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# Vision and brain in adolescents with low birth weight

Thesis for the degree of Philosophiae Doctor

Trondheim, October 2009

Norwegian University of Science and Technology
Faculty of Medicine
Department of Laboratory Medicine, Children's
and Women's Health

NTNU
Norwegian University of
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# Syn og hjerne hos ungdommer med lav fødselsvekt.

Forhold i svangerskapet og rundt fødselen har betydning for hvor godt vi fungerer på en rekke områder senere i livet. Dette gjelder ikke minst synet. For å kartlegge hvordan det går med synet til barn som fødes meget for tidlig (de som veier under 1500 g ved fødsel) og barn som fødes til termin med lavere fødselsvekt enn det forventede på grunn av dårlig ernæring i svangerskapet, har vi undersøkt synet til 14-åringer i disse to gruppene. Ungdommer i samme alder født til termin med normal fødselsvekt utgjorde kontrollgruppe.

Deltagerne i studien ble undersøkt av øyelege og fysioterapeut, og hjernens anatomi ble undersøkt med MR.

Studien viser at det synsmessig kan gjøre stor forskjell mellom å veie mindre enn 1500 g ved fødselen og å være født til termin med normal fødselsvekt. I gruppen med for tidlig fødte ungdommer hadde nesten hver tredje dårligere syn enn det normale for alderen sammenlignet med bare 4 % i kontrollgruppen. Blant de premature var det flere som hadde nedsatt evne til å skjelne små forskjeller i kontrast, og det var også vanligere med skjeling og dårlig samsyn.

Det var ikke større forekomst av nærsynthet eller langsynthet blant de premature. Derimot var det noe vanligere å trenge nye briller i prematurgruppen (53 %) enn i kontrollgruppen (34 %).

Et oppløftende funn var at ingen av ungdommene var blind eller synshemmet etter Verdens Helseorganisasjons kriterier.

Tenåringer i gruppen født til termin med lavere fødselsvekt enn det normale hadde ikke øket risiko for synsproblemer.

Både de premature og ungdommene født til termin med lav fødselsvekt hadde økt forekomst av motoriske vansker. Da vi sammenlignet syn og motoriske evner, fant vi en sammenheng i prematurgruppen, men ikke i gruppen født til termin med lav fødselsvekt.

Mange av disse problemene med syn og motorikk kan bero på skader i hjernen på grunn av den for tidlige fødselen. Vi sammenlignet hjernens anatomi med synsdata og fant at det i prematurgruppen var en sammenheng mellom syn og anatomisk struktur av den midtre hjernebjelken ("corpus callosum") som knyter sammen de to hjernehalvdelene. Hjernebjelken er et område som er spesielt utsatt for skade hos premature, men det har tidligere ikke vært vist så tydelig at skade i dette området har betydning for synet. Dessuten fant vi en sammenheng mellom skade på andre deler av hjernens synsbaner og syn i prematurgruppen.

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# Contents

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  - Ann-Mari Brubakk, who made this work possible by inviting me to participate in this study. She has throughout given warm and enthusiastic support in the planning and carrying out of this study, and in the completion of this thesis.
  - Torstein Vik, who has taught me how to write articles, always giving supervision top priority.

- Jon Skranes who has provided valuable support and advice throughout the study.
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# List of papers

This thesis is based on the following papers:

Paper I
**Visual acuity, contrast sensitivity, peripheral vision and refraction in low birth weight teenagers**
Susanne Lindqvist, Torstein Vik, Marit S. Indredavik, Ann-Mari Brubakk
*Acta Ophthalmologica Scandinavica* 2007
volume 85, issue 2, page 157-164

Paper II
**Eye movements and binocular function in low birth weight teenagers**
Susanne Lindqvist, Torstein Vik, Marit S. Indredavik, Jon Skranes, Ann-Mari Brubakk
*Acta Ophthalmologica Scandinavica* 2008
volume 86, issue 3, page 265-274

Paper III
**Do visual impairments affect risk of motor problems in preterm and term low birth weight adolescents?**
Kari Anne Evensen, Susanne Lindqvist, Marit S. Indredavik, Jon Skranes, Ann-Mari Brubakk, Torstein Vik
*European Journal of Paediatric Neurology* 2009
volume 13, issue 1, page 47-56

Paper IV
**Corpus callosum—connecting visual acuity and white matter microstructure in prematurity**
Susanne Lindqvist, Torgil Vangberg, Olav Haraldseth, Torstein Vik, Ann-Mari Brubakk, Jon Skranes
Submitted Vision Research

# Abbreviations

| | |
|---|---|
| BW | birth weight |
| CI | confidence interval |
| CVI | cerebral visual impairment |
| D | dioptres |
| DTI | diffusion tensor imaging |
| ELBW | extremely low birth weight (<1000g) |
| GA | gestational age |
| GW | gestational week |
| IUGR | intrauterine growth restriction |
| MRI | magnetic resonance imaging |
| NTNU | Norwegian university of science and technology |
| OR | odds ratio |
| PD | prism dioptres |
| ROP | retinopathy of prematurity |
| SD | standard deviation |
| SGA | small for gestational age |
| VA | visual acuity |
| VLBW | very low birth weight (<1500g) |
| WHO | World Health Organisation |

# Summary

Premature birth and pregnancy to term, but with intrauterine growth restriction (often manifesting as birth small for gestational age, SGA, at term), both represent suboptimal environments for the developing infant brain and eyes. Very low birth weight (VLBW, <1500g) increases the risk for impaired visual ability, but there are few studies on the effects in an adolescent population. There is need for broad interdisciplinary investigation of these children. Also, by using advanced magnetic resonance imaging (MRI) technology, relationships between visual dysfunctions and cerebral microstructure might be revealed. Finally, there are very few reports on the visual consequences of birth at term small for gestational age.

The aims of this study, which is part of large interdisciplinary follow up study also including cognitive, psychiatric, paediatric and motor evaluation, as well as cerebral MRI, was threefold:

to examine differences in visual functions between adolescents with VLBW, or SGA at term, compared to an age matched control group

to explore how detected impairments affect other functions (e.g. motor ability)

to search for a cerebral correlate to the impaired visual functions, by using magnetic resonance diffusion tensor imaging (DTI).

The study shows that the VLBW group was more likely to have poor visual acuity, reduced contrast sensitivity, poor convergence, strabismus, nystagmus, anisometropia, a need for new glasses and to have started with glasses earlier than the control group. The SGA group had a slight increase in hypermetropia, but did otherwise not differ from the control group. However, none of the participants were blind or had visual acuity<0.3 in the best eye, and no sequelae of severe retinopathy of prematurity were seen. In the absence of obvious ocular pathology, it is likely that many of these problems were of cerebral origin.

Both the SGA and the VLBW group had increased risk for motor problems, but these were affected by visual ability only in the VLBW group. Risk for motor problems were reduced by 25 % by controlling for poor visual acuity, but group still remained a significant factor. Visual impairments may cause motor problems, but it is also possible that cerebral damage may be the cause of simultaneous visual and motor problems.

Finally, using DTI, a positive correlation between visual acuity and the microstructure of white matter (reflecting axonal “healthiness”) was demonstrated in the splenium part of the corpus callosum. This part of the brain is responsible for the transhemispherical relay of visual data, and is particularly prone

to injury in prematurity. However, it has not been regarded as an important factor for visual acuity in prematurity before.

Premature infants are greatly at risk for perinatal cerebral injury, due to an extreme vulnerability of several cerebral systems at a crucial time, when development is particularly fast and comprehensive. This is combined with very poor ability to maintain homeostasis, causing them to suffer infections, hypoxia, unstable blood pressure, undernourishment, among others, all pathological conditions which affect the developing brain negatively.

This study confirms that adolescents with VLBW have an increased risk of visual problems. Cerebral injury probably plays a major part in causing them.

# Chapter 1. Introduction

## Background for study

Foetal development is a highly organised, complex process. Interference at any time either at the maternal, foetal or placental level can lead to defects and later impairment of function. Although birth dramatically changes the environment of the foetus, it does not change the essential order and nature of the processes involved in growth of the organism.

*Preterm birth* means that these processes must happen in an environment the infant is less well adapted to than the intrauterine (Kostovic and Jovanov-Milosevic, 2006,Krägeloh-Mann, 2004). In addition, preterm birth is often preceded by processes which have produced an unfavourable intrauterine environment even before birth (McElrath et al., 2008).

*Intrauterine growth restriction* is a condition in which the foetus fails to achieve its inherent growth potential, often due an adverse intrauterine environment

Thus the two conditions focused upon in this thesis, preterm birth and intrauterine growth restriction (with birth at term), both represent suboptimal environments for the developing infant's brain and visual system. This is reflected in an increased visual morbidity in both condi-tions, which has been particularly well documented in prematurity. Among visually impaired and blind children born 1972 -89 in Finland, 23 % were born preterm. In about half (46 %) of these, impairment was caused by ROP; optic atrophy and cerebral amblyopia (Saunders et al., 2002) made up the rest (40 %). Premature children are more likely than full term children to experience reduced visual acuity(Fledelius, 1981, Larsson et al., 2005, O'Connor et al., 2002a, Hellgren et al., 2007), a range of visual perceptive deficits (Isaacs et al., 2003, Jacobson et al., 1998a, O'Connor et al., 2004), nystagmus, impaired smooth pursuit, poor saccades, strabismus, reduced contrast sensitivity (O'Connor et al., 2002b, Powls et al., 1997, Jacobson et al., 1998b), visual field defects (Larsson et al., 2004, Hellgren et al., 2008) errors of refraction: mainly myopia (Darlow et al., 1997,Larsson et al., 2003, McGinnity and Bryars, 1992, Ricci, 1999, Saunders et al., 2002), but also hypermetropia, astigmatism and anisometropia (Jacobson et al., 1998b, Larsson et al., 2003, Saunders et al., 2002). The more premature the child is, the higher the risk (Holmström et al., 1999). Among children born at the current threshold of viability, with GA<25 weeks, severe ROP and cerebral lesions are very common, causing visual impairment or blindness (visual acuity, VA <0.3) in 33 % of the boys and 9 % of the girls (Jacobson et al., 2009).

The ophthalmological consequences of being born *at term* with intrauterine growth restriction have been less studied, and most studies also include preterm SGAs in the study group. Intrauterine growth restriction (IUGR), a common cause of SGA, has been shown to impair brain growth (Toft et al., 1995) and affect visual evoked potentials in infancy (Thordstein et al., 2004). Subtle visual field defects, reduced number of retinal vascular branching points and reduced axonal area in the optic nerve in adults born small for gestational age (SGA) have also been reported (Martin et al., 2004,Hellström, 2004,Ley et al., 2004). Chronic placental insufficiency with foetal growth restriction in sheep has been reported to cause long lasting effects on retinal thickness, photoreceptor outer segments and the dopaminergic amacrine cells in the retina (Loeliger et al., 2005). In a survey of all Swedish children with visual impairment born at term, Tornqvist and Källén (Tornqvist and Källén, 2004) found that being born small for gestational age was a risk factor for visual impairment.

In 1986-88 a prospective Norwegian-Swedish multicenter study on the causes and consequences of being born small for gestational age, was initiated in Trondheim, Bergen and Uppsala (Bakketeig et al., 1993). At the same time, in 1988, a prospective study on very low birth weight children was started (Skranes et al., 1992) in Trondheim. This study was later extended to include children born with VLBW in 1986 and 1987. The Trondheim SGA population and the VLBW population have been included in several follow up-studies, and the material for the present thesis was collected during the follow-up at age 14 of both the SGA and the VLBW subjects. Subjects in the study at age 14 were examined by paediatrician, child psychiatrist, psychologist, physiotherapist, MRI (including diffusion tensor) and ophthalmologist.

In addition to being one more piece in the puzzle contributing to our understanding of visual development in adolescents with very low birth weight, the ophthalmological part of this study has the potential to generate new knowledge in at least three areas: It is the first study to examine a wide array of visual functions in a population born SGA at term. Regarding the VLBW population, the comprehensive design enables us to study the interrelationship between visual function and psychiatric, cognitive, motor and general development, in addition to MRI and diffusion tensor findings. Furthermore, no study has previously presented data correlating visual acuity and diffusion tensor data in either a control or VLBW population.

This thesis consists of four separate papers. To fulfil the requirements for a thesis, a text which ”summarizes the work and puts it into an overall perspective”, showing that the “separate papers form a totality”, is required (Kunnskapsdepartementet, 2005). The following text is an attempt to fulfil this requirement. Regarding *overall perspective*, birth weight (particularly low and very low) as a medical concept will be presented, as well as the theoreti-

cal background for why it is reasonable to study visual functions in relation to subnormal birth weight, and a short overview on the global situation regarding visual impairment and blindness in children to give a perspective on the role of birth weight related visual dysfunction. Regarding *summarizing and connecting the separate papers* the aims and content of the papers will be summarised, and the connection between them described. The validity of the study will be discussed, as this provides the foundation for the reliability of the thesis. The results of all the papers will be briefly discussed. Finally, some thoughts on future research will end this part of the thesis.

Topics that have been presented in some depth in the separate papers will only be briefly summarized in this synthesis.

Figure 1. Rock carving portraying a pregnant woman.

Made some time between 3300-1800 B.C. From the rock carving field of Hjemmeluft, Alta, Norway. Source: Verdensarvsenter for bergkunst (The world heritage centre for rock art), Alta Museum. Photographer: Kari Tansem. The picture is printed with admission from the museum.

# Chapter 2. Birth weight

This chapter describes the emergence of the term "low birth weight" as a tool in public health, how the term is used today, the birth weight limits that are used in the current thesis, and provides data from the Medical Birth Registry of Norway on proportion and number of live births with birth weight < 1500 g, as well as perinatal mortality in this group.

## Historical background for birth weight as predictor of health

The wish to predict good health and a safe future for a newborn baby is probably as old as humanity, and size is one of the few facts known about the baby at birth. So, perhaps, the size of the baby has been noticed and discussed as a predictor of its ability to survive and thrive since prehistoric times. We can not know our prehistoric ancestors' views on birth weight, but at least in Shakespeare's time (admittedly a bit of a leap in time) a connection between preterm birth and later morbidity was made: in Shakespeare's play with the same name, Richard III refers to the negative consequences of his own preterm birth:

> *"I, that am curtail'd of this faire proportion,*
> *Cheated of feature by dissembling Nature,*
> *Deform'd, un-finish'd, sent before my time*
> *Into this breathing world, scarce half made up,*
> *And that so lamely and unfashionable,*
> *That dogs bark at me, as I halt by them."*

Thus, to say that weighing infants at birth was a routine developed in the maternal hospitals emerging in Europe in the 19th century is not quite accurate, but it is at least where some of the earliest, systematically kept records of birth weight can be found (Steckel, 1996). Possibly as a consequence of the existence of such records, low birth weight was identified as a public health problem in the 1920s, and in the 1940s 2500 g was adopted as the "distinguishing limit between prematures and full-term infants" (Ylppö, 1948). A birth weight of < 2500 g remained the WHO definition of prematurity until 1961 (World Health Organization, 2005).

## Birth weight as a public health tool today

Although no longer an official synonym for prematurity, low birth weight (i.e. <2500 g) is still widely used as a predictor of newborn health and chances of survival. Particularly in developing economies, where it may be the only available statistic regarding birth and pregnancy, the low birth weight rate is also used as an indicator of the level of maternal malnutrition, ill health and poor health care (World Health Organization, 2009).

However, low birth weight has disadvantages as a tool in public health (Godfrey, 2001, Baumgartner, 1962). Low birth weight in itself is probably not harmful, at least not at a population level (Wilcox, 2001), whereas *what causes it* often is, e.g. prematurity or intrauterine growth restriction. A focus on low birth weight *per se* may obscure the real problems. WHO is currently introducing a shift in emphasis from low birth weight to preterm birth and intrauterine growth restriction (WHO Technical consultation towards the development of a strategy for promoting optimal fetal development, 2003).

Considering that the foetus normally gains approximately 500 - 700 g between gestational age (GA) week 37 and 42, there is an obvious need to regard birth weight in relation to GA when identifying possibly growth restricted infants. In an American population a 2500 g limit would include the lightest 10% of the children born at GA week 37, however only 1% at week 39. At week 42 a birth weight of 2500 g would be 250 g below even the 1st percentile (Peleg et al., 1998). Thus birth weight alone is not a good indicator of whether a baby is small for gestational age.

Neither is 2500 g a very good limit to separate preterm from term born children. An upper weight limit of 2500 g includes approximately 3% of all term born children (most of these born at GA week 37 and 38), while it excludes the heaviest 10% of all children born week 32 and as many as 50% of those born at week 35.

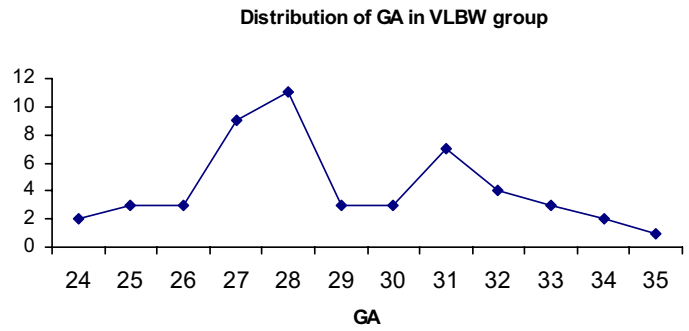
## Birth weight limits used in the current thesis

**Very low birth weight, VLBW**

WHO divides low birth weight, below 2500 g, into very low birth weight (VLBW), below 1500 g, and extremely low birth weight (ELBW), below 1000 g (World Health Organization, 2009). If "low birth weight" is not a very useful criteria to identify preterm children, as discussed above, how about the term used in this thesis, "very low birth weight"? In our study, this limit secured inclusion of only preterm children (see Figure 2). Birth weight is a

more accurate criterion than gestational age. Also, the 1500 g limit has been used in many studies, which facilitates comparisons.

