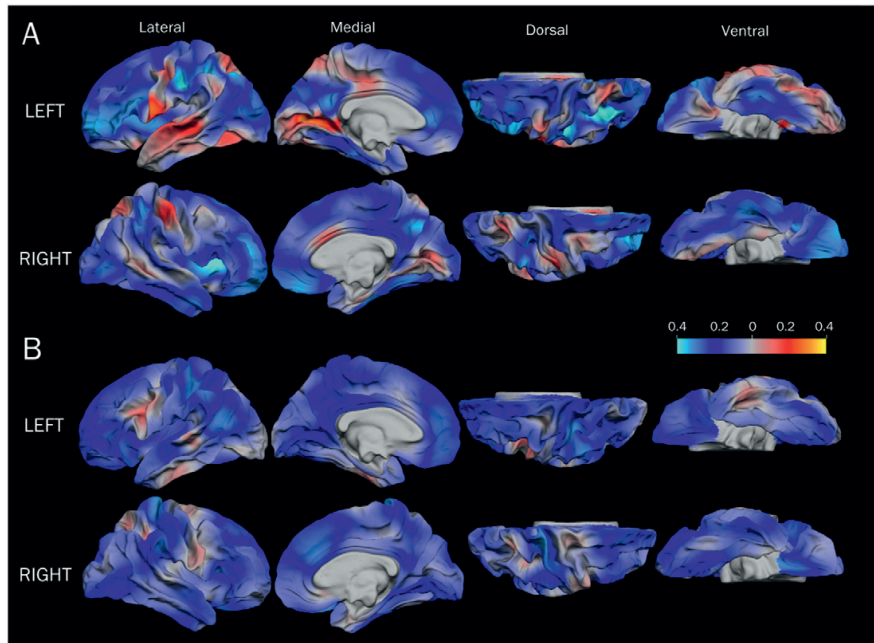


Fig. 4. Effect size maps (r) for the association between cortical thickness and Full IQ in the VLBW group (A) and the control group (B). The effect sizes are based on GLMs with cortical thickness as dependent variable, sex as categorical predictors, and age at scan and Full IQ as continuous predictors. Red to yellow indicate a positive correlation and blue to light blue indicate a negative correlation. *Abbreviations:* GLM, general linear model; VLBW, very low birth weight.

factors such as inflammation that exert an epigenetic influence on the genes controlling normal cortical development.

Performing the analyses of group differences in cortical surface area without the two children who had extreme scores on days on ventilator (32 and 45 days), did not affect the results. Excluding children who had been on ventilator for more than 10 days, in order to exclude a possible effect of prolonged respiratory support on cortical surface area, we observed similar group differences in cortical morphometry as for the full sample, albeit with reduced effect sizes in most regions. However, excluding children with more than 10 days on ventilator implies excluding many of the most immature and sickest individuals, and leaves us with a sample that is not representative of the premature birth population. Nonetheless, it is worth noting that even when subjects with prolonged respiratory support were excluded, a number of cortical regions still showed group differences. One could speculate whether this may reflect adverse prenatal factors, since these regions show cortical deviations even in the individuals who require the least amount of neonatal care.

4.2. Frontal and occipital cortical thickening in VLBW children

The VLBW children showed thicker cortex in the frontal and occipital lobes bilaterally, which is consistent with previous studies reporting increased cortical thickness in both children and adolescents born prematurely (Bjuland et al., 2013; Grunewaldt et al., 2014; Martinussen et al., 2005; Mürner-Lavanchy et al., 2014; Phillips et al., 2011). With normal development of the cerebral cortex, thickness will increase during early childhood due to late arriving interneurons then decrease, due to pruning, as neural connectivity improves (Raznahan et al., 2011; Shaw et al., 2012; Wierenga et al., 2014). Sowell et al. (2004) reported that the pattern of progressive cortical thinning varies across development, in a longitudinal study of normally developing children 5–11 years old, observing a significant cortical thinning in the dorsolateral frontal regions and bilateral parietal–occipital regions, and cortical thickening in perisylvian regions of the ventral frontal lobe and superior temporal lobe with increasing age.

Children develop at varying paces and one possible explanation for the group differences in cortical thickness in our study is delayed maturation in the VLBW group. This would be consistent with Mürner-Lavancy's (2014) study of VLBW children and term-born controls, 7–12 years old, which reported thicker frontal and parietal cortices in the youngest VLBW children compared to controls but no such group difference in the oldest children. Also partly consistent with this, Grunewaldt et al. (2014) found cortical thickness differences exclusively in the occipital lobe at 10 years of age in a cohort of ELBW. On the other hand, Bjuland et al. (2013) found increased cortical thickness in frontal and occipital regions, but also thinner cortex in frontal, parietal and temporal regions, in 19 year old VLBW adolescents. Thus, it is unclear whether the differences observed in the present study reflect aberrant development and permanent cortical changes or, rather, divergent developmental cortical trajectories that converge with increasing age. Longitudinal studies are needed to answer such questions, in order to conclusively determine whether VLBW children born after 2000 have permanent changes in cortical thickness similar to what has been reported for children born in the late 80s.

4.3. The relationship between cortical surface area and thickness

Panizzon et al. (2009) demonstrated that cortical area and cortical thickness reflect at least two distinct sources of genetic influence, consistent with the developmental origin of cortical architecture described by the radial unit hypothesis (Rakic, 1988), and other studies have suggested independent and divergent developmental trajectories for area and thickness (Raznahan et al., 2011; Shaw et al., 2012; Wierenga et al., 2014). In line with this, we found that regions displaying group differences in surface area and cortical thickness overlapped to a limited

extent (as shown in Fig. A4). Regions displaying overlapping effects were mainly located on the mesial aspect of the hemispheres; anteriorly in the anterior portion of the SFG, medial orbitofrontal cortex, and anterior cingulate, and posteriorly in the pericalcarine sulcus and cuneus.

The VLBW children in the present study were born between 23 and 35 weeks of gestation, which is a particularly sensitive period of neural migration and rapid cortical development. Disorders of migration are more likely to occur in the second trimester (Zhang et al., 2013) by either under-migration or over-migration of neurons, and both will lead to cortical abnormalities (Fogliarini et al., 2005). Preterm birth may affect processes like neuronal migration, synaptogenesis and apoptosis late in the 2nd and early 3rd trimesters (Tau and Peterson, 2010) resulting in the kind of deviant cortical thickness and reduced surface area observed here.

The migration of neuroprogenitor cells may be hindered in preterm children by germinal matrix hemorrhages that can destroy neuronal precursors, or by injury to guiding glial cells (Volpe, 2009). A reduced pool of neuroprogenitor cells and deficient migration can lead to a reduced number of founder cells in the ventricular zone and number of cerebral columns, which may result in decreased surface area (Rakic, 1995). However, in our study only three out of 37 VLBW children had intraventricular hemorrhages and none had focal PVL, suggesting that focal perinatal brain injury is probably not the cause of the cortical deviations seen in our VLBW group.