Figure 2. Distribution of gestational ages in the VLBW group in our study




By using birth weight <1500 g (very low birth weight) as a single inclusion criteria, among the heaviest children in the group there will necessarily be many with relatively high gestational age, who are small for gestational age. This bias may have consequences in any analysis of correlations between birth weight or gestational age, and outcomes in the group. If an outcome is very heavily influenced by IUGR, but not so much by low gestational age, an analysis might (misleadingly) show a positive correlation between higher birth weight and the outcome. Another aspect of the 1500 g limit is that a large part of the preterm population will not be included. This may be an advantage, e.g. if we particularly want to study the smallest preterms, where (presumably) there is more pathology to be found, and we may be able to find statistically significant group effects with smaller samples. Since the 1500 g and 1000 g limits are so commonly used in research, we may however focus less than we should on the risks of being born "late preterm", between GA 34-37 (Engle et al., 2007) although these represent over 70 % of all preterm births (Davidoff et al., 2006). The risk of adverse outcomes decreases continuously towards GA 40 weeks (Moster et al., 2008,Engle et al., 2007) (Moster 586; Engle ref 585), with no sharp demarcation at one particular age. Children weighing 1500-2500 g at birth represent approximately 5 -7 % of the neonatal population, but account for 18-37 % of all children with cerebral palsy, and 7-12 % of children with mental retardation (Amiel-Tison et al., 2002).

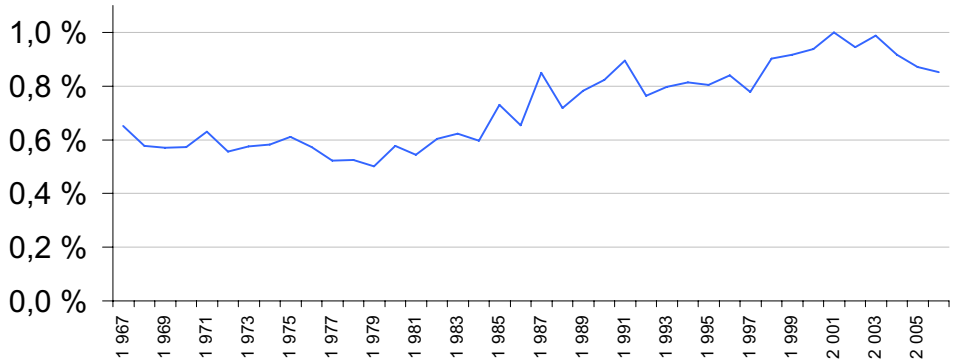
**Small for gestational age (SGA) and intrauterine growth restriction (IUGR)**

In the current thesis I have used the term IUGR to denominate the pathological situation where a restriction of growth has occurred and the child is smaller than its potential, a practice advocated by others (Mandruzzato et al., 2008). Unfortunately, foetuses do not come with information of what their exact potential for growth is, so the true extent of growth restriction is always uncertain. SGA is therefore often used as a proxy for IUGR. In this study we included children with birth weight below the 10th percentile for gestational age, a commonly used definition (Mandruzzato et al., 2008, Brodsky and Christou, 2004).

## Very low birth weight – demographics Norway

The proportion of children in Norway live born with VLBW has been rising from 0,65 % of all live births in 1967 to 0,85 % in 2006, as seen in Figure 3.

Figure 3. Live births with BW <1500g and GA> 22 weeks as a proportion of all live births in Norway.

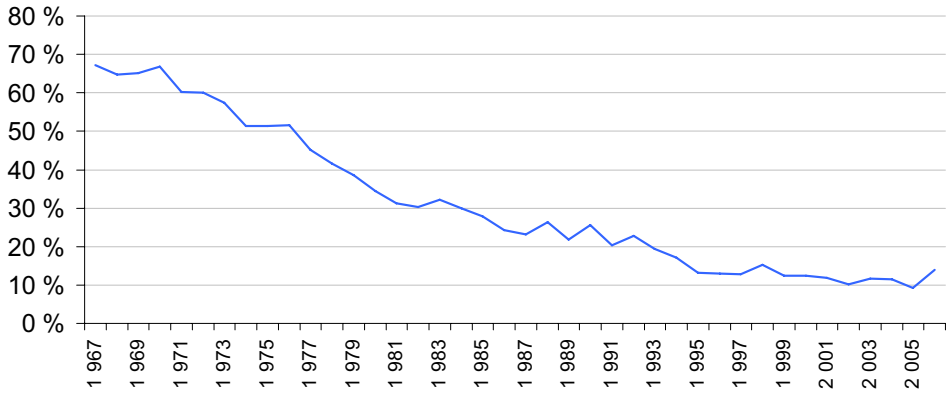



Source: Medical Birth Registry of Norway, 2009.

Neonatal mortality among preterm children has declined in this period, as shown in Figure 4. Thus, the total numbers of children surviving 28 days with BW <1500 g is increasing (Figure 5), from 136 surviving infants in 1967 to 430 in 2006 (source: Medical Birth Registry of Norway).

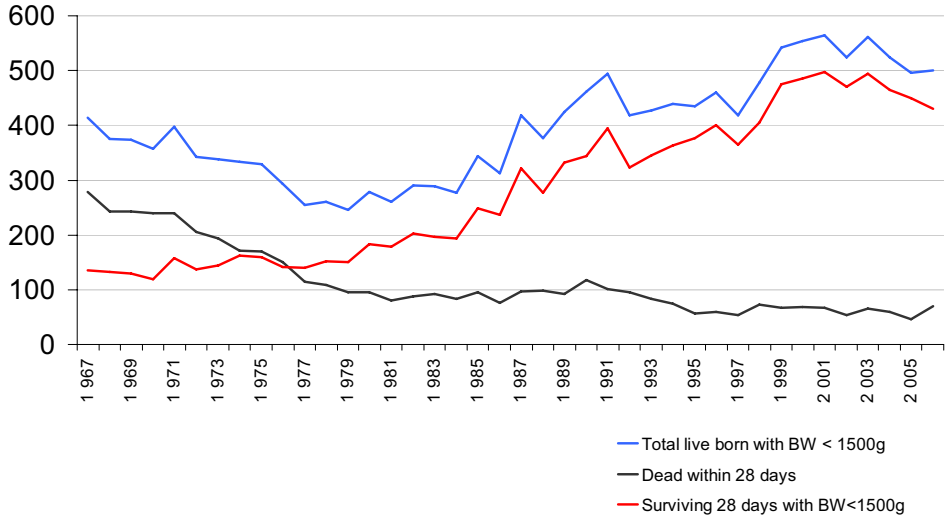
There is an increase in the proportion born with VLBW starting around 1984, which is the year the first in vitro fertilized baby was born in Norway (see Figure 3). Twin pregnancies have an increased risk of preterm birth, and their rate have doubled in Norway since 1988. Pregnancies after in vitro fertilization are responsible for many of the twin and triplet pregnancies since 1988, but there has also been a 50 % increase in non-in vitro fertilized twin gestations.

Figure 4. Neonatal mortality for live born infants with BW <1500g and GA>22 weeks in Norway 1967-2006.




Source: Medical Birth Registry of Norway, 2009.

Figure 5. Numbers of live born infants born in Norway 1967-2006 with BW <1500g and GA >22 weeks.




Source: Medical Birth Registry of Norway, 2009.

This increase has probably been caused by the rise in age and weight of pregnant women in this period (Tandberg, 2008).
There is currently a preference for single embryo transfer at in vitro fertilization, and twin rates after in vitro fertilization have fallen from 23 % in 1994 to 5 % in 2006 (Tanbo, 2008). This may be part of the reason why the rise in rate of VLBW births seems to stop and even decline in 2001-2006 (Figure 3).

# Chapter 3. Visual impairment and blindness in children – a global perspective

Depending on the level of visual acuity, WHO has categorised visual impairment and blindness into blindness (visual acuity <0.05 in Snellen decimals), severe impairment (visual acuity 0.1-0.05) and visual impairment (visual acuity <0.3 and >0.1)

(A note on terminology: In this thesis I use the WHO definition of blindness and severe visual impairment. However, in some contexts there is need for a term generally indicating a reduction of a visual function. I have therefore also used the term " a visual impairment" in a wider sense than the WHO definition. This practice seems quite uncontroversial, e.g. the term "cerebral visual impairment" does not imply a particular level of visual acuity (Eken et al., 1995).

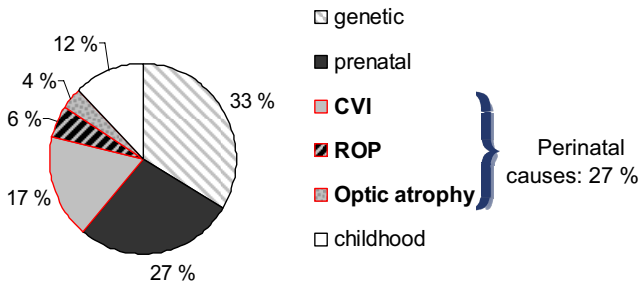
Using WHO's definition, there were 1.4 million blind children worldwide in 2000 (World Health Organization and the International agency for the prevention of blindness., 2008) with an estimate of up to 500,000 new cases each year. Many of these children die shortly after becoming blind. More than 90 % live in middle-income and low-income countries. The most important treatable causes of childhood blindness in a global perspective are cataracts, responsible for 5-20 % of cases of childhood blindness, and corneal scarring due to vitamin A deficiency and/or measles (see Figure 7). In middle income countries, however, retinopathy of prematurity is an increasing cause of blindness and severe visual impairment, in some countries responsible for up to 60 %. In low and middle income regions ROP is currently seen in infants with higher birth weights than in high income countries (Gilbert et al., 2005, Gilbert and Muhit, 2008).

However, in high income economies, improved treatment has reduced the impact of ROP, and cerebral visual impairment (CVI) is now the dominating cause of blindness in childhood (Durnian et al., 2009, Gilbert and Foster, 2001a). In Ireland in 2004, 26 % of blindness among children under 16 had a perinatal (including both term and preterm) cause, with CVI at 17 % being the largest contributor(see Figure 6) (Khan et al., 2007).

As can be seen in Figure 8, perinatal and intrauterine (including prematurity related) causes of blindness contribute to a substantial part of childhood blindness in high income countries but not in low income countries (Gilbert and Foster, 2001b). Neonatal intensive care units are not available to the majority in low income countries. Most children born very preterm in a low income country do not survive the perinatal period.

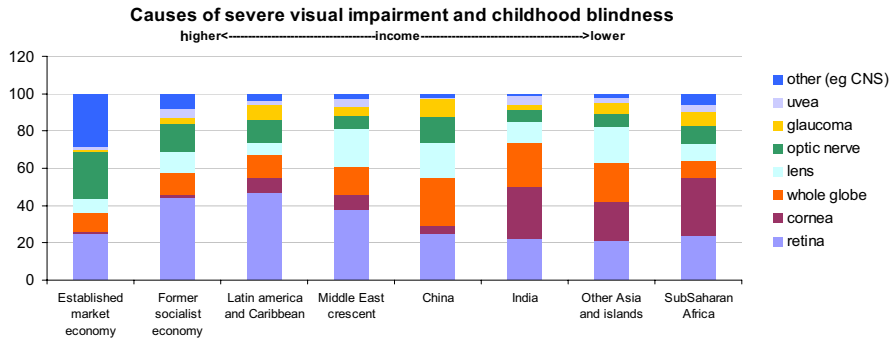
The prevalence of functional low vision (best corrected visual acuity<0.3) among children world wide is believed to be 3 million, approximately twice as many as the number of blind children (Gilbert and Muhit, 2008).

Figure 6. Causes (based on time of injury) of blindness in Ireland in children under 16.



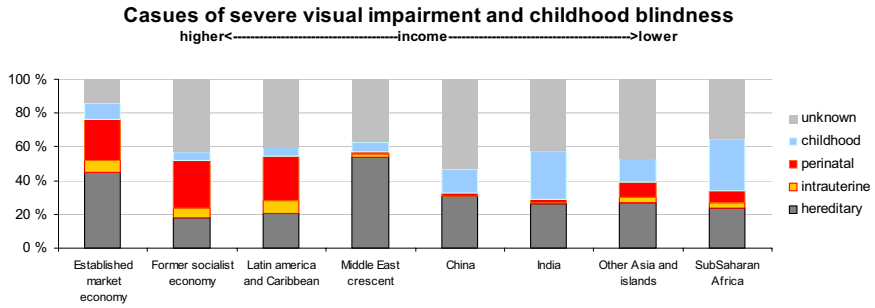

Source: Khan et al 2004.

Figure 7. Anatomical localisations to causes of severe childhood visual impairment and blindness. High income countries to the left, middle income countries in the middle and low income countries to the right.




Source: Gilbert and Foster 2001

Figure 8. Causes of severe childhood visual impairment and blindness based on when they occur. High income countries to the left, middle income countries in the middle and low income countries to the right.




Source: Gilbert and Foster 2001

# Chapter 4. Etiology

This chapter deals with etiology on several levels: both what causes ( or at least some known riskfactors for) VLBW and SGA, as well as data on the etiology of perinatal morbidity especially in the VLBW group. Finally the different pathological pathways in these conditions that may potentially lead to visual problems, with special emphasis on cerebral injury, will be presented.

## Risk factors for VLBW and SGA at term

**VLBW.** Few definitive causes of preterm birth have been determined, but several risk factors are known. These include infection, inflammation, abnormal implantation and placentation, and gene–environment interactions. In addition, socio-demographic status and lifestyle factors (such as smoking, alcohol and drug use) have an impact. As discussed above (page 15), multiple gestation is a risk factor which has increased in importance over the last decades due to the success of fertility treatments. In some countries elective inductions or caesarean deliveries before 37 weeks of gestation is an unnecessary cause of preterm births (Ashton et al., 2009). A paradox of improved health care in pregnancy is that it may actually increase the numbers of preterm births, as more stillbirths are prevented by preterm delivery (Joseph et al., 1998).

**SGA.** The reason for being SGA at term may simply be that the child is constitutionally small. However, it may also be caused by pathological conditions in the foetus, placenta, mother or the environment. Among identified risk factors are foetal chromosomal anomalies, preeclampsia, infections, twin-to-twin transfusion syndrome, maternal anaemia or high haemoglobin values, malnutrition, maternal systemic disease (e.g. diabetes, systemic lupus erythematosus, heart failure, Mb. Crohn), moderate to heavy physical effort at work, smoking, use of drugs (legal and illegal) and alcohol, previous pregnancy with IUGR, placental and umbilical anomalies and short interpregnancy interval (Haram and Gjelland, 2007, Rosenberg, 2008).

IUGR may necessitate preterm delivery, and many of the risk factors for IUGR are also risk factors for premature birth. Thus it is not surprising that preterm infants are growth retarded in a high proportion of cases. It has been estimated that 30-50 % of extremely preterm neonates are SGA (Rosenberg, 2008).

**Perinatal morbidity**
Early apparent complications of premature birth are legio, including respiratory distress syndrome (affecting approximately 50 % in an VLBW population) and chronic lung disease (23 %), poor in-hospital growth, i.e. weighing less than 10$^{th}$ centile expected at 36 weeks gestational age (97 %), intracranial hemorrhage (35 %), necrotizing enterocolitis (7 %), severe intracranial hemorrhage (11 %) (Lemons et al., 2001) as well as ROP, apnea attacks, sepsis, hypothyroxemia and hyperbilirubinemia.

In the neonatal period term SGA infants are at increased risk of perinatal asphyxia, meconium aspiration syndrome and pulmonary complications, as well as hypoglycaemia, hypothermia, polycythemia (Rosenberg, 2008), but most do not need intensive care (Vik et al., 1997).

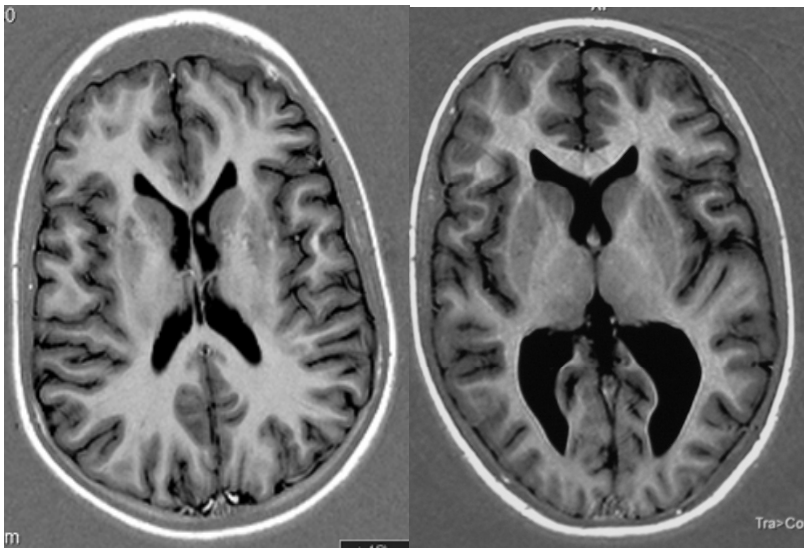
## Possible pathogenetic pathways for visual problems in prematurity

There are at least three possible pathogenetic mechanisms which may lead to visual dysfunction in prematurity: cerebral damage, retinopathy of prematurity and errors of refraction.

**Brain damage in prematurity. Cerebral visual impairment.**
Preterm born children are at high risk of having experienced perinatal inflammation and ischemia (Dammann and Leviton, 2006, Barrett et al., 2007) at a time when cerebrovascular and physiological properties of the premature brain leaves it particularly vulnerable to ischemia and inflammation (Khwaja and Volpe, 2008). Aggravating this vulnerability is the developmental situation- a flood of vital neurobiological processes are set to appear at this time in the rapidly developing foetal/infant brain (Volpe, 2009), and any disturbance of homeostasis has a high likelihood of obstructing or harming several such processes. Although white matter injury is most common, cerebral preterm injury may be described as “encephalopathy of prematurity” since the whole brain, including the thalamus, basal ganglia, cerebral cortex and cerebellum, as well as white matter, may be affected (Volpe, 2009, Skranes et al., 2005, Martinussen et al., 2005). Injury to preoligodendrocytes is central in the pathogenesis of this encephalopathy (Volpe, 2009) . Preoligodendrocytes are highly susceptible to exitotoxicity and free radical attack caused by ischemia and inflammation (Dammann and O'Shea, 2008, Volpe, 2009) and primary injury of preoligodendrocytes may cause axonal injury (and vice versa) . However, other celltypes and processes are also prone to injury at this time, e.g. the subplate neurons (McQuillen et al., 2003) and the migration process where neurons migrate from the germina-

tive zones to their final destinations (Leviton and Gressens, 2007, Judas et al., 2005). In addition, any acute neuronal damage sets the stage for a slower developing chronic phase of programmed cell loss (apoptosis), primarily in the periventricular zone and cortex. This process may be particularly intense in premature infants due to low levels of insulin-like growth factor (Barrett et al., 2007).

Figure 9. Axial magnetic resonance images of one control (left) and one VLBW (right) subject in the study at 6 years of age.



Enlarged occipital horns, atrophy of peritrigonal white matter and periventricular white matter area hyperintensity are typical MRI findings in periventricular leukomalacia.

White matter damage may be visualised with MRI in 50 % of unselected VLBW populations (Skranes et al., 1997) presenting as cystic periventricular leukomalacia (PVL), where macroscopic areas of necrosis brings about cyst formation, and noncystic PVL, where necrotic areas are microscopic, but with MR findings of dilated ventricles and periventricular white matter reduction due to white matter loss, and focal gliosis (Figure 9). Cerebral pathology visualised with MRI has been shown to correlate to visual dysfunction, but even VLBW populations with normal conventional MRI have increased risk of vis-

ual impairment (Hellgren et al., 2007). Diffuse white matter injury without necrosis but with astrogliosis (Khwaja and Volpe, 2008, Volpe, 2009) and diffuse widespread damage noticeable only with diffusion tensor imaging (Counsell et al., 2006) has been described, and such damage may be the cause of visual impairment in preterms with normal MRI. Given the frequency and extent of cerebral injury in VLBW subjects, it is not surprising that a varied combination of problems in areas of perception, attention, cognition, behaviour and motor function are seen in up to 50 % of this population (Indredavik et al., 2004, Kulseng et al., 2006, Evensen et al., 2004, Hård et al., 2000).

Cerebral visual impairment is a clinical condition or functional deficit due to damage of the posterior visual pathways and/or visual cortex (Jacobson et al., 2004). Dysfunction in cerebral visual impairment varies both in severity and combinations of manifestations, neither of which can be exactly predicted by cerebral imaging (Pike et al., 1994). Periventricular leukomalacia, brain malformations, hypoxic-ischemic encephalopathy at term, hydrocephalus, meningitis and encephalitis and traumatic head injury may all cause cerebral visual impairment (Dutton and Jacobson, 2001). In preterm children the cause is most often periventricular leukomalacia (Jacobson et al., 1998a). A patient with cerebral visual impairment can present with (almost any combination of) subnormal visual acuity, crowding, restricted visual fields (most often the inferior fields), cognitive visual dysfunction (in preterms particularly in the form of visuospatial problems, defects in simultaneous perception, depth perception, face recognition and movement perception) as well as ocular motor problems such as strabismus, nystagmus and deficiencies in fixation, saccades, and smooth pursuit (Jacobson and Dutton, 2000). The impairment in function is typically more severe than what would be expected from visual acuity, motility, stereopsis and visual fields, and diagnosing the cognitive visual dysfunction is important in order to help these children (Dutton and Jacobson, 2001). Cerebral visual impairment is often associated with other developmental disorders, such as uneven cognitive performance, attention problems, autistic-like behaviour, cerebral palsy and learning difficulties (Jacobson et al., 2004), further complicating the pattern of (dys-)function in the patient. The variable pattern of strong and weak sides in these children necessitate a highly individual approach both to diagnostics and habilitation.

**Retinopathy of prematurity (ROP)**

Retinopathy of prematurity is responsible for approximately 3- 10 % of all new cases of childhood blindness/severe visual impairment in high income countries (Khan et al., 2007, Rahi and Cable, 2003, Rahi and Cable, 2003, Wheatley et al., 2002), but up to 60 % in middle income countries (Gilbert

and Foster, 2001b). The disorder almost exclusively affects preterm children. It is a vasoproliferative condition where the vessels of the immature retina develop aberrantly. The disease is divided into five stages, with mild vascular pathology at the transition between the vascularised central retina and the immature, avascular peripheral retina at stage 1, and total retinal detachment at stage 5. The disease is caused by interaction of several factors, where the immaturity of the retina at birth is one of the most important (Holmström et al., 1998) along with postnatal relative hyperoxia, followed by later retinal hypoxia, influencing growth factors like insulin-like growth factor I and vascular endothelial growth factor (Hellström et al., 2003,Fleck and McIntosh, 2008). Most ROP regresses spontaneously, but approximately 10 % may progress to partial (stage 4) or complete (stage 5) retinal detachment (Repka, 2002). At stage 5 reattachment of the macula can be achieved surgically in some cases, but even so, only 2 % will achieve visual acuity > 0.1, and 26 % end up with no light perception (Cusick et al., 2006) . Cryo- or laser ablation of peripheral retina prevents progress to stages 4 and 5 (Palmer, 1990) and screening programs aim to detect ROP at a stage where treatment is both necessary and effective. Thanks to screening, efficient prophylactic treatment and improved neonatal care, ROP in high income countries is less often a blinding condition now than 30 years ago (Fledelius and Dahl, 2000).

Visual outcome of grade 5 ROP is dismal. The outcome post laser (or cryo) treatment is better, but visual acuity of 0.1 or less is still reported in 45 (Cryotherapy for retinopathy of orematurity cooperative group., 2005) to 14 % (Good and early treatment for retinopathy of prematurity cooperative group, 2004) of eyes in treated groups. The influence of mild (grade 1,2 and non progressing grade 3) ROP on visual acuity is uncertain, but there is evidence that even mild, resolved ROP may have lasting physiological and structural effects on the retina (Fulton and Hansen, 1996, Hammer et al., 2008).

The current study, however, was not set up to research outcome of ROP in the VLBW group. The results of the multicentre study showing a protective effect of cryotreatment were published in 1990 (Cryotherapy for retinopathy of prematurity cooperative group, 1990), after our children were born. Systematic ROP screening data not was available to an extent that allowed analysis. So although we have no indication of any ROP grade 4 or 5 in our subjects (which presumably would have been detected during the fundus examination at age 14), we lack information on regressed ROP in the group.

**Errors of refraction**

Prematurity has been linked to an increase of refractive errors, mainly myopia (Fledelius, 1996b, Darlow et al., 1997, Larsson et al., 2003, Holmström et al., 1998, Saunders et al., 2002), but also hypermetropia (Jacobson et al., 1998b) astigmatism (Larsson et al., 2003, Hellgren et al., 2007) and aniso-

metropia (Larsson et al., 2003, Saunders et al., 2002). Although ROP, and particularly cryo-treatment for it, has been shown to be a riskfactor for myopia (Larsson et al., 2003, Holmström et al., 1998, Fledelius, 1996b, Ricci, 1999), the incidence has been increased also among preterm children with no previ-ous ROP (Holmström et al., 1998). Unlike myopia, hypermetropia has not been linked to ROP (Ricci, 1999, Darlow et al., 1997). Cerebral pathology has also been shown to correlate to refractive errors, but not explain all increase of the risk (Hellgren et al., 2007). Thus the observed increased risk of refractive errors in prematurity may have an etiology (in part) independent of cerebral injury and ROP.

**Possible pathogenetic pathways for visual problems in term SGA**

As stated in the introduction, IUGR has been shown to affect brain growth (Toft et al., 1995, Kjellmer et al., 1992) and retinal thickness (Loeliger et al., 2005). Furthermore, some of the known causes of IUGR, such as use of alcohol in pregnancy, are also known to affect the eyes and visual system (Strömland, 1982). Thus, in a population with SGA adolescents, of which a substantial part must be assumed to be IUGR as well, one might expect to find an increased risk of reduced visual function and strabismus.

# Chapter 5. Aims of study

The aim of the study was to examine the long term effects of preterm birth with very low birth weight and birth at term small for gestational age on visual functions and ocular motility in adolescents. We also wanted to examine the association between visual ability and motor functions in these two groups. Thirdly, we wished to examine if subtle changes in cerebral white matter might explain any detected visual dysfunctions.

**Paper I and II:**

To examine and describe visual function in adolescents born preterm with a birth weight <1500 and adolescents born small for gestational age at term (birth weight <10$^{th}$ percentile adjusted for gestational age), and to compare these to the control group (born at term with a birth weight above the 10$^{th}$ percentile adjusted for gestational age), using an array of ophthalmological examinations readily available to the paediatric ophthalmologist in an ordinary clinical practice:

Paper I: visual acuity, contrast sensitivity, visual fields, errors of refraction and use of correction.

Paper II: latent and manifest strabismus, near point of convergence, accommodative amplitude, binocular vision/ stereopsis, nystagmus, smooth pursuit and saccades, asthenopia, split lamp evaluation.

To, via a semi-structured history, examine the occurrence of (in paper I:) prior use of correction, worries about vision, and (in paper II:) asthenopia and history of occlusion treatment for amblyopia.

**Paper III**

To examine the relationship between visual function and motor skills in the two study groups compared to a control group.

**Paper IV:**

To study cerebral correlates to impaired visual function in the VLBW group and compare these to findings in the control group using advanced magnetic resonance imaging (MRI).

# Chapter 6. Materials and methods

## Study design

This is a population-based follow-up study including three groups of adolescents; one born with VLBW , one born SGA at term, both of which have been compared to an age matched control group, but not to each other. In paper III and IV (both correlational studies) we also included VLBW participants outside the original cohort.

## Study population

**VLBW.** The subjects born with VLBW were all the children admitted to the neonatal intensive care unit (NICU) at the University Hospital in Trondheim 1986 -1988. All VLBW newborns in the counties of Nord- and Sør-Trøndelag were admitted to the Trondheim NICU. Trondheim was also referral hospital mainly for the county of Møre and Romsdal, and in this period 22 children were admitted referred from this county.

In paper I and II, which describe the ophthalmological findings in these cohorts, only the population based sample is used. In paper III and IV correlations between visual function and other variables (motor function and cerebral white matter microstructure respectively) are made, and in these papers we included the referred children as well. (However, a number of MRI-diffusion tensor imaging exams were not of good enough technical quality, and among the excluded exams were all the referred adolescents.)

**SGA and control.** The SGA and control children were born to mothers of Caucasian origin (all with one or two previous births) living in the Trondheim region. They were enrolled before 20 weeks of pregnancy in Trondheim in a multicentre study between January 1986 and March 1988 (Bakketeig et al., 1993, Vik et al., 1997). A 10 % random sample of these women was selected for follow-up during pregnancy. All the children born at term to mothers in the random sample and all the term born SGA children were included for follow–up. SGA was defined as birth weight below the 10$^{th}$ percentile for gestational age of all infants in the multicentre study. Term birth was defined as birth in gestational age week 37-42.

The present study was carried out from November 2000 to June 2003 and is based on the ophthalmological assessment, the assessment of motor development and ability and cerebral magnetic resonance diffusion tensor imaging

(DTI). Information gained during the paediatric and neuropsychological assessments some weeks before the ophthalmological assessment is also used. The VLBW group had a mean gestational age at birth of 29 weeks (range: 24-35), mean birth weight was 1170 g (550-1500). The SGA group had a mean gestational age of 39.5 weeks (37-42 weeks), and a mean birth weight of 2900 g (2390-3250g). The control group had a mean gestational age of 39.6 weeks and a mean birth weight of 3680 g (2670-4950g). The study population is further described in Table 1 (from paper I).

Table 1. Demographic characteristics of participants (paper I)

| | VLBW (n=51) | SGA (n=59) | Control (n=77) |
|---|---|---|---|
| Birth weight, g [a] | 1172 * [236] (550-1500) | 2920 * [213](2390-3250) | 3675 [432](2670-4950) |
| Gestational age at birth, weeks [a] | 29.0 * [2.7] (24-35) | 39.5 [1.1] (37-42) | 39.6 [1.2] (37-42) |
| Age at assessment, years [a] | 14.5 [0.38](13.6-15.4) | 14.6 [0.42] (14.0-16.6) | 14.6 [0.49] (13.6-16.8) |
| Socio-economic class [b] | 3.4 [*4.0*](1-5) | 3.4 [*4.0*](1-5) | 3.8 [*4.0*](1-5) |
| Male [c] | 28 (55 %) | 28 (47 %) | 32 (42 %) |
| CP [c] | 7 (14 %)* | 1 (2 %) | 0 (0%) |

[a] Data given as mean [SD] (min-max values) T-test [b] Data given as mean [*median*] (min-max values) Mann Whitney test [c] Data given as n (% )
*p≤0.001 vs controls

**Exclusion criteria**. Congenital anomalies (defined as a ICD9 diagnose number between 740-759), presenting at the neonatal examination, was an exclusion criteria in all the study groups. Three adolescents with congenital anomalies diagnosed at birth were included in paper I, but excluded from analysis in the following papers. Results in paper I did not change significantly when reanalysed with the population used in paper II.

Table 2. Flow of participants in the study

| | VLBW | | | SGA | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| paper | I and II | III | IV | I | II | III | IV | I | II | III | IV |
| based on population of | Trøndelag | Hospital | | Trondheim | | | | Trondheim | | | |
| original population | 99 | 121 | 121 | 104 [a] | 107 [a] | 104 [a] | × | 120 | 120 | 120 | 120 |
| died | -23 | -33 | -33 | 0 | 0 | 0 | × | 0 | 0 | 0 | 0 |
| excluded congenital anomaly | -1 | -1 | -1 | 0 | -4 [b] | -1 [b] | × | 0 | -2 [b] | -2 [b] | -2 [b] |
| excluded due to CP | × | -8 | × | × | × | -1 | × | × | × | 0 | × |
| moved | -6 | -6 | -6 | -12 | -12 | -12 | × | -10 | -10 | -10 | -10 |
| potential participants | 69 | 73 | 81 | 92 | 91 [c] | 90 | × | 110 | 108 [d] | 108 | 108 |
| no consent | -18 | -22 | -35 | -33 | -33 | -34 | × | -33 | -33 | -33 | -53 |
| DTI data excluded | × | × | -16 | × | × | × | × | × | × | × | -10 |
| final number of participants | 51 | 51 | 30 | 59 | 58 | 56 | × | 77 | 75 | 75 | 45 |

[a] The original SGA population was 107 subjects, including three subjects with congenital anomalies excluded from the study at the beginning. In paper I and III subjects excluded at the beginning of the study due to congenital anomalies were not registered, original population therefore reported as 104. [b] Three subjects (one SGA, two control) with congenital anomalies who should have been excluded at birth, were included in paper I, but excluded in paper II-IV [c] Not 92 as stated in paper II [d] Not 110 as stated in paper II. x= not applicable

## Ophthalmological examination

The ophthalmological examination lasted for approximately 60 minutes and consisted of:

- Visual acuity with habitual and best correction, near and distance, mono- and binocularly. I used a Snellen chart for distance for most subjects, which measures visual acuity up to 2.0 (visual acuity given in Snellen decimals). For two VLBW participants having problems naming letters a Lea Hyvärinen distance chart with four symbols was used. For near I used a Lea Hyvärinen near chart for all subjects, at 40 cm distance.
- Subjective refractioning
- Contrast sensitivity. I used the VISTECH contrast sensitivity chart, at 40 cm distance. Both eyes were tested independently. For each eye, contrast sensitivity was tested at five frequencies (i.e stripes at different frequency) with eight images of decreasing contrast at each frequency. The last correctly seen image was noted for each frequency. All testing was done in the same artificial light, thus variations in daylight did not influence results.
- Visual fields. Automatic perimetry was performed, using the Humphrey 120 point twozone. This tests visual fields to 60 degrees.
- Ophthalmoscopy in slit lamp, with particular interest in detecting nystagmus, media opacities, retinal detachment or dragging, observing the retinal vascular pattern, optic disc cup/disc ratio and any iris translucency.
- To detect ocular malalignment (manifest or latent strabismus): Alternating prism cover test with the subject fixating at distance in five directions of gaze (primary position, up, down, right, left) and at near in primary position.
- Near point of convergence was measured with the Royal Air Force (RAF) ruler.
- Stereopsis /binocularity: Binocular vision was measured with the TNO-test. For those subjects who did not manage the easiest stereograms on the TNO test, we tried the Titmus test, which goes up to 3600". If even that was too difficult, the Bagolini striated glasses-test at distance and near were peformed.
- Accommodative amplitude was measured with the Royal Air Force (RAF) ruler for each eye.

- Nystagmus was evaluated during the alternating cover test and during examination in split lamp, and the type of nystagmus was described (physiological endpoint, latent, manifest latent or other)
- Smooth pursuit and saccades were evaluated horizontally and vertically by having the subject either follow an object (smooth pursuit) or alternating looking at one of two objects (saccades). Any forced head posture was evaluated during the history taking and also during examinations.
- The subjects were asked at the beginning of the examination about their history of habitual and previous correction, if they had any ophthalmological concerns or worries, if they had experienced asthenopia and if they had a history of treatment of amblyopia with occlusion.