Within 28–32 weeks of gestation a fast emergence of short-range connectivity, in addition to the long-range association pathways, is observed (Takahashi et al., 2012). In the VLBW population, reduced fractional anisotropy has been reported in the inferior longitudinal and the longitudinal occipito-frontal fascicles (Eikenes et al., 2011; Skranes et al., 2007). Whether diffuse white matter injury causing disrupted connectivity and cortical reorganization leads to reductions in surface area and increased cortical thickness in the VLBW is not known, but cannot be excluded as an explanation for the presently observed cortical changes. The frontal, parietal and occipital regions with deviant cortical surface area and/or increased thickness in the VLBW children are all regions involved in networks receiving long-range association tracts. We therefore speculate that the deviations seen in cortical morphology in the VLBW group may be both primary changes due to cortical maldevelopment as well as secondary to altered white matter microstructure and connectivity.

4.4. Cortical morphology and cognitive measures

A positive association between cortical surface area and IQ was observed in both VLBW and control subjects, albeit as a non-significant trend in the VLBW group. However, the magnitude of the effect was larger in frontal, temporal and medial parietal regions in the VLBW group than that in the control group, although these structure–function associations survived significance testing only in the control group due to its larger sample size.

The frontal regions in which surface area was related with IQ included the caudal middle frontal gyrus, lateral orbitofrontal gyrus, medial orbitofrontal gyrus, pars orbitalis, rostral anterior cingulate, frontal pole and insula. These are regions where the VLBW children have significantly reduced surface area in comparison with controls, and are believed to be important for cognitive functions such as decision making, executive functions, semantics, attention, and working memory. Previous studies have consistently shown poorer executive abilities in individuals born with VLBW than term-born peers, as well as problems with attention and working memory (Aarnoudse-Moens et al., 2009; Bayless and Stevenson, 2007; Anderson, 2014; Lohaugen et al., 2010; Anderson et al., 2004), and in the present study, the VLBW group had lower IQ scores than those of the controls. Our results indicate that a larger surface area is positively correlated to higher IQ, consistent with Skranes et al. (2013), and it is tempting to speculate that

reduced cognitive function in the VLBW group may be caused, at least in part, by the observed reduction in surface area.

There was a negative association, albeit not significant, between IQ and cortical thickness in both groups. In the VLBW group, the regions with the strongest negative associations between IQ and cortical thickness were also the regions where the VLBW children displayed thicker cortex than controls. This is consistent with previous studies of the relationship between cortical thickness and cognitive functions in normally developing 5–11 year old children, where cortical thinning in the left dorsal frontal and parietal lobes was correlated with improved verbal performance (Sowell et al., 2004). Moreover, in VLBW adolescents with low IQ, Full IQ and cortical thickness were negatively correlated in the frontal and positively correlated in the parietal lobes (Bjuland et al., 2013). Taken together, our findings suggest that altered cortical development in VLBW children seems to affect their cognitive abilities; however, longitudinal studies are needed to determine whether these deviations persist during further brain maturation throughout school age, adolescence and into early adulthood also for these recent year cohorts of VLBW children.

4.5. Conclusion

The present study demonstrates altered development of cortical surface and cortical thickness in VLBW children born in 2003–2007, and these deviations are associated with poorer cognitive abilities. The present brain morphological deviations are evident even in VLBW children without cerebral palsy who have received state of the art medical treatment in the perinatal period, and who did not present with focal brain injuries on neonatal ultrasonography.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgments

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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.nicl.2015.04.004>.

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Appendix

Table A1 Perinatal characteristics for children in the VLBW group

	n	VLBW Mean (range/median)
Apgar score 1 min	37	7.4 (8)
Apgar score 5 min	37	8.4 (9)
Antenatal steroids, n (%)	37	22 (59.5)
Mechanical ventilation, days	37	5.4 (0-47)
Intraventricular hemorrhage		
- Grade 1, n (%)	37	2 (5.4)
- Grade 3, n (%)	37	1 (2.7)
Days in NICU	37	45.2 (44)
SGA, n (%)	37	3 (8)

Abbreviations: NICU: Neonatal Intensive Care Unit; SGA: Small for gestational age (BW below the 10th percentile)

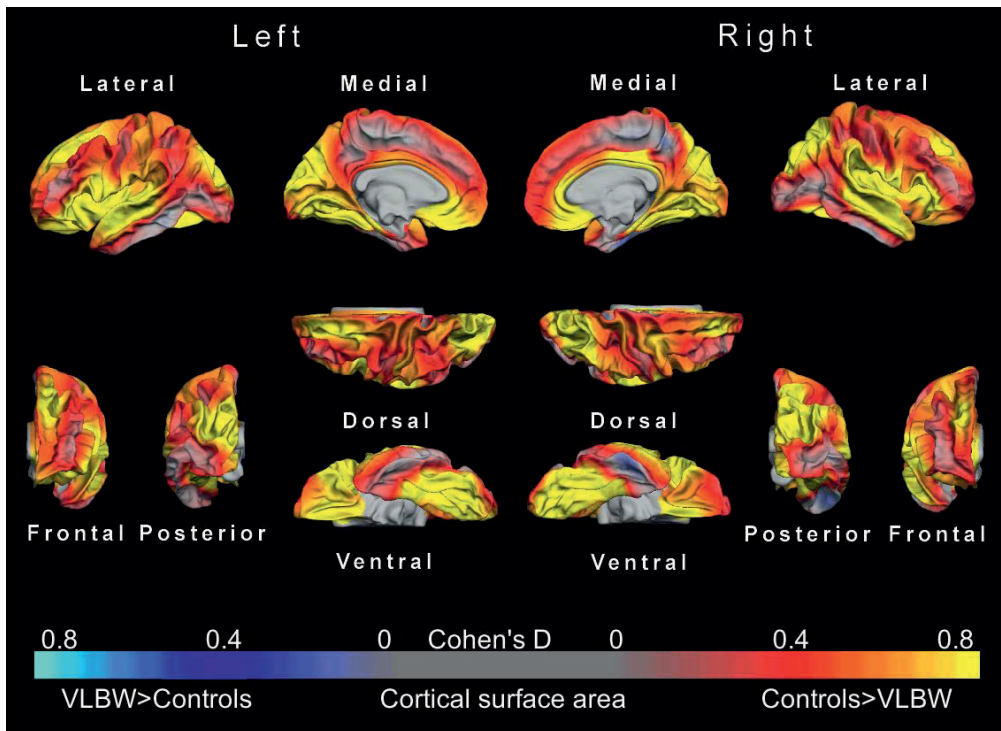


Figure A1: Maps of effect size (Cohen's d) for the difference in cortical surface area between the VLBW group and the control group. The maps are based on a GLM with cortical surface area as dependent variable, group and sex as categorical predictors, and age at MRI scan as continuous predictor. Red to yellow represents areas with smaller surface in the VLBW group. The strongest effects were observed bilaterally in superior temporal gyrus, middle temporal gyrus, insula, superior parietal gyrus and parahippocampal gyrus, bilaterally.
Abbreviations: GLM: general linear model; VLBW: very low birth weight.