## Motor examination

The test battery Movement assessment battery for children (”Movement ABC”) (Henderson and Sugden, 1992) was used, and all testing was done by one physiotherapist, blinded to group assignment. Movement ABC is a development of the Test of Motor Impairment (TOMI), first published in 1972, and later revised in 1984 and 1992 (Henderson and Sugden, 1992). The test aims to identify children with problems in motor control and ability age 4-12. It consists of eight items, where optimal function in each gives a score of zero, and the lowest score in each is five. Thus total score can range form zero (best) to 40 (worst). The test takes approximately 20-40 minutes to complete and gives three subscores: manual dexterity, ball skills and static/dynamic balance. We used the highest age-band, designed for 11-12 year old children. As the study population was examined at age 14, we used the 5$^{th}$ percentile from the control group (a total score of 14) to define a result indicating motor problems. This level was in accordance with the 5$^{th}$ percentile in the manual (Evensen et al., 2004). Results between the 5$^{th}$ and 15$^{th}$ percentile suggest possible motor problems, whereas results below the 5$^{th}$ percentile indicate definite motor problems (Henderson and Sugden ,1992).

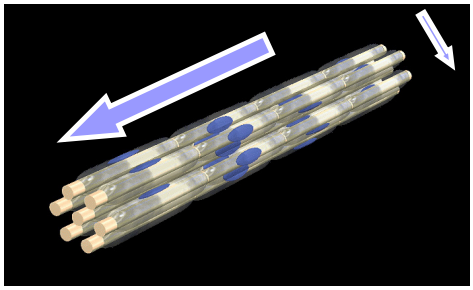
## Diffusion tensor imaging

Diffusion tensor imaging is an MRI method which investigates the white matter microstructure (Basser et al., 1994, Hüppi and Dubois, 2006), by measuring the amount and direction of water molecule diffusion, the

Brownian motions, in three dimensions (Le Bihan and van Zijl, 2002). Water diffusion is random and equal in all directions (isotropic) as long as nothing interferes with the movement. Diffusion can be described by the two variables "mean diffusion", which measures the total molecular motion averaged over all directions, and "fractional anisotropy", which refers to the degree of directionality of diffusion.

In the brain, water diffusion is relatively isotropic in grey matter, i.e. the fractional anisotropy is low. In white matter the diffusion is facilitated along the main direction of axons, and hampered across (see Figure 10). In a voxel where the axons run parallel, the fractional anisotropy is high. Thus fractional anisotropy can be said to measure the orderliness of axons in a given voxel. However, this is obviously an oversimplification, since low fractional anisotropy in the white matter not necessarily represents disarray of the axons in a voxel. If two or more axons cross each other perpendicularly, and orderly, this will result in low fractional anisotropy. However, in white matter pathways where nerve bundles are normally uniformly oriented, such as the callosal tracts, this is less of a problem (Toosy et al., 2004) .

Figure 10. Illustrating how water diffusion is facilitated along axons (large arrow) and hampered across (small arrow).



Reduced fractional anisotropy may be caused by a disarrangement of axons, but other factors, such as disturbed axonal growth, loss of axons and impaired myelinisation may also affect the fractional anisotropy. By measuring the axial diffusivity (this is the largest diffusion vector) and comparing it to radial diffusivity (perpendicular to axial diffusivity) further information about the state of the axon can be gained (Song et al., 2002, Song et al., 2003, Song et al., 2005).

# Chapter 7. Summary of papers

This thesis attempts to address the "what, how and why" (in *what* way does this population differ from the control group, *how* does this affect their life and *why* is there a difference?) of impaired visual functions in a VLBW and an SGA at term adolescent population. The first two papers describe the findings, the third explores how visual (dys-)functions affect motor abilities (an important aspect of everyday life), and in the fourth we try to pinpoint anatomical areas in the brain responsible for some of the visual impairments registered in the VLBW group.

## Paper I and II – *what* is the level of visual functions?

In paper I and II we describe the results of the population based analysis of the ophthalmological examination in the three groups. All p-values and odds ratios are in comparison to the control group. There were very few positive findings in the SGA group and unless specifically mentioned in the following no significant differences between them and the control group were found.

**Paper I**

- Visual acuity: The VLBW adolescents had statistically significantly lower mean visual acuity both at distance and near, and a larger proportion of VLBW subjects had visual acuity <1.0 in either one (24 and 31 %, $p<0.001$) or both eyes (12 %, $p<0.05$) compared to controls (3, 4 and 0 % respectively). Lower visual acuity was particularly seen among the subjects with lowest birth weight in the VLBW group. No subjects in either group had binocular visual acuity <0.3.
- Use of correction: Approximately 15 % in all groups were currently using correction. Among SGA and control subjects a third to half of correction users preferred contact lenses, compared to none ($p=0.055$) in the VLBW group. In all groups a substantial part (34-47 %) had ever used glasses. VLBW subjects were younger (mean 7.2 years, $p>0.05$) when they got their first glasses than control subjects (9.2 years). Under-correction (defined as improving distance binocular visual acuity two Snellen lines or more) was seen in 53 % ($p<0.05$) of the VLBW group, and 34 % of the control group.

- Errors of refraction: We did not detect any significant difference in the distribution of refractive errors between the VLBW and control group, apart from a slightly higher mean anisometropia in the VLBW group (0.32 D, p< 0.01) compared to the control group (0.19 D). In the SGA group hypermetropia > +1 D spherical equivalent was seen in 14 % (p =0.057, odds ratio, OR3.9, 95 % confidence interval, CI 1.0-15, significant) compared to 4 % of controls. When analysing girls and boys separately, the difference was significant for girls (OR 5.2, 95 % CI 1.0-28,).
- Visual fields: No significant group effects demonstrated.
- Contrast sensitivity: Fewer in the VLBW group (48 %, p<0.01) presented a completely normal result, as defined by the test manufacturer, than in the control group (73 %).

**Paper II**

- Latent or manifest strabismus (deviations outside the physiological range) was seen in 36 % (p=0.001) of VLBW adolescents, compared to 11 % of control adolescents. Exodeviations were significantly larger in the VLBW group than in the control group, esodeviations were not significantly different. All VLBW subjects with cerebral palsy had a nonphysiological deviation.
- A higher proportion of VLBW subjects (29 %, p= 0,01) had poor convergence compared to control subjects (11 %).
- A higher proportion of VLBW subjects (14 %, p= 0.006) had poor stereopsis than control children (1 %). The difference was no longer significant when the children with cerebral palsy were excluded.
- Occlusion treatment for amblyopia was reported in 8 % (p=0.02), compared with none in the control group.
- Accommodative amplitude was similar in the three groups.
- Pathological nystagmus was observed in 10 % (p = 0.01) of the VLBW subjects, and in none of control subjects. Pathological nystagmus was in all subjects associated with visual acuity <1.0, as well as various other ophthalmological problems.
- There were no statistically significant differences regarding smooth pursuit, saccades, and forced head posture in the groups.
- Multiple ocular motility and binocularity deficits: Failure in at least two of the following functions: ocular alignment, stereopsis, convergence, accommodative amplitude, nystagmus, saccades and

smooth pursuit was seen in 38 % of VLBW adolescents versus 4 % of control subjects (p<0.000).

**Unpublished descriptive data**

- Retinal vasculature: retinal vasculature was graded as very tortuous, having some tortuosity or not tortuous. 17 % of VLBW adolescents had very tortuous vessels versus 0% of control adolescents. (p< 0.001). Two percent of the SGA group had very tortuous vessels, not significant. However, when analysing subjects with either very or some tortuosity, the SGA group differed near- significantly from the control group, with 14 % versus 4 % , p =0.054. In the VLBW group 53 % had very tortuous or any tortuosity, p < 0.000 versus control group (4 %).
- No cases of iris translucency were recorded. Iris translucency is a sign indicative of albinism, and a rather high prevalence of 1 % has been reported in a Swedish population (Sjöström et al., 2001).
- Mean cup disc ratio (C/D) in the VLBW group was 0.19 (SD 0.16) in the right eye and 0.18 (SD 0.17) in the left eye. This was significantly different from the C/D in the control group's right eyes (mean C/D 0.13, SD 0.15, p = 0.019 Mann-Whitney U), but not when compared to their left eyes (mean 0.14, SD 0.15, p = 0.18 Mann-Whitney U). The figures for the SGA group were 0.14 in the right eye and 0.15 in the left eye, which did not differ significantly from measurements in the control group.

## Paper III – *how* do visual functions influence motor ability?

In this study we explored how visual impairments influenced the risk of motor problems.

The odds ratio (OR) for having general motor problems were 10.4 (95 % CI, 2.2-50) in the VLBW group compared to the control group. When controlling for poor visual acuity the OR was reduced by 25 % to 7.8 (95 % CI 1,6-38). The variables poor contrast sensitivity, nystagmus, strabismus, poor stereoacuity and visual perception all lowered OR with approximately 10 %, when adjusted for separately. An abnormality score, combining all these variables, influenced the OR the most, decreasing it 35 % to 6.8 (95 % CI 1.3-34). Poor convergence and accommodative ability did not affect the odds of having motor problems.

## Paper IV – *why* are visual functions impaired in the VLBW group?

In this paper we correlated data on cerebral white matter microstructure (as indicated by diffusion tensor findings) with visual variables. Our findings indicate that subnormal visual acuity in VLBW adolescents may be related to changes in the microstructure of the splenium part of the corpus callosum. The splenium is particularly prone to injury in prematurity. It also constitutes the route for transhemispherical relay of visual information and favours foveal data. In the paper we speculate that a normal splenium may contribute more to the development of optimal visual acuity than previously acknowledged.

# Chapter 8. Discussion

## Main results

The main findings ( i.e. statistically significant group effects) of this thesis are almost all in the VLBW group.

Being born prematurely with a birth weight <1500 g has consequences for many aspects of visual development, lasting at least until adolescence. Reduced visual acuity, contrast sensitivity, latent or manifest strabismus, poor stereopsis, poor convergence and nystagmus were more common in the VLBW group. However, on the positive side, there were no significant differences regarding visual fields, errors of refraction (other than anisometropia and undercorrection), accommodative amplitude, saccades or smooth pursuit, and none of the participants were visually impaired according to the WHO definition (visual acuity <0.3)

In the SGA group there was slightly more hypermetropia than among control subjects, but other than that no significant differences were found.

Comparing visual and motor abilities exposed a statistical influence of several visual functions, strongest by visual acuity, on motor ability in the VLBW group, but not among the SGA subjects.

Finally visual acuity was shown to correlate to the microstructure (as measured by diffusion tensor) of cerebral white matter in the the splenium part of the corpus callosum, as well as to periventricular anatomy.

## Strengths and limitations

**Chance and power**. In paper I and II the majority of statistically significant observed VLBW group effects were highly significant, with p-values of less than 0.01 or 0.001.

In paper III the odds ratio for having motor problems was strongly affected by the combined abnormality score (adjusting for which reduced the crude odds ratio from 10.4 to 6.8, a 35 % reduction) and by visual acuity (a 25 % reduction).

Multiple comparisons increase the risk of making type I faults. In Paper IV, thousands of correlations were made, and this calls for particular caution in analysis and interpretation of results (Ridgway et al., 2008). Special statistical procedures have been developed to compensate for the risk of making a type I fault in multiple comparisons, and these tests need to be different for small-and large scale multiple comparisons. We have used false discovery

rate (Benjamin and Hochberg, 1995), which is recommended when correcting for large scale multiple comparisons (Genovese et al., 2002). The threshold of 0.05, which we used, is conservative in this context (Genovese et al., 2002) thus reducing the risk that a chance finding has been interpreted as real. Other steps, described in paper IV, were also taken to avoid making a type I fault.

Thus, I conclude that our results are very unlikely to be caused by chance findings.

Due to the sample size the study was not powered to detect smaller, but real, group differences in the underlying population. This means we must be careful in drawing conclusions from our negative results.

**Selection bias**. It is a strength of our study that paper I and II are population based and prospective, as this minimises selection bias. Loss to follow up must be expected in a long term follow up study (Fewtrell et al., 2008). The attendance in our study of 74, 65 and 70 % (VLBW, SGA and control group respectively) of the eligible population in paper I and II is comparable to other with a similar length of follow up (Hellgren et al., 2007,O'Connor et al., 2004). Furthermore, although nonattenders did not differ from attenders on known background data, it is possible that the loss to follow up is not random, but that subjects performing worse have had a stronger tendency to drop out. This is supported by a study by Pennefather et al (Pennefather et al., 1999).

In the two studies correlating visual function to another variable (motor ability in paper III and white matter microstructure in paper IV), selection bias is less likely. Results will only be biased if the association between a visual function and motor skills/white matter microstructure is systematically different between attenders and nonattenders. Although loss to follow up is always undesirable, as it weakens a study's power, it is less detrimental in a correlational than in a prevalence study.

Thus, although difficult to avoid in a long term follow up study, loss to follow up may have caused us to underestimate pathology in paper I and II. This does not weaken our conclusions in the VLBW group, rather the opposite, but is important to remember when interpreting the negative findings in the SGA group.

**Interviewer bias:** It is a strength for our study that the examiner was blinded to group during examinations. In a few subjects not able to walk independently CP made me suspect they were in the VLBW group, and a few parents (approximately less than five) mentioned that the child had had a check up "after leaving the neonatal intensive care unit", but in the large majority of cases blinding was effective.

**Misclassification bias:** There should be no risk of misclassification (i.e all subjects were born preterm) in the VLBW group.

Random misclassification may have caused underestimation of risk in the SGA group. SGA was used as a proxy for IUGR in this study. Some of the children defined as SGA are only constitutionally small, healthy and not growth restricted, whereas some constitutionally large children may have been growth restricted but still ended up in the control group with a birth weight above the 10$^{th}$ percentile. Again, this means negative SGA results must be interpreted with caution.

**Recall bias:** The VLBW & SGA parents and adolescents were probably aware that they belonged to risk groups. However, recall bias seems unlikely to affect results as most are based on tests, and little was based on the history of the subjects and their parents. Recall bias can not be ruled out as a possible source of bias in the history based results (e.g. age first glasses), but these results are not crucial for the thesis.

**Confounding:** In this material sex was somewhat unevenly distributed (55 % male in the VLBW group, 47 % in the SGA and 42 % in the control group), and this is a potential confounder. Although a sex effect has been reported in preterm populations, where boys tend to fare worse regarding brain growth and visual functions (Kapellou et al., 2006, Jacobson et al., 2009), there is little evidence that visual functions in the normal population correlate to sex, apart from a possible effect on refractive errors (Zadnik et al., 2003). In paper I refractive errors, perimetry and near point of convergence were analysed separately for boys and girls. This did not change results, except regarding hypermetropia in the SGA group which was borderline more common among SGA girls than control girls.

Another conceivable confounder is low IQ (defined as an IQ below 70. This concerns eleven subjects in the VLBW group and two in the control group). In paper III we corrected for low IQ and sex and this did not change results. After publication of paper I and II, I have adjusted for sex and low estimated IQ in a general linear model for continuous variables and in logistic regression analysis for dichotomous variables in the VLBW and control group. The variables which were analysed in a general linear model were:

- best corrected distance binocular visual acuity
- age at first glasses
- mean anisometropia
- number of points seen visual field
- accommodative amplitude, mean of both eyes
- multiple ocular motor and binocularity defects
- contrast sensitivity

and in logistic regression:

- poor stereopsis
- strabismus - any unphysiological deviation
- poor convergence

Group effect remained statistically significant after correcting for sex and low IQ in all these variables. Sex hardly changed means and odds ratios, but correcting for low IQ had some impact on visual acuity in VLBW group (uncorrected mean: 1.17, corrected: 1.20), multiple ocular motor and binocularity defects (uncorrected mean: 1.14, corrected: 1.06), any strabismus (uncorrected OR: 4.7, corrected: 3.9) and poor convergence (uncorrected OR: 3.4, corrected: 3.0). However, group remained statistically significant. Thus neither sex nor low IQ are likely to be confounding the results.

However, as both low IQ and poorer visual acuity are connected to brain injury in this study the results above are to be expected.

**Causality.** Causality between exposure and outcome has been made biologically plausible in the discussion above on possible pathogenetic pathways for visual injury in both groups (page 21 and following). Brain injury is the most likely causal agent in the VLBW group. This assumption is strengthened by the results in paper IV, where a strong correlation is demonstrated between visual acuity and structure of the corpus callosum and periventricular areas in the VLBW group. Brain damage is also likely to be causing at least part of the observed connection between visual impairments and motor problems presented in paper III.

Other prerequisites for causality are strength of association and temporality (the cause must precede the effect). Outcomes were measured (long) after birth and this should make the time-sequence appropriate. The association between having VLBW and impairments in ophthalmic functions is generally strong, affects almost all the variables tested and persists after adjusting for confounders. Finally, as shown in the discussion parts of the papers, our results are generally consistent with what others have reported.

I therefore conclude that we have found a valid association between VLBW and long term visual and ocular motor problems, and that it is reasonable to assume causality.

Regarding birth at term SGA we did not expose any increased ophthalmic morbidity in this group (except for a small, borderline significant increase in hypermetropia). As discussed above, however, it is more likely that we have under –than overestimated pathology. Thus, the negative results in the SGA group must be interpreted with caution.

## Choice of ophthalmological tests

The subjects had agreed to take part on the condition that examinations would not be painful.

Some tests which we considered including in the protocol, but finally chose not to, were tonometry (in 2000, this meant a drop of stinging local anesthesia had to be applied, and the tonometry itself can also be frightening), ultrasound for measuring axial length etc (local anaesthesia, time consuming, unpleasant). We tried fundus photography without dilating the pupils, but did not get good enough pictures. Applying dilating eyedrops stings, is time consuming and causes blurry vision for several hours after the exam. Cycloplegic refractioning was discarded for the same reason.

## Discussing the main results

In this study we have demonstrated a significantly increased proportion of impairments or poor performance in the VLBW group in the majority of the variables tested. In paper I we found lower visual acuity and contrast sensitivity as well as a higher likelihood of being undercorrected (i.e needing new glasses). This is the first study to present data on undercorrection in a preterm population, but reduced visual acuity has been reported in several other studies (see Figure 11), ranging from a prevalence of 5 % to over over 50 %. Cerebral white matter damage of immaturity has been linked to reduced visual acuity (Hellgren et al., 2007, Fazzi et al., 2004). However, retinal pathology can not be ruled out, even when no sequelae of ROP is seen, as a retinal dysfunction can be demonstrated in children with only mild ROP long after the ROP has completely resolved (Fulton and Hansen, 1996).

Unlike other studies (O'Connor et al., 2002a, Darlow et al., 1997, McGinnity and Bryars, 1992, Saunders et al., 2002, Larsson et al., 2003, Hellgren et al., 2007) we found no increase in refractive errors, other than a slight increase in anisometropia, and no visual field defects. However, Hellgren et al ( 2007) whose VLBW population was about the same age as ours (they were 15 years old) like us did not report any increase in myopia and hypermetropia, only an increase in astigmatism. They speculate that the myopisation often encountered in term born adolescents, may have counter balanced the effect of prematurity on refraction (Hellgren et al., 2009). The low prevalence of refractive errors in our study might also suggest a low incidence of ROP, a risk factor for refractive errors (O'Connor et al., 2002). We know that none in our group were cryo-treated for

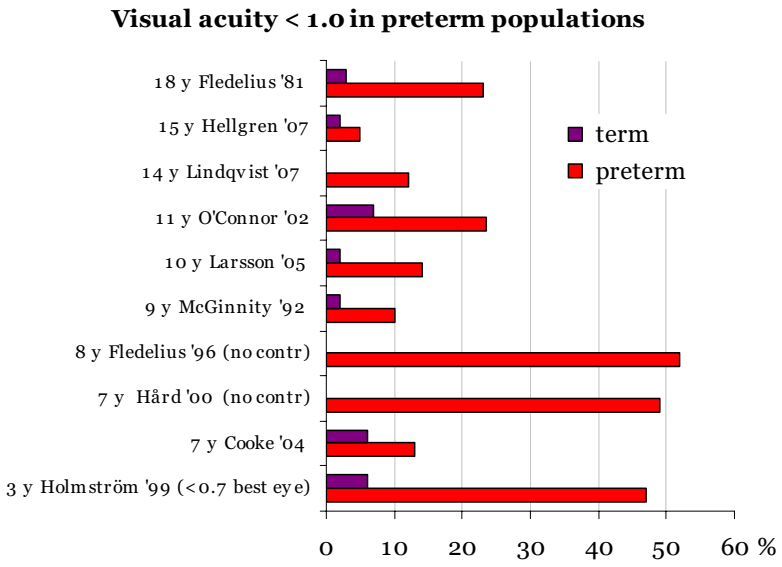



Figure 11. Proportion of population with subnormal binocular visual acuity (i.e. below 1.0, in Holmström's study of 3 year olds 0.7 was set as limit) in several studies of preterm subjects of different ages (y =years old, no contr= no control group)

ROP , another known risk factor for myopia (Larsson et al., 2003), but other than that we have no ROP data to support this assumption.
Visual field defects, particularly in the lower hemifields, have been reported by other studies of unselected VLBW populations, using more sensitive techniques than we did (Larsson et al., 2004, Hellgren et al., 2008).
Impaired visual functions related to binocularity and ocular motor control, such as latent or manifest strabismus, poor stereopsis, poor convergence and nystagmus were all more frequent in the VLBW group. Our results concur well with what others have reported in younger (Fledelius, 1996, McGinnity and Halliday, 1993, Holmström et al., 1999, Holmström et al., 2006), and adolescent preterm populations (Hellgren et al., 2008). Strabismus has been linked to cerebral damage both in preterm and other populations (Jacobson et al., 1998, Hellerstein et al., 1995), and although poor stereopsis is often linked to strabismus, it has also been described in preterm children without this obvious cause (Holmström et al., 1999). It is likely that brain injury should cause reduction in stereopsis, since this visual function is completely

dependant on cerebral processing of visual data. Our finding of normal stereopsis in the VLBW group when children with cerebral palsy were excluded also suggest that brain damage is an important causative factor. The report of an association between MRI findings and poor stereopsis in a VLBW cohort by Hellgren et al (2008) further strengthens this assumption.

Whereas control subjects very seldom (4-13 %) failed in two or more of the visual functions included in the two (partly overlapping) "abnormality scores", VLBW subjects frequently (38-43 %) failed in at least two variables. This tendency to "multi fail" is also apparent in our study of the association between visual impairments and motor ability (paper III). The risk of motor problems in the VLBW group was significantly influenced (OR fell by 25 %) when controlling for poor visual acuity. The association between poor visual functions and motor problems has been reported by others in both preterm (O'Connor et al., 2009, Torrioli M.G. et al., 2000, Powls et al., 1997) and general populations (Sigmundsson et al., 2003).

The nature of this association may both be one of cause and effect, and one of a shared common etiology. It is likely that perinatal brain damage in many of these children will have affected both visual and motor pathways (Skranes et al., 2005,van den Hout et al., 2004), and that some of the observed association is one of a common etiology. However, visual functions also have a direct influence on motor ability (Haegerstrom-Portnoy, 1993). We suggest that both explanations are right.

Regarding the tendency to "multi-fail": A problem with having several suboptimally functioning systems is that the strategies available for compensation are limited. Compensating for e.g. a learning disability is much more difficult if your reading speed is reduced by poor visual acuity, crowding and poor convergence. Thus a child with seemingly few, or no, severe disabilites, but several smaller ones, may be disproportionally disadvantaged. Parents of such children might perceive the child's struggle, and serve as their child's compensatory mechanism. For an outsider unaware of *all* the child's limitations this might appear as unjustified overprotection. Not surprisingly, parents of preterm children are sometimes described as overprotective, and parental overprotectiveness is sometimes even claimed to cause the child's problems (O'Mara and Johnston, 1989, Gunn et al., 1983). However, the assumed overprotection may be quite adequate assistance for that child. A broad, interdisciplinary diagnostic approach to a struggling preterm child may help avoid such misunderstandings.

A cerebral cause has been suggested for all the variables above where the VLBW group differed from the control group, and the demonstration of a significant correlation between visual acuity and white matter microstructure in the brains of the VLBW group (paper IV) further strengthens this assumption. A correlation with visual acuity was detected in two major

anatomical areas. The one most reliably associated with white matter microstructure was seen in the splenium part of the corpus callosum. This is the most posterior part of the corpus callosum, known to convey visual fibres (Dejerine and Dejerine-Klumpke, 1895, Dougherty et al., 2005). It is also an area particularly prone to damage in prematurity (Judas et al., 2005, Benjak et al., 2008) and thinning of the splenium has been associated with impaired visual perceptual impairment in preterm children (van den Hout et al., 2004). Midline information is favoured for callosal transfer (Ptito, 2003), and visual acuity is perhaps the best example there is of a midline function. The other correlation was seen in the periventricular regions. This finding may reflect the enlarged ventricles in some of the subjects, rather than irregular white matter structure, but is nevertheless interesting in that is links reduction of visual acuity to the periventricular anatomy. The association between impaired visual function and enlarged ventricles has been described previously (Serdaroglu et al., 2004) with other techniques, however not the callosal findings.

## Future perspectives for research on the ophthalmological effects of preterm birth

Based on the known increased risk for several potentially treatable ophthalmic conditions in the VLBW population (Holmström et al., 1999, Holmström et al., 2006), ophthalmological screening for all ELBW children, and for other premature children with added risk factors is currently in effect in Norway (Sosial- og Helsedirektoratet, 2007). Future research should evaluate this program. Are we screening the right children at the right time? What about the late preterms? Is our diagnostic setup working for what we should be looking for, and are we helping? Are we good at communicating our findings so that the information makes a positive difference in the child's life at school and at home?

One slightly surprising finding from the current thesis was that adolescents in the control group had better habitual correction and were in less need of new glasses than VLBW adolescents, in spite of both groups having similar pattern of refractive errors. If the VLBW subjects are in some way less capable of getting new glasses, they may be less able to give notice in other problem areas as well. One justification for screening is that it is beneficial for the patient/subject to find out about the problem before it becomes so apparent to him that he does something about it by his own accord. Possibly VLBW subjects are less aggressive in getting health care than normal birth weight subjects , and this, in addition to their known wide range of higher risks (both

in motor ability, psychiatric health, cognitive and learning ability), may call for long term follow up. It may be that we underestimate the usefulness of screening /follow-up because we mistakenly believe that the high risk population seeks medical advice as successfully as the normal population.

Using existing visual data and comparing them to the ongoing neuropsychological, motor, psychiatric and/or MRI follow up at age 20 is also planned.

## Conclusion

Being born prematurely with a birth weight below 1500 g brings on an increased risk of subnormal or impaired function in a range of visual functions which lasts at least until adolescence. However, in this population, none were blind or severely visually impaired (i.e. with a visual acuity < 0.3).

Motor problems are also common in this group, and motor and vision dysfunction frequently appear in the same subject.

Visual acuity in the "mild subnormal range", from 0.5 to 1.0 in Snellen decimals, was seen frequently in this group of VLBW adolescents and has been reported as a characteristic problem by other authors as well. As the first to report an anatomical correlate to these findings, we describe a correlation between visual acuity and the microstructure of the posterior part of the corpus callosum, the splenium, in the VLBW group. We present an argument for why the splenium part of the corpus callosum may be of importance for the development of normal visual acuity as well as for why it may be prone to injury in prematurity.

To end by stating the obvious: eyes are important for vision. But, perhaps less obviously, so is the brain. Although retinal damage by ROP is declining in high income countries, brain damage is emerging as the biggest threat to the visual health of preterm born children, adolescents, and probably, adults.

# Corrections

Number of potential SGA subjects in paper II to be 91, not 92.
Number of potential control subjects in paper II to be 108, not 110
Paper I: Table 5 page 161. § indicates p = 0.057, not 0.57 as written
PaperII: reference to Snir et al 2004 at page 271 incorrect , should be "Ricci 1998". In the reference list Snir et al should instead be "Ricci B. Refractive errors and ocular motility disorders in preterm babies with and without retinopathy of prematurity. Ophthalmologica 1999; (213): 295-299."

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# Paper III

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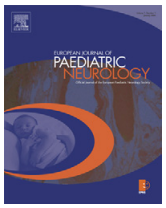

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Original article

# Do visual impairments affect risk of motor problems in preterm and term low birth weight adolescents?

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ABSTRACT

*Background:* Increased prevalence of motor and visual problems has been reported in low birth weight populations, but the association between them is less studied.
*Aim:* To examine how visual impairments may be associated with the increased risk of motor problems in low birth weight adolescents.
*Methods:* Fifty-one very low birth weight adolescents (VLBW), 56 term small for gestational age (SGA) and 75 term control adolescents, without cerebral palsy, were examined at the age of 14. Motor skills were examined by the Movement Assessment Battery for Children. Visual functions included visual acuity, contrast sensitivity, nystagmus, strabismus, stereoacuity, accommodation, convergence and visual perception (Visual-Motor Integration test). An abnormality score was calculated as the sum of visual impairments. We used odds ratio as an estimate of the relative risk of having motor problems.
*Results:* The odds of having motor problems were 10.4 (95% CI: 2.2–49.4) in the VLBW group and 5.1 (95% CI: 1.0–25.8) in the SGA group compared with the control group. The odds of having motor problems in the VLBW group were influenced by all visual variables, and most by visual acuity, when we adjusted for these separately. The greatest reduction in OR was found when adjusting for the abnormality score (adjusted OR: 6.8; 95% CI: 1.3–34.5). In the SGA group the odds of having motor problems were relatively unaffected by the visual variables and the abnormality score.
*Conclusions:* Visual impairments influence motor problems in VLBW adolescents, whereas motor problems in SGA adolescents seem to be unaffected by visual impairments.
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## 1. Introduction

Premature birth and intrauterine growth restriction both represent risk factors for motor problems and visual impairments. Motor problems are frequently seen in children with birth weight below 1500 g (very low birth weight: VLBW) at preschool[1–3] and school age.[4–7] Some studies also report motor problems in VLBW adolescents.[8,9]

VLBW children and adolescents also have poorer visual functions, including poorer visual acuity,[10–14] stereoacuity,[2,10,11,15] contrast sensitivity[10,13] and more strabismus[10–13] than controls. Visual perception is also more frequently reduced in preterm children.[16–18]

Children who have been growth retarded in utero are usually diagnosed by having a low birth weight for their gestational age (small for gestational age: SGA). Studies on motor skills in term SGA children are few and have shown inconsistent results.[19–23] We have previously reported that term SGA adolescents, in particular boys, more often had motor problems, especially poor manual dexterity, compared with non-SGA adolescents.[9] Also, visual functions have been less studied in SGA populations, primarily in infants[22,24] and young children.[20] A couple of studies have found some support for impaired visual function among adolescents who were born SGA.[25,26]

Vision is one of the most important sources of information for motor control[27,28] and plays an essential role in both motor and cognitive development.[29] Vision is necessary to identify objects and movements important for interacting with the environment and for controlling body movements.[27] Poor visual perception has been shown to contribute to movement problems of clumsy children.[30]

Associations between visual functions and motor skills have been less studied in low birth weight populations, but there seems to be a relationship between motor skills and stereoacuity[2,11,15] as well as visual acuity, strabismus and contrast sensitivity[11] in younger VLBW children. In VLBW adolescents, a strong association between impaired vision and motor problems has been reported, especially in children with strabismus and poor contrast sensitivity.[10]

None of these previous studies of VLBW children have looked at the risk of motor problems and how this risk may be affected by visual functions. Secondly, no studies have looked at the association between vision and motor skills in SGA children or adolescents.

In this study, we wanted to examine how visual impairments may be associated with the increased risk of motor problems in VLBW and SGA adolescents.

## 2. Material and methods

### 2.1. Study design

This is a follow-up study of two groups of adolescents with low birth weight (VLBW and term SGA) compared with a control group of normal birth weight. The VLBW adolescents had been admitted to the Neonatal Intensive Care Unit (NICU) at the University Hospital in Trondheim in 1986-88. The SGA and control children were born in the same time period to mothers enrolled before week 20 of pregnancy in a multicenter study,[31,32] where a 10% random sample of women (with one or two previous pregnancies) was selected for follow-up during pregnancy. At birth, all SGA children and all children born to mothers in the random sample were included for follow-up. Children with cerebral palsy (CP) and congenital malformations were excluded.

At 14 years of age, motor, visual and neuropsychological examinations were performed as part of a comprehensive follow-up assessment. We have previously reported the prevalence of motor, visual and neuropsychological problems in VLBW and SGA adolescents.[9,26,33,34,61]

### 2.2. Study population

#### 2.2.1. VLBW adolescents

One hundred and twenty-one children with a birth weight $\leqslant$1500 g were admitted to the NICU at the University Hospital in Trondheim (the referral hospital) in 1986–88. Of these, 33 died, one child with trisomy 21 was excluded, eight had CP and six children had moved. Of the remaining 73 children, 22 did not consent to at least one of the examinations (motor, visual and/or neuropsychological examination). Thus, a total of 51 (70%) VLBW adolescents (28 boys, 23 girls) underwent all three examinations.

#### 2.2.2. SGA adolescents

Of 1200 eligible women, 104 (9%) gave birth to a SGA child, defined by a birth weight $<$10th centile, adjusted for gestational age, gender and parity. One child had CP and one child had a congenital malformation. At follow-up, 12 children had moved. Of the remaining 90 children, 34 did not consent to motor, visual and/or neuropsychological examination, leaving 56 (62%) SGA children (25 boys and 31 girls) in this study group.

#### 2.2.3. Control adolescents

The control group comprised 120 children with birth weight $\geqslant$10th centile for gestational age, born at term to mothers in the 10% random sample. Two children had congenital malformations. At follow-up, 10 children had moved, while 33 did not consent to at least one of the examinations. In total, 75 (69%) children in the control group (32 boys and 43 girls) were examined.

#### 2.2.4. Non-participants

There were no significant differences in maternal age, duration of pregnancy, the infants' birth weight, body length and head circumference between those who participated and those who did not consent to participation in any of the groups.

## 3. Methods

All examiners were blinded to group assignment.

**Table 1 – Gestational age, birth weight and anthropometric measurements at follow-up in two groups of adolescents with low birth weight compared with a control group**

| | VLBW ($n = 51$) Mean (SD) | SGA ($n = 56$) Mean (SD) | Control ($n = 75$) Mean (SD) |
|---|---|---|---|
| Birth weight (g) | 1206 (228)[a] | 2919 (214)[a] | 3679 (431) |
| Gestational age (weeks) | 29.4 (2.7)[a] | 39.5 (1.1) | 39.6 (1.1) |
| Age at follow-up (years) | 14.2 (0.3) | 14.2 (0.3) | 14.2 (0.3) |
| Weight (kg) | 52.1 (13.7)[c] | 52.3 (8.6)[b] | 57.5 (10.7) |
| Height (cm) | 162.4 (9.0)[b] | 163.4 (7.2)[b] | 167.6 (7.6) |
| Head circumference (cm) | 54.6 (1.8)[a] | 54.8 (2.0)[a] | 56.0 (1.5) |

[a] $p < 0.001$.
[b] $p < 0.01$.
[c] $p < 0.05$ vs. controls (gestational age and birth weight were the selection criteria, and differed by definition vs. the control group).