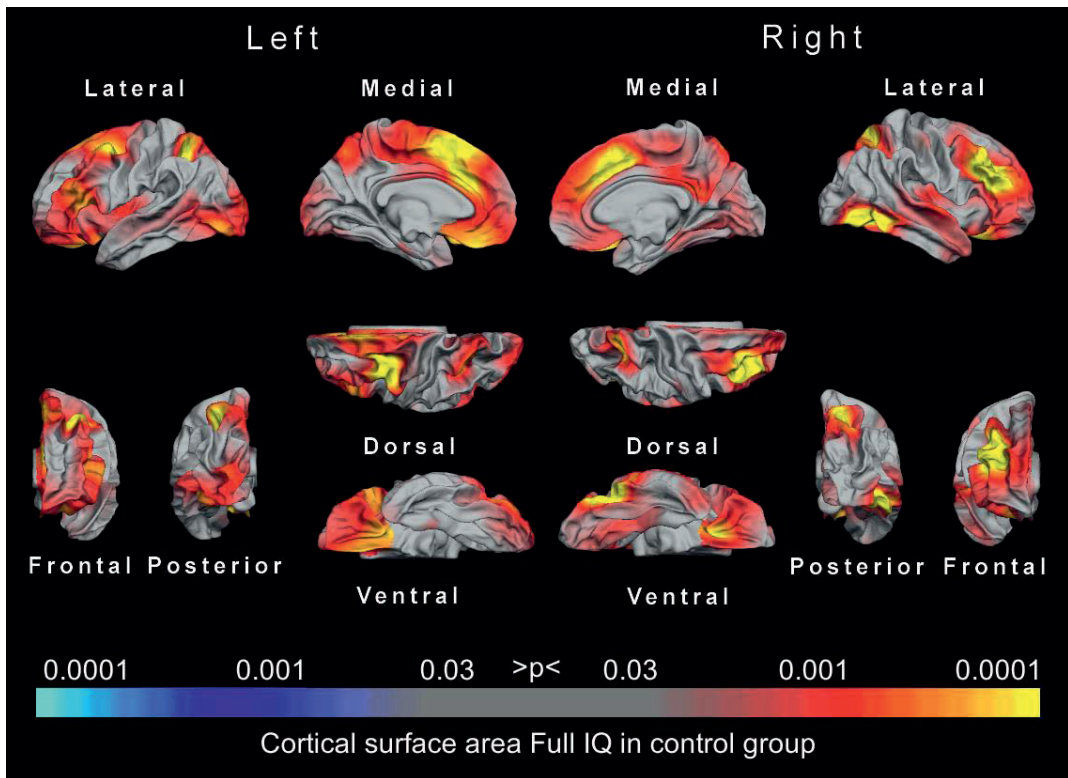


Figure A2: Statistical p-maps showing cortical regions with a significant relationship between cortical surface area and Full IQ scores in the control group. The maps were produced from GLMs fitted at each location (vertex) across the surface, with cortical surface area as dependent variable, and Full IQ as independent variable, co-varying for age and sex. The maps were thresholded to yield an expected 5% FDR. The FDR threshold was obtained for left and right hemispheres conjointly. Red to yellow indicates a significant, positive relationship between Full IQ and surface area.
Abbreviations: FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight.

Table A2: Proportion (%) of cortical regions showing significant relationship between Full IQ and cortical surface area in the control group.		
Cortical regions	Proportion (%) of region	
	LEFT	RIGHT
Banks of the superior temporal gyrus	82	81
Caudal anterior cingulate gyrus	100	66
Caudal middle frontal gyrus	96	99
Corpus Callosum	0	0
Cuneus	56	76
Entorhinal cortex	51	0
Fusiform gyrus	47	87
Inferior parietal gyrus	100	50
Inferior temporal gyrus	29	18
Isthmus cingulate	39	73
Lateral occipital gyrus	11	63
Lateral orbitofrontal gyrus	96	69
Lingual gyrus	100	55
Medial orbitofrontal gyrus	100	100
Middle temporal gyrus	46	83
Parahippocampal gyrus	100	98
Paracentral gyrus	63	81
Pars opercularis	29	86
Pars orbitalis	99	90
Pars triangularis	92	67
Pericalcarine sulcus	100	100
Postcentral gyrus	100	100
Posterior cingulate	61	95
Precentral gyrus	15	20
Precuneus	95	88
Rostral anterior cingulate	60	6
Rostral middle frontal gyrus	58	93
Superior frontal gyrus	100	100
Superior parietal gyrus	80	100
Superior temporal gyrus	92	91
Supramarginal gyrus	85	71
Frontal pole	68	88
Temporal pole	14	4
Transverse temporal gyrus (Heschl's gyrus)	100	35
Insula	75	100

The table presents the percentage of each of the cortical parcellations (from the Desikan-Killiany parcellation scheme implemented in FreeSurfer) that showed a significant relationship between Full IQ and surface area in the control group. *Abbreviations:* FDR, false discovery rate; GLM, general linear model

Table A3 Proportion (%) of cortical regions showing significant differences in cortical thickness between VLBW and controls		
Cortical regions	Proportion (%) of region affected	
	LEFT	RIGHT
Banks of the superior temporal gyrus	20	29
Caudal anterior cingulate gyrus	9	0
Caudal middle frontal gyrus	0	0
Corpus Callosum	0	0
Cuneus	59	57
Entorhinal cortex	0	0
Fusiform gyrus	5	22
Inferior parietal gyrus	20	31
Inferior temporal gyrus	1	26
Isthmus cingulate	32	43
Lateral occipital gyrus	50	64
Lateral orbitofrontal gyrus	47	35
Lingual gyrus	34	30
Medial orbitofrontal gyrus	99	100
Middle temporal gyrus	23	16
Parahippocampal gyrus	0	0
Paracentral gyrus	0	0
Pars opercularis	34	71
Pars orbitalis	0	0
Pars triangularis	0	23
Pericalcarine sulcus	58	96
Postcentral gyrus	0	10
Posterior cingulate	2	15
Precentral gyrus	0	9
Precuneus	2	8
Rostral anterior cingulate	99	87
Rostral middle frontal gyrus	54	41
Superior frontal gyrus	27	13
Superior parietal gyrus	8	6
Superior temporal gyrus	2	4
Supramarginal gyrus	26	3
Frontal pole	100	100
Temporal pole	0	0
Transverse temporal gyrus (Heschl's gyrus)	0	0
Insula	0	4