### 3.1. *Background data*

At birth, the VLBW infants were weighed to the nearest gram on an electronic scale, whereas the SGA and control infants were weighed to the nearest 10 g on a standard scale.

At follow-up, weight was measured on an electronic scale to the nearest 100 g. Height and head circumference was measured to the nearest 0.1 cm.

Gestational age, birth weight and anthropometric measurements at follow-up are shown in Table 1.

Socioeconomic status (SES) was calculated according to Hollingshead's Two Factor Index of Social Position.[35]

An estimate of intelligence quotient ($IQ_{est}$) was calculated using four subscales (vocabulary, arithmetic, block design and picture arrangement) of Wechsler Intelligence Scales (WISC-III).[36,37] We defined "low $IQ_{est}$" as below two standard deviations (SDs) of the control group mean value.

### 3.2. *Motor skills*

Each adolescent was tested with the Movement Assessment Battery for Children (Movement ABC)[38] by a physiotherapist (KAIE). The Movement ABC consists of eight items, scored between zero (optimal score) and five, and grouped as three subscores: manual dexterity, ball skills and static/dynamic balance. Scores below the 5th centile indicate definite motor problems and scores below the 15th centile indicate borderline motor problems.[38] We used the highest age band, designed for 11–12-year-old children. Since the study population was examined at 14 years of age, we used the 5th and 15th centile derived from all adolescents in the control group who met for motor assessment ($n = 81$). This corresponded to a total score of 14 and 10.5, well in accordance with the 5th and 15th centile in the manual.

### 3.3. *Visual functions*

All visual examinations were performed by a paediatric ophthalmologist (SL). In addition to the following examinations, subjects were also examined in a split lamp and with indirect binocular ophthalmoscopy.

#### 3.3.1. *Visual acuity*

Binocular distance visual acuity was examined by a Snellen letter chart at 4 m distance. Two VLBW adolescents were tested with Lea Hyvärinen symbols test[39] for distance due to problems with naming letters.

Visual acuity was assessed both with own (if any) correction, and also with best correction after subjective refraction. Poor visual acuity was defined as visual acuity below 1.0 Snellen decimals.

#### 3.3.2. *Contrast sensitivity*

Contrast sensitivity was assessed by the Vistech contrast sensitivity chart for near at 40 cm distance.[40] Both eyes were tested monocularly. The Vistech chart tests at five frequencies: 1.5, 3, 6, 12, and 18 cycles per degree. At each frequency the lowest contrast at which the direction of lines could be detected was noted. A frequency was regarded as normal if the result was equal to, or better than, the minimum level designated as normal by the manufacturer of the test.[40] We defined poor contrast sensitivity as having one or more values below normal in at least one eye. Since visual acuity has been shown to correlate with contrast sensitivity in the higher frequencies,[41] analysis was also done excluding the 18 cycles per degree frequency in order to minimise the influence of visual acuity on the results.

#### 3.3.3. *Stereoacuity*

Stereoacuity was measured with the TNO test (Lameris Ootech BV, Nieuwegein). If a subject did not manage the easiest stereograms on the TNO test (480 s of arc), the Titmus test (Stereo Optical, Chicago, IL, USA), which examines stereoacuity up to 3600 s of arc, was used. Those who still did not manage to prove stereoacuity were tested with the Bagolini striated glasses at distance and near, and a positive Bagolini was given a numerical value larger than 3600 s of arc. We defined poor stereoacuity as above 240 s of arc.

#### 3.3.4. *Strabismus*

Strabismus was measured with the alternating prism cover test at distance and near. Presence of strabismus was defined as a heterophoria or heterotropia (i.e. manifest or latent strabismus) with any prism deviation below the 5th and

above the 95th centile in the control group; i.e. any esodeviation, exodeviations larger than −8 prism diopters (PD) at near, or −2 PD at distance and any vertical deviations.

#### 3.3.5. *Nystagmus*

Investigation for nystagmus was done in all directions of gaze, mono- and binocularly, as well as with magnification during examination in a split lamp. Only pathological nystagmus was included, cases of physiological end point nystagmus were not recorded as nystagmus.

#### 3.3.6. *Accommodation*

Accommodative amplitude was measured with a Royal Air Force (RAF) ruler. The adolescents were instructed to report when an image, which was slowly moved towards them, got sustainedly blurred. The mean value for the right and the left eye was used in the analysis in this study. Poor accommodation was defined as any value below the 5th centile in the control group, i.e. below 6.5 diopters.

#### 3.3.7. *Convergence*

The near point of break of convergence was measured with an RAF ruler. Poor convergence was defined as a near point of convergence larger than 10 cm.[42,43]

#### 3.3.8. *Visual perception*

Visual perception was assessed by the Visual Perception supplementary task of the Developmental Test of Visual-Motor Integration (VMI-IV)[44] by a psychologist. The VMI consists of 27 geometric designs in increasing order of difficulty that have to be copied. The Visual Perception task requires the adolescent to identify the exact match for as many as possible of the designs that he/she has copied earlier. The time limit to complete this task is three minutes. The number of correct performances was judged and scored according to the manual.[44] Poor performance was defined as a score below 22, corresponding to 1 SD below the mean in the control group.

#### 3.3.9. *Abnormality score*

An *abnormality score* was calculated as the sum of visual impairments, including distance visual acuity (best correction), contrast sensitivity, stereoacuity, strabismus, nystagmus, accommodation, convergence and visual perception. An abnormality score of zero was given if an adolescent did not have impairments in any of the visual functions, and the highest possible abnormality score of eight would indicate impairments in all functions.

### 3.4. *Ethics*

The Regional Committee for Medical Research Ethics approved the study protocol. Written informed consent was obtained from both adolescents and parents.

### 3.5. *Statistical analysis*

SPSS 13.0 was used for data analysis, and a significance level of 0.05 was chosen. Two-group comparisons were made using the Student's t-test for variables with a normal distribution and the Mann-Whitney U test for variables with a non-normal distribution. The chi-square test was used to analyse differences in proportions between groups.

We used odds ratio (OR) as an estimate of the relative risk of having motor problems in the low birth weight groups compared with the control group. The visual variables were used as dichotomous variables and entered separately in the model to calculate adjusted odds ratios. The abnormality score for visual problems was used as a continuous variable in the logistic regression model.

## 4. Results

### 4.1. *Background data (Table 1)*

The VLBW and SGA adolescents were shorter, lighter and had a smaller head circumference than control adolescents at follow-up (Table 1), whereas socioeconomic status did not differ between the groups (data not shown). There were seven (14%) VLBW (non-significant vs. controls), three (5%) SGA and three (4%) control adolescents with low $IQ_{est}$. Of these, four VLBW (non-significant vs. controls), one SGA and no control adolescents had motor problems (Total ABC score below the 5th centile).

### 4.2. *Motor skills (Tables 2 and 3)*

#### 4.2.1. *Definite motor problems*

The VLBW group had poorer median scores on the Movement ABC, both total score and all subscores (Table 2), and a higher proportion of adolescents in this group (22%) had definite motor problems (total ABC score below the 5th centile) compared with 3% in the control group (OR: 10.4; 95% CI: 2.2–49.4) (Table 3).

In the SGA group, the median scores on the Movement ABC did not differ significantly from the scores in the control group (Table 2). However, a higher proportion of SGA adolescents (13%) had definite motor problems (OR: 5.1; 95% CI: 1.0–25.8) (Table 3).

Both in the VLBW and the SGA group a higher proportion of adolescents had poor manual dexterity compared with the control group, whereas there were no significant group differences regarding ball skills. In the VLBW group a higher proportion of adolescents had poor balance compared with the control group (Table 3).

#### 4.2.2. *Borderline motor problems*

Forty-five percent of the VLBW group had borderline motor problems (total ABC score below the 15th centile) compared with 14% of the control group (OR: 5.2; 95% CI: 2.2–12.5) (Table 3). The VLBW group also had a higher proportion of adolescents with manual dexterity and balance scores below the 15th centile compared with the control group (Table 3). There was no difference in borderline motor problems, ball or balance problems between the SGA and the control group (Table 3). However, although not statistically significant, 27% of the SGA group had borderline manual dexterity compared with 15% in the control group (OR: 2.1, 95% CI: 0.9–5.0).

**Table 2 – Median scores and interquartile range of the Movement ABC in two groups of adolescents with low birth weight and a control group**

| | VLBW ($n = 51$) | | SGA ($n = 56$) | | Control ($n = 75$) | |
|---|---|---|---|---|---|---|
| Total ABC | 10.0 | (5.0–14.0)[a] | 5.3 | (4.0–9.5) | 6.5 | (3.0–9.0) |
| Manual dexterity | 1.5 | (0.5–3.5)[b] | 1.0 | (0.0–3.0) | 0.5 | (0.0–2.5) |
| Ball skills | 2.0 | (0.5–4.0)[b] | 1.0 | (0.0–2.0) | 1.0 | (0.0–2.5) |
| Static/dynamic balance | 5.0 | (3.0–7.5)[b] | 3.0 | (2.0–5.0) | 3.0 | (1.0–5.0) |

[a] $p < 0.001$.
[b] $p < 0.01$ vs. controls.

**Table 3 – Odds ratio (OR) with 95% confidence intervals (CI) as an estimate of the relative risk for definite and borderline motor problems in two groups of adolescents with low birth weight compared with a control group**

| | <5th centile | | <15th centile | |
|---|---|---|---|---|
| | *n* (%) | Crude OR (95% CI | *n* (%) | Crude OR (95% CI) |
| *Total ABC* | | | | |
| VLBW ($n = 49$) | 11 (22) | 10.4 (2.2–49.4) | 22 (45) | 5.2 (2.2–12.5) |
| SGA ($n = 56$) | 7 (13) | 5.1 (1.0–25.8) | 8 (14) | 1.1 (0.4–2.9) |
| Control ($n = 74$) | 2 (3) | 1.0 | 10 (14) | 1.0 |
| *Manual dexterity* | | | | |
| VLBW ($n = 51$) | 8 (16) | 4.4 (1.1–17.5) | 15 (29) | 2.4 (1.0–5.7) |
| SGA ($n = 56$) | 9 (16) | 4.5 (1.2–17.6) | 15 (27) | 2.1 (0.9–5.0) |
| Control ($n = 74$) | 3 (4) | 1.0 | 11 (15) | 1.0 |
| *Ball skills* | | | | |
| VLBW ($n = 51$) | 6 (12) | 3.2 (0.8–13.4) | 9 (18) | 1.8 (0.6–5.0) |
| SGA ($n = 56$) | 0 (0) | [a] | 3 (5) | 0.5 (0.1–1.9) |
| Control ($n = 75$) | 3 (4) | 1.0 | 8 (11) | 1.0 |
| *Static/dynamic balance* | | | | |
| VLBW ($n = 49$) | 11 (22) | 6.9 (1.8–26.4) | 12 (25) | 5.8 (1.7–19.1) |
| SGA ($n = 56$) | 6 (11) | 2.9 (0.7–12.1) | 6 (11) | 2.1 (0.6–7.9) |
| Control ($n = 75$) | 3 (4) | 1.0 | 4 (5) | 1.0 |

[a] OR cannot be computed due to the value 0 in one cell (no SGA adolescents had poor ball skills).

### 4.3. *Visual functions (Table 4 and Fig. 1)*

Table 4 shows the results of the ophthalmologic examination and the visual perception task in the three groups.

Poor *visual acuity* was significantly more frequent in the VLBW, than in the control group. Visual acuity ranged from 0.5 to 2.0 in the VLBW group, from 0.8 to 2.0 in the SGA group and from 1.0 to 2.0 in the control group. Mean visual acuity was 1.2 in the VLBW group and 1.3 in both the SGA and control group. The difference in means between VLBW and control group did not reach statistical significance.

A higher proportion of VLBW adolescents also had *strabismus* compared with the control group ($p < 0.05$).

The higher proportions of poor *contrast sensitivity* ($p = 0.07$), *nystagmus* ($p = 0.06$) and poor *visual perception* ($p = 0.06$) in the VLBW group did not reach statistical significance. The results for contrast sensitivity were unchanged when we excluded the 18 cycles per degree frequency, which may correlate with visual acuity.

*Stereoacuity*, *accommodation* and *convergence* did not differ between VLBW and control adolescents.

The SGA group did not differ from the control group in any of the visual functions.

Fig. 1 shows the abnormality score for visual impairments in each of the three groups. Whereas approximately 50% of SGA and control adolescents were free of visual impairments, this was the case for only 30% of the VLBW adolescents ($p = 0.05$ vs. controls). In the VLBW group, 22 (43%) adolescents had two or more visual impairments (i.e. abnormality score equal to or above two) compared with 10 (13%) in the control group ($p < 0.001$) and 8 (14%) in the SGA group (non-significant vs. controls) (Table 4).

The ophthalmologic examination did not reveal any major ocular pathology such as retinal detachments or cataracts. ROP screening had not yet started when these VLBW children were born, thus no information about their ROP status is available, although we know that no children in this study were treated with cryotherapy, and no

**Table 4 – Visual functions in two groups of adolescents with low birth weight compared with a control group**

| | VLBW ($n = 51$) $n$ (%) | SGA ($n = 56$) $n$ (%) | Control ($n = 75$) $n$ (%) |
|---|---|---|---|
| *Visual impairment* | | | |
| Visual acuity < 1.0 Snellen decimals | 4 (8)[b] | 1 (2) | 0 (0) |
| Poor contrast sensitivity | 23 (45) | 12 (21) | 22 (29) |
| Nystagmus | 3 (6) | 1 (2) | 0 (0) |
| Strabismus | 14 (28)[b] | 11 (20) | 8 (11) |
| Stereoacuity > 240 s of arc | 4 (8) | 3 (5) | 1 (1) |
| Accomodation < 6.5 D | 3 (6) | 2 (4) | 2 (3) |
| Convergence > 10 cm | 12 (24) | 4 (7) | 9 (12) |
| Visual perception < 1 SD | 14 (28) | 7 (13) | 10 (14) |
| *Abnormality score* | | | |
| ⩾1 Visual impairment(s) | 36 (71)[b] | 26 (46) | 40 (53) |
| ⩾2 Visual impairments | 22 (43)[a] | 8 (14) | 10 (13) |

[a] $p < 0.001$.
[b] $p \leqslant 0.05$ vs. controls.

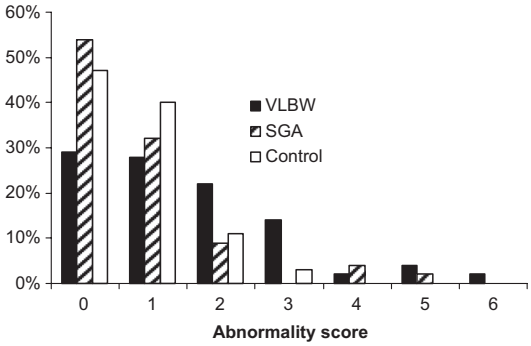


**Fig. 1 – Proportion of adolescents with no, one or more visual impairments. The x-axis shows the number of visual impairments (abnormality score) and the y-axis shows the proportion of adolescents in each group.**

sequelae of severe ROP were found at the examination at 14 years of age.

### 4.4. *Association between visual functions and motor skills (Tables 5 and 6)*

#### 4.4.1. *Total ABC score*

In the VLBW group, the OR for definite motor problems was reduced when we adjusted for each of the visual variables separately (Table 5). Of these, the greatest reduction in the crude OR of 10.4 was seen when we adjusted for visual acuity (adjusted OR: 7.8; 95% CI: 1.6–38.5). When we separately adjusted for the abnormality score the OR was reduced even more (adjusted OR: 6.8; 95% CI: 1.3–34.5) (Table 6). Still, the increased odds of having motor problems were significant.

In the SGA group, the greatest reduction in odds of having definite motor problems was observed when we adjusted for strabismus and nystagmus (Table 5). However, adjusting for the abnormality score did not change the odds of having definite motor problems (Table 6).

#### 4.4.2. *Manual dexterity*

Adolescents in the VLBW and the SGA group had about 4.5 times increased odds of having poor manual dexterity compared with the control group. In the VLBW group, OR was however no longer significantly higher when adjusting separately for visual acuity, strabismus, stereoacuity (Table 5) and the abnormality score (Table 6).

In the SGA group nystagmus and strabismus each reduced the odds of having manual dexterity problems from 4.5 to 4.0 (95% CI: 1.0–16.0), whereas the other visual variables only had small effects (Table 5) and the abnormality score did not have any effect on the OR (Table 6).

#### 4.4.3. *Ball skills*

In the VLBW group the crude OR of 3.2 (95% CI: 0.8–13.4) for having poor ball skills was reduced when we adjusted separately for each of the visual variables (Table 5) and for the abnormality score (Table 6).

None of the SGA adolescents had poor ball skills.

#### 4.4.4. *Static and dynamic balance*

The increased odds of having definite balance problems in the VLBW group were most reduced when we adjusted separately for visual acuity, nystagmus and stereoacuity (Table 5). Adjusting for the abnormality score reduced the OR to 4.9 (95% CI: 1.2–20.1) (Table 6). However, the odds of having poor balance were still significantly increased after adjustment (Tables 5 and 6).

The SGA group did not have significantly increased odds of having poor balance.

#### 4.4.5. *Borderline motor problems*

The odds of having a total ABC score below the 15th centile were also influenced by visual functions, although the percentage reduction in OR was somewhat smaller (data not shown). Again, the greatest reduction in OR was found when adjusting for visual acuity in the VLBW group (adjusted OR: 4.7; 95% CI: 1.9–11.4). The effect of the other visual variables on borderline manual dexterity, ball skills and balance were essentially the same as for definite problems (data not shown). Table 6 shows that the abnormality score reduced the odds considerably in the VLBW group, both for the total ABC score and for all subscores.

In the SGA group, the odds of borderline motor problems, both total ABC and all subscores, were non-significant compared with the control group, and relatively unaffected by visual impairments (data not shown) and the abnormality score (Table 6).

**Table 5 – Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) as an estimate of the relative risk of definite motor problems in two groups of adolescents with low birth weight compared with a control group**

| | <5th centile | Adjusted OR (95% CI) for each of the visual variables separately | | | | | |
|---|---|---|---|---|---|---|---|
| | Crude OR (95% CI) | Visual acuity | Contrast sensitivity | Nystagmus | Strabismus | Stereoacuity | Visual perception |
| *Total ABC* | | | | | | | |
| VLBW | 10.4 (2.2–49.4) | 7.8 (1.6–38.5) | 9.4 (1.9–45.8) | 8.8 (1.8–42.6) | 9.1 (1.9–44.0) | 9.4 (1.8–50.3) | 9.7 (2.0–46.7) |
| SGA | 5.1 (1.0–25.8) | 5.3 (1.0–26.4) | 4.7 (0.9–24.1) | 4.4 (0.9–22.7) | 4.2 (0.8–21.9) | 4.8 (0.9–24.4) | 5.4 (1.0–28.0) |
| Control | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| *Manual dexterity* | | | | | | | |
| VLBW | 4.4 (1.1–17.5) | 2.8 (0.6–12.4) | 4.3 (1.1–17.2) | 4.0 (1.0–16.5) | 3.8 (0.9–15.6) | 3.5 (0.8–14.9) | 5.4 (1.1–27.6) |
| SGA | 4.5 (1.2–17.6) | 4.6 (1.2–18.0) | 4.2 (1.1–16.6) | 4.0 (1.0–16.0) | 4.0 (1.0–16.0) | 4.3 (1.1–17.0) | 7.8 (1.5–39.6) |
| Control | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| *Ball skills* | | | | | | | |
| VLBW | 3.2 (0.8–13.4) | 2.2 (0.5–10.5) | 2.9 (0.7–12.3) | 2.2 (0.5–10.2) | 2.8 (0.6–12.3) | 2.3 (0.5–10.7) | 2.6 (0.6–11.3) |
| SGA | [a] | [a] | [a] | [a] | [a] | [a] | [a] |
| Control | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| *Static/dynamic balance* | | | | | | | |
| VLBW | 6.9 (1.8–26.4) | 6.0 (1.5–23.5) | 6.3 (1.6–24.4) | 5.8 (1.5–22.9) | 6.6 (1.7–25.8) | 6.0 (1.4–24.8) | 6.5 (1.7–25.3) |
| SGA | 2.9 (0.7–12.1) | 2.9 (0.7–12.3) | 2.6 (0.6–11.2) | 2.9 (0.7–12.3) | 2.5 (0.6–10.9) | 3.0 (0.7–12.7) | 2.8 (0.7–12.0) |
| Control | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |

[a] OR cannot be computed due to the value 0 in one cell (no SGA adolescents had poor ball skills).

#### 4.4.6. *Visual variables that did not affect the odds of motor problems*

Accommodation and convergence did not reduce the odds of having motor problems in any of the low birth weight groups.

#### 4.4.7. *Possible confounders*

The results were essentially the same when including sex or low $IQ_{est}$ as possible confounders of the association between visual functions and motor skills (data not shown).

## 5. Discussion

In this study, we found that visual impairments significantly influenced motor problems among VLBW adolescents. In particular, problems in manual dexterity were mainly affected by impairments in vision. However, the risk of total motor and balance problems in this group were still increased after adjustment for visual impairments.

Among term SGA adolescents, motor problems were essentially unaffected by visual impairments.

One physiotherapist did all motor evaluations, one paediatric ophthalmologist performed all visual examinations and one psychologist did all neuropsychological tests, avoiding any problems of inter-tester reliability. The three examiners were blinded to group assignment and to the results of the other assessments, reducing the risk of information bias.

In all, 33% of eligible adolescents did not meet for follow-up. However, it is unlikely that the association between vision and motor skills in these adolescents were systematically different from those who met.

Since we wanted to examine associations between visual functions and motor skills that were not determined by extreme abnormal values, we excluded children with CP. Moreover, the results were essentially the same when controlling for sex and low $IQ_{est}$ as possible confounders.

Movement ABC is standardised up to 12 years of age, whereas we have studied 14-year-old children. A ceiling effect could mask subtle differences in motor skills. However, a ceiling effect would theoretically affect mean and top centile values, whereas we have studied adolescents with scores below the 5th and 15th centile derived from our own control group. Thus, in our opinion, a possible ceiling effect is unlikely to influence our results.

The 5th centile cut-off for defining motor problems is common[2,5,8,11] and in accordance with the Movement ABC manual.[38] We also included analysis with a less strict cut-off, i.e. scores below the 15th centile, which indicates borderline motor problems. These analyses gave essentially the same results as using the 5th centile, which gives further support to our conclusions.

Other studies of VLBW populations have also reported associations between motor problems and visual functions, in particular stereoacuity,[2,10,11,15] visual acuity, contrast sensitivity and strabismus.[10,11] Which of these that are most important for motor skills varies between the studies. In our study, total motor problems were most strongly associated with impaired visual acuity, but apart form this observation the material is not large enough to safely allow speculation on the internal relative importance of the other visual variables.

The number of participants in this study was too small to include more than two variables in regression analysis. However, when we adjusted for the abnormality score

**Table 6 – Crude odds ratios (OR) with 95% confidence intervals (CI) as an estimate of the relative risk of definite and borderline motor problems and adjusted for abnormality score for visual impairments in two groups of adolescents with low birth weight compared with a control group**

| | <5th centile | | <15th centile | |
|---|---|---|---|---|
| | Crude OR (95% CI) | Adjusted OR (95% CI) | Crude OR (95% CI) | Adjusted OR (95% CI) |
| *Total ABC* | | | | |
| VLBW | 10.4 (2.2–49.4) | 6.8 (1.3–34.5) | 5.2 (2.2–12.5) | 4.0 (1.6–10.1) |
| SGA | 5.1 (1.0–25.8) | 5.1 (1.0–25.6) | 1.1 (0.4–2.9) | 1.1 (0.4–2.9) |
| Control | 1.0 | 1.0 | 1.0 | 1.0 |
| *Manual dexterity* | | | | |
| VLBW | 4.4 (1.1–17.5) | 3.0 (0.7–13.4) | 2.4 (1.0–5.7) | 1.4 (0.5–3.8) |
| SGA | 4.5 (1.2–17.6) | 4.5 (1.2–17.5) | 2.1 (0.9–5.0) | 2.1 (0.9–5.0) |
| Control | 1.0 | 1.0 | 1.0 | 1.0 |
| *Ball skills* | | | | |
| VLBW | 3.2 (0.8–13.4) | 1.7 (0.3–8.4) | 1.8 (0.6–5.0) | 1.2 (0.4–3.8) |
| SGA | [a] | [a] | 0.5 (0.1–1.9) | 0.4 (0.1–1.8) |
| Control | 1.0 | 1.0 | 1.0 | 1.0 |
| *Static/dynamic balance* | | | | |
| VLBW | 6.9 (1.8–26.4) | 4.9 (1.2–20.1) | 5.8 (1.7–19.1) | 4.4 (1.2–15.7) |
| SGA | 2.9 (0.7–12.1) | 2.9 (0.7–12.1) | 2.1 (0.6–7.9) | 2.1 (0.6–8.0) |
| Control | 1.0 | 1.0 | 1.0 | 1.0 |

[a] OR cannot be computed due to the value 0 in one cell (no SGA adolescents had poor ball skills).

(i.e. the sum score of all visual variables), the odds of having motor problems in the VLBW group were reduced more than by each visual variable separately. Our results therefore indicate that several visual functions are important for motor problems, and that additive effects may play an important role. None the less, we found that even after adjustment for visual impairments, adolescents born VLBW had a substantially increased risk of motor problems in general (total ABC) and in static and dynamic balance in particular.

There are several ways in which visual abilities may affect motor skills in VLBW adolescents. Vision plays an essential role in early motor learning and development,[27,45,46] and tends to dominate as a source of sensory information in the control of coordinated, voluntary movement.[28] Even in persons with otherwise normal neurodevelopment, visual deficits may directly affect their motor skills, as seen in elderly populations.[27,47]

Motor skills seem to be affected by the whole range of visual acuity, from the most severe effects seen in congenital blindness[45,46] to an association between superior motor ability and visual acuity seen in athletes.[48] Subtle visual disturbances, such as deficits in stereoacuity and contrast sensitivity, are also important.[10] Good stereoacuity is known to be an advantage especially at near distance and in tasks requiring complex hand–eye coordination.[48–50] Contrast sensitivity is important in control of movement, since it allows the detection of shape and edges of objects.[27] Improvement in contrast sensitivity has been shown to improve visually guided behaviour,[51] and reduction in contrast sensitivity on the other hand has been shown to affect tasks requiring distance judgements and mobility.[52]

There is a well known increased prevalence of brain lesions, especially periventricular leucomalacia (PVL), in VLBW children, which is not found in term SGA and control children.[53] Both the optic radiations and the corticospinal motor tracts pass through the periventricular white matter and therefore PVL is strongly associated with cerebral visual impairment as well as cerebral palsy.[54] So, in addition to the above-mentioned cause-and-effect theory, with visual impairments leading to motor deficits, the association between visual and motor problems in the VLBW group may be of a shared common aetiology. This point of view has also been advocated by other authors.[10,11] Cooke et al.[11] claim that the association of poor visual acuity and low contrast sensitivity with minor motor impairment suggests a diffuse lesion such as defective myelination of the cerebrum, which has been shown to occur in preterm infants.[55]

Finally, our finding of increased total motor and balance problems even after adjusting for visual deficits, may suggest that specific motor areas, independent of vision, have also been insulted.

We are not aware of other studies describing the association between vision and motor skills in SGA children or adolescents. Our results suggest that the motor problems in SGA adolescents cannot be explained by poor visual functions.

We have previously argued that the motor problems in term SGA adolescents may have a different origin than those of VLBW adolescents[9,33] The different effects of visual impairments on motor problems in the current study support this. Martinussen et al.[56] found reduced brain volume in SGA adolescents; however there is no evidence of increased cortical thinness[56] or increased prevalence of white matter

reduction, ventricular dilatation or thinning of corpus callosum compared with controls.[53]

Animal studies have shown that growth restriction before and after birth may result in reduced myelination and weight of the cerebellum.[57,58] In the previous study we speculated whether this mechanism may be responsible for the manual dexterity problems seen in the SGA group.[9] If this is the case, it may be reasonable to assume that deficits in visual functions may not influence the motor problems in this group, since vision and visual perception is predominantly a cerebral function.[59]

It has also been shown in animal studies that intrauterine growth retardation (IUGR) does not affect all cerebral metabolic pathways equally[60] and perhaps visual functions are dependent on pathways more resilient to IUGR.

Interestingly, the proportions of SGA adolescents with definite and borderline motor problems were approximately the same. This suggests that there is a subgroup of the SGA adolescents with very poor performance, especially in manual dexterity, whereas the rest of the SGA group does not have motor problems.

The strong associations between visual impairments and motor problems found in VLBW children in this and previous studies[2,10,11,15] suggest that visual functions are of importance for motor skills in this population. The nature of this association may be both one of cause and effect (visual impairment causing motor problems) and one of a shared common aetiology.

Our results may contribute to an increased understanding among caregivers, teachers and health professionals that it is insufficient to address visual and motor problems independently. Instead, combinations of minor impairments in different functions need to be met by a multidisciplinary approach. Especially, the findings highlight the importance of a wide assessment of visual functions in VLBW children, since having several visual impairments is more frequent among VLBW adolescents.

Although our study was not set up to investigate this, it seems possible that some visual problems may be improved with adequate treatment, for instance optimal correction for refractive errors, thereby improving motor skills.

In conclusion, visual impairments influence the motor problems in VLBW adolescents, whereas the motor problems in SGA adolescents seem to be relatively unaffected by visual impairments.

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# Paper IV

# Corpus callosum - connecting visual acuity and white matter microstructure in prematurity.

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***Abstract***

Premature birth is associated with visual impairments, due to both cerebral and ocular pathology. This study examined the relationship between cerebral white matter microstructure, evaluated by diffusion tensor imaging (DTI), and visual function, in 30 adolescents born prematurely with birth weight ≤ 1500g and a control group of 45 term born adolescents. Visual acuity correlated positively to diffusion anisotropy in the posterior part of the corpus callosum, the splenium, of the prematurely born teenagers. Callosal visual connections may play a more important role in the development of good visual acuity than previously acknowledged.

***Keywords:*** Corpus callosum, splenium, visual acuity, periventricular white matter injury, prematurity

## *Introduction*

Preterm birth and very low birth weight reduces the child's prospects of normal visual development, greatly increasing the risk of blindness and severely reduced vision(Crofts et al., 1998). There is also a high prevalence of less dramatically reduced, but nevertheless subnormal visual acuity (below 1.0 in Snellen decimals) in preterm populations (Fledelius, 1981, Lindqvist et al., 2007)

Magnetic resonance imaging (MRI) has over the last two decades improved our knowledge of how severe visual disability in prematurely born children can be caused by cerebral lesions such as periventricular leucomalacia (Eken et al., 1995, Jacobson et al., 1998) Although the relationship between major neurological disabilities and periventricular leucomalacia is strong (Olsen et al., 1997), correlations between brain lesions and minor neurodevelopmental dysfunctions have been more difficult to detect (Counsell et al., 2003, Krägeloh-Mann et al., 1999, Olsen et al., 1997). It has been suggested that the slight reduction in visual acuity commonly seen in ex-prematures may have a cerebral origin even with normal conventional MRI findings (Cooke et al., 2004, Hellgren et al., 2007, Holmström et al., 1999, Pike et al., 1994). The use of advanced imaging techniques such as diffusion tensor imaging (DTI) has been proposed to help unravel possible correlations between neurological dysfunction and cerebral pathology in these high risk children (Hellgren et al., 2007, Hüppi and Dubois, 2006a, Nagy et al., 2003,Toosy et al., 2004);. DTI is a very sensitive method for investigating the integrity of white matter microstructure(Hüppi and Dubois, 2006a) by measuring and visualising the direction and the magnitude of water movement at the molecular level (Brownian motions) in brain tissue (Basser et al., 1994). DTI

findings are commonly reported as changes in the fractional anisotropy (FA) and as mean diffusion (MD). In white matter, diffusion is largest parallel to the main direction of axons, and smaller perpendicular to them, where cell membranes and myelin sheaths restrict the diffusion of water molecules. Higher FA values signify a high degree of directionality (i.e. a large portion of the available water molecules move in one direction) and may indicate better axonal organization and maturation (Hüppi and Dubois, 2006b). MD signifies the mean level of diffusion in the three dimensions. In water, diffusion is free in all directions, producing high MD values. MD will be lower in structures with more cellular content.

FA values of white matter have been shown to be lower in VLBW than in control subjects, and lower values have been correlated to perceptual, cognitive, motor and mental health impairments (Skranes et al., 2007). It has also been possible to correlate reading ability and working memory to DTI findings in specific anatomical areas of the brain in non-VLBW populations (Klingberg et al., 2000, Nagy et al., 2004). However, no study has previously investigated the potential relationship between visual acuity and white matter integrity using DTI.

In normal adolescent and young adult populations, visual acuity will be 1.0 (in Snellen decimals) or better in approximately 95% of the subjects. Thus, 1.0 represents the lower limit of normality, rather than the expected value (Elliott et al., 1995, Fledelius, 1981, Frisén and Frisén, 1981). In an earlier study we have reported monocular distance visual acuity (with best correction) below 1.0 in approximately a third of adolescents with VLBW, compared to 4 % of control subjects (Lindqvist et al., 2007). The aim of this study was to examine a possible correlation between brain DTI findings and visual acuity, as well as contrast sensitivity, near point of convergence, stereopsis and strabismus, in a group of

VLBW and control adolescents, using voxel-wise regression analysis, to test the hypothesis that there is a relationship between white matter microstructure and vision. Comparing visual abilities and white matter microstructure in children born preterm may help us better understand the origin of impairments in prematurity, as well as increase our knowledge of normal visual development.

## *Methods*

### Subjects

This is a population based follow-up study of a group of prematurely born 14 year old adolescents with very low birth weight (VLBW), and an age-matched control group of adolescents born at term with normal birth weight.

VLBW was defined by a birth weight of 1500 g or less. In 1986–88, 121 VLBW children from the two Norwegian counties of North- and South-Trondelag were admitted to the neonatal intensive care unit at the University Hospital in Trondheim. Of the 121 admitted children, 33 died, one child with trisomy 21 was excluded and six had moved out of the region at the time of assessments. Of the remaining 81, 46 (57 %) attended both the cerebral MRI and the ophthalmological examination. The DTI data were excluded in 16 cases due to signal dropouts and distortions- most caused by the use of dental braces, motion or incorrect slice position. In 30 VLBW subjects (14 males and 16 females) both DTI and ophthalmological data were available. There were no differences in birth weight, gestational age, birth head circumference, anthropometrics at examination, MRI assessment age, mother's education and social class between the participating VLBW adolescents with and without DTI available. Four of the VLBW subjects had mild to moderate cerebral palsy (three walking and one not walking spastic diplegia). As the aim of our study was to find a correlation between visual function

and varying degrees of structural integrity of white matter we did not exclude participants with known brain lesions.

The control group was born in the Trondheim region from the same birth cohorts as the VLBW children, and comprised a population based random sample of 122 term born children with a birth weight equal to or above the 10$^{th}$ centile for gestational age. At follow-up, ten had moved and two were excluded due to congenital malformations (one Goldenhaar syndrome and one congenital anomaly of the urinary system). Of the remaining 110, 55 (50 %) consented to both MRI scanning and ophthalmological examination. Ten MRI scans had to be excluded (because of dental braces or missing imaging sequences), leaving 45 MRI investigations suitable for DTI analysis (17 males and 28 females). Some characteristics of the children in the two study groups are summarized in table 1.