The table presents the percentage of surface area in each of the cortical parcellations (from the Desikan-Killiany parcellation scheme implemented in FreeSurfer) that showed a significant result in the GLM (after 5% FDR correction). *Abbreviations:* FDR, false discovery rate; GLM, general linear model; VLBW, very low birth weight

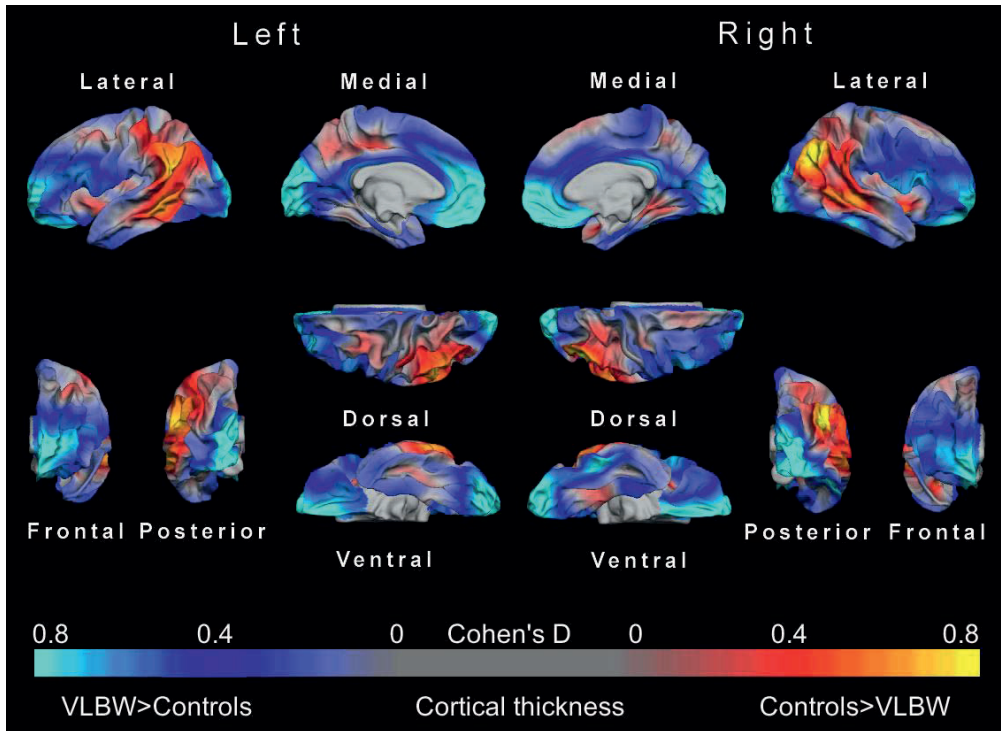


Figure A3: Maps of effect size (Cohen's d) for the difference in cortical thickness between the VLBW group and the control group. The effect size is based on a GLM with cortical thickness as dependent variable, group and sex as categorical predictors, and age at scan and as continuous predictor. Blue regions represent thicker and red to yellow regions thinner cortex in the VLBW group relative to the control group

Abbreviations: GLM: general linear model; VLBW: very low birth weight.

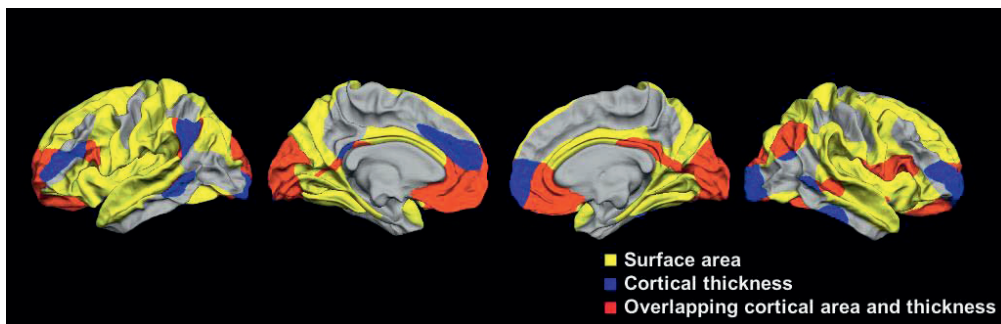


Figure A4: The figure shows p-value maps from analyses of group differences in cortical surface area and cortical thickness. Yellow regions represent significant group differences exclusively in cortical surface area; blue regions represent significant group differences exclusively in cortical thickness only; and red regions represent significant group differences in both surface areas and cortical thickness.

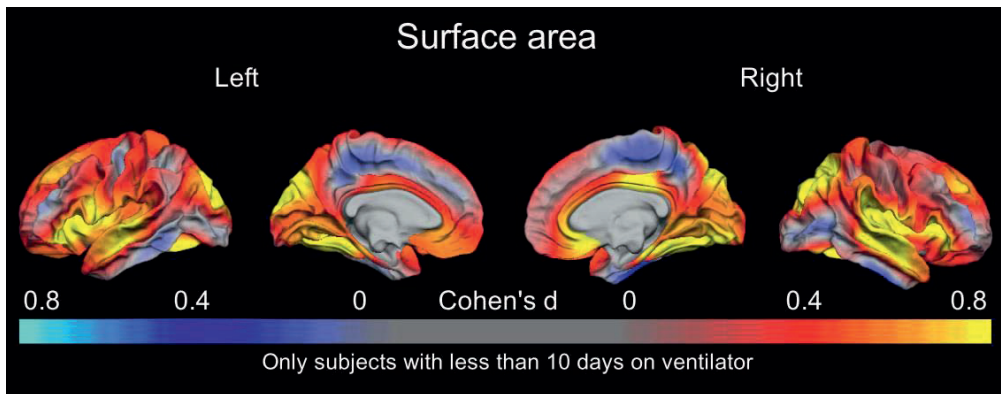


Figure A5: Maps of effect size (Cohen's d) for the difference in cortical surface area between the VLBW group without subjects with more than 10 days on ventilator (5 children excluded) and the control group. The effect size is based on a GLM with cortical surface area as dependent variable, group and sex as categorical predictors, and age at scan and as continuous predictor. Blue regions represent thicker and red to yellow regions thinner cortex in the VLBW group relative to the control group

Abbreviations: GLM: general linear model; VLBW: very low birth weight.

PAPER 4

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 diffusion tensor imaging (DTI) and structural magnetic resonance imaging (MRI) study, we investigated differences in subcortical brain volumes and their relationship to white matter tract properties in children born preterm with VLBW compared to term-born controls. Subcortical volumes and cortical thickness were obtained in FreeSurfer, and fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were generated by the

TRACULA tractography tool for 18 white matter tracts. We also assessed structural relationships between white matter tracts of interest and cortical thickness of the tract endpoints. Compared to controls, the VLBW group had reduced volumes of thalamus, globus pallidus, hippocampus, corpus callosum, cerebral white matter, ventral diencephalon, and brain stem, while the ventricular system was larger in VLBW subjects, after controlling for age, sex, and estimated total intracranial volume. For the DTI parameters, the group differences were significant in AD in the left superior longitudinal fasciculus (SLFP) and arcuate fasciculus (SLFT). IQ did not correlate with either subcortical volumes or DTI measures in the VLBW group. While the deviations in subcortical volumes were substantial, similar to previous reports from a cohort born in the 1980s, there were few differences in DTI measures between the two groups, which may reflect that advances in perinatal care influence connectivity more than postnatal brain growth.

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). But while survival rates have improved due to a reduction in severe focal brain injuries including intraventricular hemorrhages grades III and IV and cystic periventricular leukomalacia, 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 \leq 1500 grams) and preterm birth (Løhaugen et al., 2010; Aarnoudse-Moens et al., 2009; Lund et al., 2012). Diffuse white matter injury including gliosis and axonal abnormalities 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).

Magnetic resonance imaging (MRI) research has identified white matter tracts that appear specifically sensitive to the effects of preterm birth and VLBW, such as corpus callosum and

long-range association tracts (Pandit et al., 2013; 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; Hart et al., 2008). White matter near the lateral ventricles and in centrum semiovale has long been known to be especially vulnerable to perinatal injury among preterm-born individuals (Banker and Larroche, 1962), and diffusion-weighted MRI is used to measure the Brownian motion of water diffusion of white matter bundles in the brain (Le Bihan et al., 2012; Johansen-Berg and Behrens, 2014). Hypoxia-ischemia and inflammation are considered the underlying causes behind periventricular white matter injury in preterms (Ortinou and Neil, 2015).

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). Smaller cerebral white matter, thalamus, hippocampus, cerebellar white matter, and anterior cingulate volumes have been reported in prematurely born toddlers (Lowe et al., 2011). Deep gray matter abnormalities have been found in tandem with diffuse white matter injury in infancy (Boardman et al., 2006) and childhood (Murray et al., 2014). 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).

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 2011; Bjuland et al., 2013; Martinussen et al., 2005). It is not known if 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 and white matter properties and possible relationships to the cortical changes previously reported in the same cohort of children. We

explored group differences in DTI using TRACULA, a novel tool for automated reconstruction of 18 major white matter tracts, as well as segmentation of subcortical brain 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

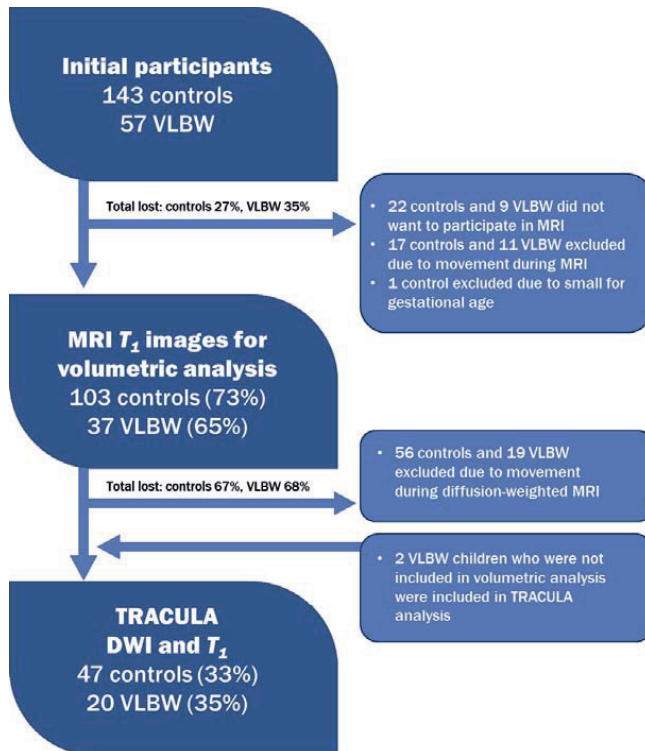
Preterm-born VLBW subjects (birth weight \leq 1500 g), born between 2003 and 2007, were recruited based on admittance to the Neonatal Intensive Care Unit at St. Olav's University Hospital in Trondheim, Norway. Sixty-three children were invited and 57 agreed to participate in the study (**Figure 1**). Age ranged from 5.0 to 10.5 years old (mean age=7.7 years). Exclusion criteria were cerebral palsy, severe sensory impairments, and/or MRI contraindications. Perinatal health data collected included gestational age, birth weight, and number of days on mechanical ventilator after birth. Two children with birth weights of 1784 and 2090 grams (each a twin of VLBW children) were included in the VLBW group to promote collaboration with the participating families, and post-hoc analysis showed similar IQ scores as the rest of the VLBW cohort. Thirty-seven VLBW subjects had successful structural MRI and were included in the subcortical volume analysis, and 20 with high-quality diffusion data were included in the DTI analysis.

Control subjects

The control subjects were recruited from the national Norwegian Mother and Child Cohort Study (MoBa), 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 grams, and/or MRI contraindications. Subcortical volume analysis included 103 controls

subjects, and 47 controls were included in the DTI analysis based on quality of their diffusion data (**Figure 1**).

Figure 1. Overview of participation and retention.



Abbreviations: DWI: diffusion-weighted imaging; VLBW: very low birth weight.

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: WPPSI-III (four subtests) or Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Full-scale IQ scores were used for analysis.

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 minutes. 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 $240 \times 240 \text{ mm}^2$, and TA=4 min and 18 min. Each volume consisted of 160 sagittal slices with voxel sizes of $1.25 \times 1.25 \times 1.20 \text{ mm}^3$.

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

Each MPRAGE series and the DTI data were visually inspected, and only scans with no or minimal movement artifacts were included in the analyses. Calculation of head motion during DTI 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 DTI 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; Segonne et al., 2004). The subcortical volumetric analysis was conducted based on MR images 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 labelling procedure in FreeSurfer (Fischl et al., 2002, 2004a), and each structure's volumes from both hemispheres were combined to generate a bilateral volume value.

TRACULA

TRACULA (TRActs Constrained by UnderLying Anatomy), as implemented in FreeSurfer 5.3.0, was used for DTI 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 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. Twenty 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 CST, and right cingulate gyrus; but remaining values were used for group-level analysis. Eighteen of 20 subjects from the DTI analysis were also included in the subcortical volume analysis, while two VLBW subjects with too poor subcortical data to be analyzed in the volume analysis could be included in Tracula (see **Figure 1**).

TRACULA reconstructs 18 white matter pathways: 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 DTI 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 endpoints onto the gray/white matter surface by sampling along the surface normal vector, anywhere within 6mm (3 DWI-space voxels) of the gray/white junction, and then smoothing along the surface with a 2D Gaussian kernel of 6mm 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 continuous 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, US) was used for statistical analyses of subcortical and cortical morphometry and DTI data. The software package IBM SPSS 21 (Chicago, USA) was used to

generate group differences and correlations between morphometric, DTI, IQ, and clinical measures. General linear models were fitted for group comparisons of subcortical brain structure volumes, controlled for age at scan, sex, and 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 DTI 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 was tested for significance using Fisher's exact test. Holm-Bonferroni step-down (Holm, 1979) was used to correct for multiple comparisons.

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**. 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 DTI analysis (97 vs 112). IQ scores were still significantly lower in the VLBW group after additionally controlling for socioeconomic status, ($p < 0.001$). VLBW subjects were approximately 6 months younger than control subjects (7.7 vs 8.3 years) in the subcortical sample, while both groups had a mean age of 8.7 years in the TRACULA sample. 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 significantly more help in school and preschool than controls ($p < 0.0001$ in subcortical sample and $p < 0.01$ in TRACULA sample).

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

1a. Subcortical analysis	VLBW (n=37)			Control (n=103)			p-value
	Mean	SD	Range	Mean	SD	Range	
Birthweight, g	1048	361	416–2090	3661	485	2510–4950	<0.0001
Gestational age, weeks(days)	29(0)	2(6)	23(4)–35(1)	Term-born			--
Age at MRI, years	7.7	1.7	5.0–10.5	8.3	1.0	5.3–10.7	0.03
Full-scale IQ	99	9.7	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	0.02
Sex: male / female	16 / 21			49 / 54			0.65
Subjects with twin	6			0			<0.0001
Special education, n (%)	10 (27)			2 (1.9)			<0.0001
1b. DTI analysis	VLBW (n=20)			Control (n=47)			p-value
	Mean	SD	Range	Mean	SD	Range	
Birthweight, g	1103	365	500–1784	3696	521	2550–4950	<0.0001
Gestational age, weeks(days)	29(4)	3(1)	23(4)–35(1)	Term-born			--
Age at MRI, years	8.7	1.3	5.0–10.5	8.7	0.7	7.5–10.6	0.85
Full-scale IQ	97	8.0	82–117	112	13.7	73–134	<0.0001
Socioeconomic status (n=19, 39)	4.0	0.9	2–5	4.4	0.8	2–5	0.05
Sex: male / female	9 / 11			22 / 25			0.89
Subjects with twin	4			0			<0.01
Special education, n (%)	5 (25)			1 (2.1)			<0.01

Displayed with *p*-values based on ANOVA between control and VLBW groups.

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 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. **Figure 2** 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. Only the corpus callosum posterior subsegmentation volume correlated significantly to gestational age among VLBW subjects ($R=0.58, p<0.0001$). 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 ($R=0.50, p<0.0001$), cerebellar gray matter ($R=0.36, p<0.0001$) 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 ($R=0.37,$

$p < 0.0001$). Correlations in both groups were not significant with correction for estimated total intracranial volume.

Table 2. Bilateral subcortical volumes (mm^3) in VLBW and control subjects with p -values (shown for those < 0.05) for group differences.

Structure	VLBW		Control		p -value
	mean	95% CI	mean	95% CI	
Amygdala	2830	(2746, 2915)	2857	(2808, 2907)	ns
Brain stem	17889	(17429, 18349)	18957	(18687, 19227)	$1.6 \times 10^{-4} *$
Caudate	8070	(7794, 8347)	8128	(7967, 8291)	ns
Cerebellar cortex	114166	(110971, 117362)	113822	(111949, 115697)	ns
Cerebellar white matter	23493	(22699, 24288)	24480	(24014, 24946)	.039
Cerebral white matter	399596	(391982, 407211)	420558	(416093, 425025)	$9.0 \times 10^{-6} *$
Corpus callosum anterior	758	(721, 796)	806	(785, 829)	.033
Corpus callosum central	313	(290, 337)	392	(379, 406)	$7.7 \times 10^{-8} *$
Corpus callosum mid-anterior	346	(323, 370)	404	(391, 419)	$6.5 \times 10^{-5} *$
Corpus callosum mid-posterior	297	(274, 322)	385	(372, 400)	$6.8 \times 10^{-9} *$
Corpus callosum posterior	660	(622, 699)	774	(752, 797)	$2.2 \times 10^{-6} *$
Globus pallidus	3483	(3372, 3594)	3755	(3690, 3820)	$6.9 \times 10^{-5} *$
Hippocampus	7856	(7650, 8064)	8278	(8157, 8399)	$8.4 \times 10^{-4} *$
Nucleus accumbens	1344	(1284, 1405)	1397	(1362, 1432)	ns
Putamen	11691	(11318, 12065)	11965	(11746, 12185)	ns
Thalamus	14000	(13712, 14288)	14715	(14546, 14885)	$5.6 \times 10^{-5} *$
Ventral diencephalon	6836	(6692, 6981)	7112	(7028, 7197)	0.0017 *
Ventricular system	20820	(18467, 23174)	11912	(10532, 13293)	$3.1 \times 10^{-9} *$

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, denoted by * ($p < 0.0029$). Nonsignificant differences denoted by ns. Abbreviations: CI: confidence interval; VLBW: very low birth weight.

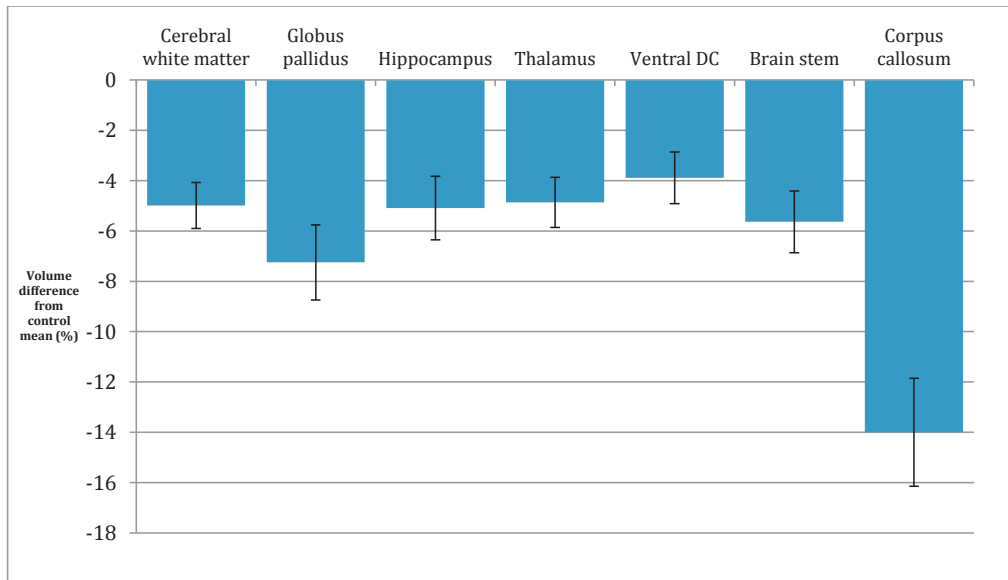


Figure 2. VLBW subcortical volumes as percentage difference from control mean. Volumes controlled for age, sex, and estimated total intracranial volume. Corpus callosum volume aggregated from all 5 subsegmentations. Abbreviations: DC: diencephalon; VLBW: very low birth weight.

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 (**Figure 3**). Means and p -values for the diffusion tensor imaging (DTI) measures for tracts with significant group differences are presented in **Table 4**.

Higher AD in the left SLFP and SLFT in the VLBW group was significant after Holm-Bonferroni step-down, with group differences in several additional structures nominally significant at the uncorrected $p < 0.05$ level. Higher MD in the left and right SLFP in the VLBW group was driven by higher AD in those structures. By contrast, higher MD in the VLBW group in the forceps minor and left cingulate gyrus was driven by higher RD. AD was also increased

among VLBW subjects in the corticospinal tract bilaterally. Left corticospinal tract showed higher FA in the VLBW group, while FA in the forceps minor was lower in the VLBW group compared with controls. Control and VLBW groups did not differ in terms of head motion.

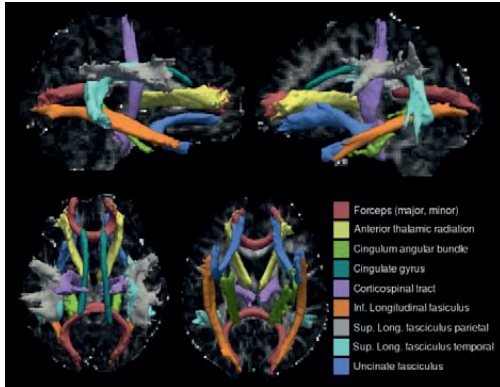


Figure 3. Probabilistic reconstruction of 18 white matter tracts generated by TRACULA, illustrated here in a control subject.

Table 4. Mean values for FA, MD, RD, and AD in both groups and Cohen's *d* and *p*-values (shown for those with $p < 0.05$) for group differences.

White matter tract	FA				MD [$\times 10^{-5} \text{mm}^2/\text{s}$]				RD [$\times 10^{-5} \text{mm}^2/\text{s}$]				AD [$\times 10^{-5} \text{mm}^2/\text{s}$]			
	Control mean	VLBW mean	<i>d</i>	<i>p</i> -value	Control mean	VLBW mean	<i>d</i>	<i>p</i> -value	Control mean	VLBW mean	<i>d</i>	<i>p</i> -value	Control mean	VLBW mean	<i>d</i>	<i>p</i> -value
ATR, left	0.45	0.44	0.27	ns	7.9	7.95	0.19	ns	5.84	5.9	0.24	ns	12.04	12.05	0.03	ns
ATR, right	0.44	0.44	0.17	ns	7.98	8.02	0.21	ns	5.93	5.97	0.16	ns	12.07	12.12	0.12	ns
CAB, left	0.37	0.35	0.4	ns	8.47	8.44	0.1	ns	6.7	6.79	0.2	ns	12.02	11.75	0.65	0.019*
CAB, right	0.39	0.37	0.27	ns	8.31	8.25	0.17	ns	6.48	6.51	0.05	ns	11.96	11.74	0.51	0.033*
CCG, left	0.54	0.53	0.27	ns	7.66	7.88	0.66	0.015*	5.1	5.36	0.53	0.023*	12.78	12.92	0.17	ns
CCG, right	0.47	0.47	0.05	ns	7.76	7.8	0.18	ns	5.62	5.64	0.06	ns	12.03	12.14	0.15	ns
CST, left	0.56	0.58	0.53	0.017*	7.93	7.92	0.04	ns	5.09	4.97	0.44	ns	13.61	13.82	0.55	0.0081*
CST, right	0.55	0.56	0.11	ns	7.92	7.97	0.34	ns	5.14	5.14	0.02	ns	13.47	13.61	0.43	0.040*
Forceps major	0.63	0.62	0.25	ns	8.21	8.22	0.06	ns	4.74	4.85	0.22	ns	15.14	14.98	0.33	ns
Forceps minor	0.61	0.59	0.54	0.032*	8	8.19	0.57	0.026*	4.75	5.04	0.61	0.018*	14.49	14.5	0.02	ns
ILF, left	0.51	0.52	0.14	ns	8.44	8.38	0.2	ns	5.82	5.77	0.14	ns	13.68	13.61	0.15	ns
ILF, right	0.52	0.53	0.26	ns	8.49	8.47	0.09	ns	5.83	5.77	0.19	ns	13.82	13.87	0.15	ns
SLFP, left	0.44	0.45	0.37	ns	7.77	7.91	0.57	0.013*	5.87	5.9	0.11	ns	11.58	11.93	1.02	$3.9 \times 10^{-5}^{**}$
SLFP, right	0.44	0.44	0.07	ns	7.96	8.07	0.47	0.037*	6.03	6.1	0.25	ns	11.82	12.01	0.47	0.037*
SLFT, left	0.47	0.49	0.52	ns	7.89	7.98	0.38	ns	5.75	5.72	0.1	ns	12.18	12.52	1.07	$4.3 \times 10^{-5}^{**}$
SLFT, right	0.45	0.46	0.12	ns	8.03	8.07	0.16	ns	5.95	5.95	0.01	ns	12.2	12.31	0.32	ns
UNC, left	0.43	0.43	0.01	ns	8.32	8.33	0.04	ns	6.3	6.31	0.04	ns	12.38	12.37	0.01	ns
UNC, right	0.46	0.45	0.43	ns	8.19	8.26	0.33	ns	5.98	6.1	0.44	ns	12.6	12.58	0.07	ns

Nonsignificant differences denoted by ns; * nominally (uncorrected) significant at the $p < 0.05$ level; ** significant after Holm-Bonferroni step-down. *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.

Relationships between DTI 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 ($R=0.87$, $p < 0.0001$) and AD in left uncinate fasciculus in the control group with birth weight ($R=0.52$, $p < 0.001$). 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 DTI 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) in the VLBW group (**Figure 4**). The left CCG posterior endpoint cortical thickness correlated positively with mean tract FA ($R=0.61$, $p=0.008$) and AD ($R=0.66$, $p=0.003$) but negatively with RD ($R=-0.51$, $p=0.03$). The left SLFT frontal endpoint cortical thickness correlated positively with mean tract MD ($R=0.67$, $p=0.003$) and RD ($R=0.57$, $p=0.014$). The left SLFP frontal endpoint cortical thickness also had a positive correlation with mean tract MD ($R=0.51$, $p=0.029$). The right ATR frontal endpoint cortical thickness correlated positively with mean tract RD ($R=0.53$, $p=0.025$). Group differences in cortical thickness based on the 34 anatomical regions for each brain hemisphere defined in FreeSurfer have been previously reported by Sølvsnes et al. (2015).

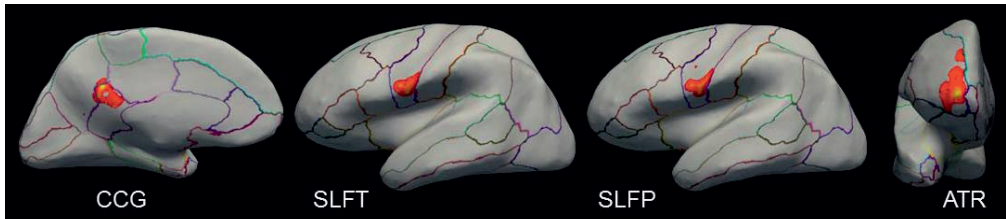


Figure 4. Examples of projections of left CCG posterior endpoints, left SLFT frontal endpoints, left SLFP frontal endpoints, and right ATR frontal endpoints onto inflated cortical surface, illustrated in a control subject. The red-yellow overlays are the probability distributions of the position of the 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.

CCG endpoints terminated primarily in the isthmus cingulate cortex, and to a lesser extent in adjacent posterior cingulate and precuneus. SLFT and SLFP 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 ($p < 0.05$) (**Table S1**). In SLFT in both hemispheres, MD and AD values were higher in the VLBW group than in controls in the middle of the tracts. Forceps minor had higher RD and MD and lower FA in the VLBW group, impacted along a medial segment of the tract. Left CCG showed higher RD and lower FA anteriorly in the VLBW group. VLBWs had higher AD values in left CST dorsally. Finally, the pointwise analysis indicated that the left SLFP group differences were driven by higher AD posteriorly in the VLBW group, though the longest contiguous tract length showing significant group differences for this tract was approximately 1.2 cm.

DISCUSSION

This follow-up study of children born in the 2000s, comparing individuals born preterm with VLBW and a control group of term-born individuals, 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. 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 DTI measures in the VLBW group. VLBW subjects had higher AD in left SLFP and SLFT, especially in the middle segment of the SLFT and posterior SLFP. Several nominally significant correlations ($p < 0.05$, uncorrected) were found in the VLBW group between tract endpoint cortical thickness and DTI measures in left CCG posteriorly, left SLFT frontally, left SLFP frontally, and right ATR frontally.

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, globus pallidus, and hippocampus, 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 (Nasgunder 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 (Bjaland 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 *in utero* on subcortical developmental processes, such as intrauterine growth restriction, with consequences for postnatal brain growth, independent of the differences in perinatal medicine available when these two cohorts were born.

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, which included measures of locomotor skills, personal–social skills, hearing and language, eye and hand coordination, performance, and practical reasoning, suggesting that the influence of white matter injury on the development of basal ganglia and thalami could have functional consequences (Boardman et al., 2010). Several of our findings 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 seems less influenced by better perinatal care and may be due to a continuation of mechanisms causing intrauterine growth failure and/or ongoing inflammatory processes in the immature brain with epigenetic effects on genes regulating normal brain growth and development.

DTI findings

The VLBW group had significantly higher AD in left SLFT and SLFP compared to controls, with higher AD in the middle segment of the SLFT and posterior SLFP driving the group differences. The SLFT, which corresponds to the arcuate fasciculus, links Wernicke's and Broca's areas (Catani et al., 2002). The SLFP connects parietal cortex and ventral premotor cortex, including posterior Broca's area (Rushworth et al., 2014). We previously described (Sølsnes et al., 2015) significant surface area reductions among the same group of VLBW children in the left precentral gyrus, where we found a portion of the SLFP to terminate. We also found positive correlations ($p < 0.05$, uncorrected) between endpoint cortical thickness and MD in both SLFT and SLFP, as well as with RD in the SLFT. We identified specific segments of white matter tracts in the CCG, SLFT, SLFP, CST, and forceps minor 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). 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. (2012) 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, other recent 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. FA has been more associated with complications of preterm birth than with extreme preterm birth in itself (Bonifacio et al., 2010). 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, and chronic lung disease.

In general, the limited DTI 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). In contrast to the findings in the present study cohort, Eikenes et al. (2011) reported significantly lower FA and higher MD in several major white matter tracts in our young adult VLBW cohort born in 1986-1988. Moreover, FA in the older cohort correlated negatively to number of days in intensive care and on mechanical ventilator. Thus, although total brain growth is still affected in this cohort born in the 2000s, with smaller volumes, reduced surface area, and signs of possible cortical reorganization with frontal and occipital thickening (Sølsnes et al., 2015), diffusion measures appear to have almost normalized compared to the older cohort. 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.

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 DTI 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 special education in 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. The smaller hippocampal volumes reported here were also seen in our cohort of VLBW young adults (Aanes et al., 2015). 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 this 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 special education 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 DTI 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 DTI 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).

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 42% the size of the sample used for subcortical volume analysis. Subjects in the TRACULA sample were on average 6 to 12 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 the VLBW group still had significantly lower IQ scores after correction for socioeconomic status.

Conclusion

This study aimed to relate abnormal white matter diffusion measures in tracts connecting brain regions with cortical deviations and subcortical structures with reduced volumes in children born preterm with VLBW. Consistent with previous reports, we found significantly reduced volumes of gray and white matter structures including thalamus, globus pallidus, hippocampus, cerebral white matter, and corpus callosum, along with enlarged ventricles in the VLBW group. By contrast, group differences in DTI measures were minor and limited to higher AD in left SLFP and SLFT in VLBW subjects. This VLBW cohort born in the 2000s showed similar subcortical volume deviations to our VLBW cohort born in the late 1980s, while white matter connectivity seemed to have almost normalized, potentially reflecting the influence of more advanced perinatal treatment.

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Supplemental Material

Table S1. Difference between VLBW group and controls in pointwise tractography analysis.

Anterior part of the tract	Middle part of the tract	Posterior part of the tract	Dorsal part of the tract
Left CCG ↓ RD, ↑ FA	Bilateral SLFT ↑ AD, ↑ MD Forceps minor ↑ RD, ↑ MD	Left SLFP* ↑ AD	Left CST ↑ AD

Table shows pointwise analysis used to identify tract segments with significant group differences ($p < 0.05$) in DTI values where VLBW group displays higher ↑ or lower ↓ values than controls. *Significant differences only along 1.2 cm contiguous tract length.

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