The study was carried out in keeping with the guidelines of the Declaration of Helsinki. The Regional Committee for Medical Research Ethics approved the study protocol. Written informed consent was obtained from both adolescents and parents. The Norwegian Data Inspectorate assigned the license for keeping a data register with personal information.

Table 1. Characteristics of the groups

| | Birth weight g [a] | GA at birth weeks [a] | Distance visual acuity, Snellen decimal mean (RE+LE)/2 [a] | Socio-economic status at 14 years [b] | Age at eye exam [a] | Age at MRI [a] |
|---|---|---|---|---|---|---|
| VLBW (n =30) | 1234 (219) [550-1500] p0.000 | 29.3 (2.8) [24-35] p0.000 | 1.08 (0.29) [0.25-1.6] p0.029 | 3.27 (3.5) [1-5] p0.206 | 14.5 (0.37) [13.6-15.4] p0.5 | 15.1 (0.62)[14.1-16.9] p0.07 |
| Control (n =45) | 3691 (437) [2670-4710] | 39.5 (1.1) [37-42] | 1.21 (0.16) [0.9-1.5.9] | 3.69 (4) [2-5] | 14.6 (0.49) [13.6-16.8] | 15.3 (0.45) [14.2-16.4] |

[a] Data given as mean (SD)[min-max values] T-test [b] Data given as mean (median) [min-max values] Mann Whitney test [c] Data given as n (% ) Fischer exact test . All p values vs control.

**Assessment**

We have previously reported that visual acuity, contrast sensitivity and several binocular functions were poorer in the VLBW than in the control group, and details of ophthalmological assessment is available in those publications (Lindqvist et al., 2007, Lindqvist et al., 2008). No media opacities were found, none had retinal pathology suggestive of earlier severe retinopathy of prematurity and none had been treated in infancy with cryo- or laser-therapy for severe retinopathy of prematurity(Lindqvist et al., 2007). The ophthalmologist performing the examination was blinded to group assignment.

The image acquisition was performed approximately half a year after the ophthalmological exam (see table 1), with control and VLBW adolescents in a random mix. Technicians and radiologists were blinded to group allocation during image acquisition.

**Selection and processing of visual variables**

The visual variables with statistically significant differences in performance between the VLBW and the control group, which were selected for analysis of correlations to FA and MD values were: best corrected distance visual acuity, near point of convergence, stereopsis (all as continuous variables), contrast sensitivity (as a discrete variable) and strabismus (as a dichotome variable). The mean value of the best corrected distance visual acuity of the right and left eye was used, since information in all visual fibres post chiasm will be a mixture of equal proportions originating in the right and left eye.

**Image Acquisition**

All subjects were scanned in a 1.5 T Siemens Magnetom Symphony with Quantum gradients (30 mT/m) and a quadrature head coil. The protocol consisted of a structural $T_1$-weighted magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence with TR = 7.1 ms, TE = 3.45 ms, TI = 1000 ms, flip angle 7°, FOV 256 x 256 mm and slab thickness 170 mm. The acquisition matrix was 256 x 192 x 128, reconstructed to 256 x 256 x 128, giving a reconstructed voxel resolution of 1 x 1 x 1.33 mm. The DTI sequence was a single-shot balanced-echo EPI sequence that significantly reduces eddy current distortions compared to a Stejskal-Tanner sequence (Reese, Heid, Weisskoff & Wedeen, 2003). Timing parameters were TR = 6000 ms and TE = 97 ms. The 20 contiguous transverse slices with a slice thickness of 5 mm were aligned parallel to the anterior commissure and posterior commissure plane and covered all but the topmost part of the brain. The FOV was 228 x 228 mm, acquisition matrix 96 x 128, reconstructed to 128 x 128, giving a reconstructed in-plane resolution of 1.78 x 1.78 mm. For each slice, one image without diffusion weighting, and six images with diffusion gradients (b = 1000

s/mm$^2$) applied along six non-collinear directions were acquired. The DTI sequence was repeated six times for increased signal to noise ratio.

**Calculation of diffusion tensor and scalar indices**

The six DTI acquisitions acquired for each subject were first co registered to the first non-diffusion weighted volume ($S_0$ volume) using a mutual information cost function and a 12-parameter affine transformation. This procedure corrects for patient motion and eddy current distortions. The FLIRT program, part of the FSL program package from the Image Analysis Group, FMRIB, Oxford, UK (http://www.fmrib.ox.ac.uk/fsl), was used for the image registration. After image registration, the six acquisitions were averaged, the diffusion tensor diagonalized, and the FA maps calculated from the eigenvalues. In addition to the FA maps, the mean of the six $S_0$-volumes, the MD maps and the axial and radial diffusivity maps were calculated for each subject. Axial diffusivity measures the magnitude of water diffusion parallel to the voxel of interest and radial diffusivity is the mean of the two diffusion eigenvalues perpendicular to the axial diffusion. The mean of the $S_0$-volumes was later used for co-registering the FA maps to the anatomical images.

**Post-processing of diffusion maps and anatomical images**

We used the SPM2 package (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK, http://www.fil.ion.ucl.uk/spm) for the subsequent post-processing and statistical analysis.

The standard templates supplied with SPM2 are not optimal for younger subjects (Wilke et al., 2003), and a study-specific template generated from the anatomical $T_1$ images of all the subjects in the study was used to provide better normalization of the images. The transformation derived from normalizing the $T_1$ images was then

applied to the co registered FA images, thus normalizing the FA maps. Finally the FA maps were resampled to 2 $mm^3$ isotropic voxels using trilinear interpolation. The axial and radial diffusion maps were normalized in the same way as the FA maps. Additional details regarding the processing of the images have been published previously (Vangberg et al., 2006).

**Statistical analysis**

The normalized diffusivity maps were smoothed with a four mm FWHM (full width at half maximum) Gaussian kernel prior to statistical analysis. An FA value of 0.15 provides a reliable threshold between grey and white matter (Jones et al., 1999), and we therefore only analyzed the FA maps in the areas where all subjects included in the analysis had a FA value greater than 0.15. The linear correlation between the normalised diffusion maps (FA or MD) and the different visual measurement scores were calculated in a voxelwise manner. Only clusters with more than 10 contiguous voxels were reported. The parametric maps were thresholded with a false discovery rate (FDR)-corrected (Benjamin and Hochberg, 1995) threshold of 0,05.

**Confirmatory ROI analysis**

A confirmatory region of interest (ROI) analysis was performed by placing a spherical ROI with a radius of two mm (seven voxels of two $mm^3$) in the centre of the anatomical area with the most significant correlation from the regression analysis. The ROIs were created with MANGO (Research Imaging Center, University of Texas Health Science Centre San Antonio, USA; http://ric.uthscsa.edu/mango/). ROIs were drawn on the normalized $S_0$-images for each subject, and later used to extract values from the FA maps, radial diffusion maps and axial diffusion maps.

## *Results*

### Visual acuity

Mean best corrected distance visual acuity was below 1.0 (Snellen decimals) in nine (30 %) VLBW subjects, compared to four (9 %) of the control subjects (p = 0.027, Fisher exact). The 50 % in both groups performing best did not differ, as can be seen in figure 1, where the top performers overlap completely. However, among the worst 50 % in both groups there was a significant difference (p<0.000 Mann Whitney *U*).

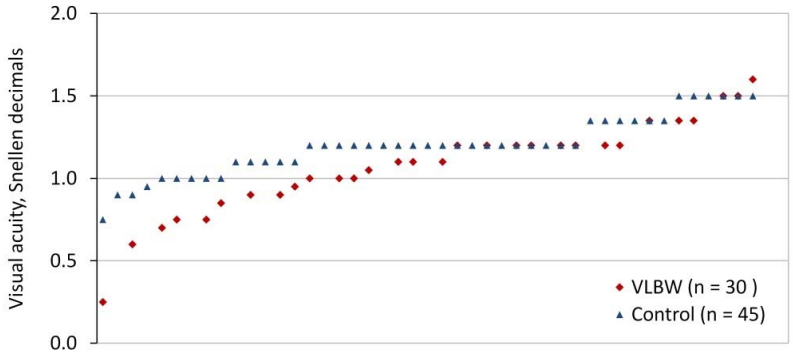



Figure 1. Visual acuity of the participants. Best corrected distance visual acuity, mean of results of monocular testing of right and left eye. Results given as Snellen decimals.

### FA values and visual acuity

Voxels in the posterior part of the corpus callosum, the splenium, showed significant correlation between visual acuity in the VLBW group and FA values($r^2$ =0.50 in the voxel with highest significance). See figure 2. This correlation was achieved by a positive correlation ($r^2$=0.54) between visual acuity and axial diffusivity, and a weaker negative correlation ($r^2$=0.34) between acuity and radial

diffusivity. The findings were confirmed by an individually placed region of interest analysis in the splenium. In the control group, no correlations between visual acuity and FA values were seen.

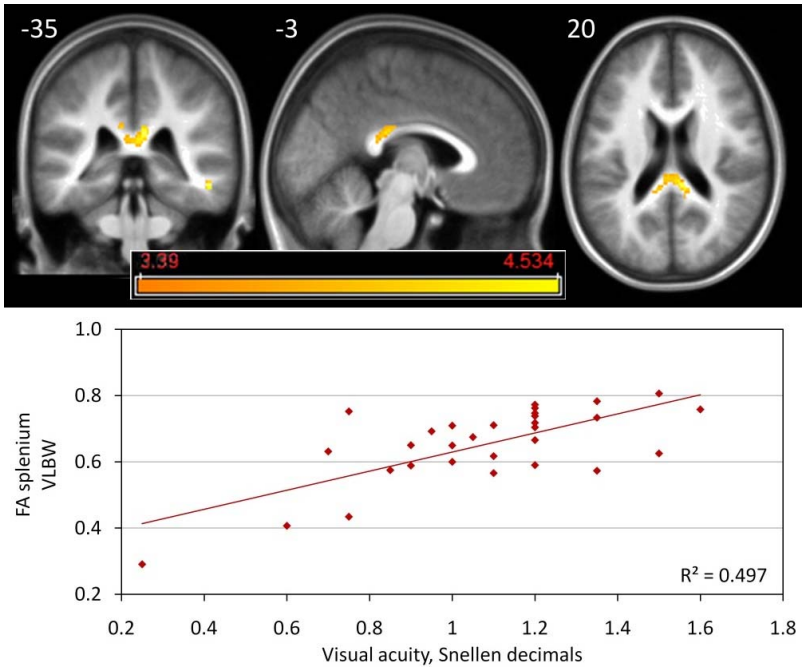



Figure 2. The relationship between visual acuity and FA values in VLBW adolescents, showing an area of significant correlation in the splenium part of the corpus callosum. Voxels with significant correlation p (FDR) < 0.05 (t > 3.87 ) and 10 voxels cut-off are shown in yellow. The anatomical underlay is the mean of the normalized anatomical images for the study groups. In the coronal and transversal slices, the left side in the image corresponds to the subject's left side (neurological convention). Coordinates are in millimetres and refer to slice position in Montreal Neurological Institute (MNI) space. The colour bar represents the t score. The graph shows the linear regression plot in the most significant voxel.

**MD and visual acuity**

In the control group there were no correlation between visual acuity and diffusion values using the FDR corrected threshold. However using a less stringent threshold of $p < 0.001$ and no threshold on the FA values, there was a negative correlation ($r^2=0.59$) between visual acuity and MD values in occipital periventricular white matter in the VLBW group. See figure 3.

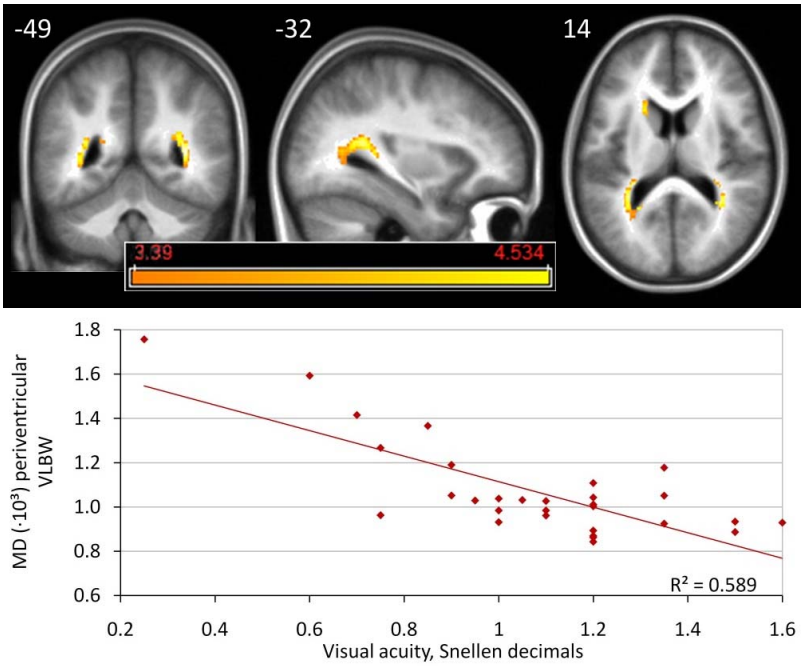
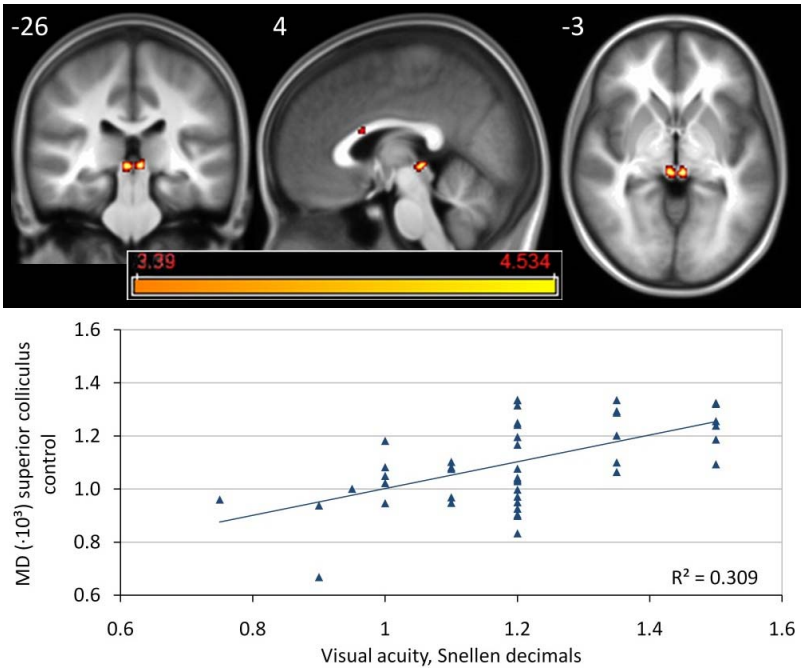



Figure 3. The relationship between visual acuity and MD in the VLBW group, showing significant correlation in the posterior periventricular regions. Voxels that correlated significantly, p (FDR) < 0.05 (t > 3.55 ) and 10 voxels cut-off are shown in yellow. The anatomical underlay is the mean of the normalized anatomical images for the study groups. In the coronal and transversal slices, the left side in the image corresponds to the subject's left side (neurological convention). Coordinates are in millimetres and refer to slice position in Montreal Neurological Institute (MNI) space. The colour bar represents the t score. The graph shows the linear regression plot in the most significant voxel.

In the control group a positive correlation ($r^2$=0.31) between visual acuity and MD values was seen in both superior colliculi. See figure 4.

**Other visual variables**

Near point of convergence, strabismus, stereopsis, and contrast sensitivity did not correlate significantly to diffusion (neither FA, nor MD values) in either group.




Figur 4. The relationship between visual acuity and MD in the control group, showing significant correlation in the superior colliculi. Voxels that correlated significantly ($p < 0.001$, $t > 3.29$) with visual acuity are presented in yellow using a 10 voxels cut-off. The anatomical underlay is the mean of the normalized anatomical images for the study groups. In the coronal and transversal slices, the left side in the image corresponds to the subject's left side (neurological convention). Coordinates are in millimetres and refer to slice position in Montreal Neurological Institute (MNI) space. The colour bar represents the t score. The graph shows the linear regression plot in the most significant voxel.

## *Discussion*

The main finding of this study is a relationship between visual acuity and structural integrity (indicated by FA values) in the posterior part of the corpus callosum, the splenium, in prematurely born adolescents with VLBW. We find that subjects in the VLBW group with low visual acuity also have low FA values in the splenium. No such correlation was seen in the control group. This strengthens the assumption that the correlation in the VLBW group is connected to adverse events related to prematurity.

We will discuss this finding in relation to two questions: what is the relationship between premature birth and structural changes in the corpus callosum, and what is the connection between visual acuity and the corpus callosum?

### Relationship between premature birth and structural changes in the corpus callosum

Periventricular white matter, including the corpus callosum, is particularly prone to perinatal injury in prematurity (Volpe, 2008b). This injury seems to be mediated to a large extent by damage to pre-oligodendrocytes, a cell population particularly abundant around gestational week 23-32, and also very vulnerable to hypoxic-ischemic and/or inflammatory processes(Back et al., 2001). Other risk factors in prematurity are vascular immaturity and low blood flow to deep cerebral white matter and in addition immature autoregulation of cerebral blood flow (Volpe, 2008a) . Finally the germinal matrix in the subependymal layers of the lateral ventricles, a source of both neurons and glia cells in the developing brain is, during this period, highly vascular and prone to hemorrhage (Goldman et al., 1986, Gressens, 1992,Mo et al., 2007,Volpe, 2003). During the later half of pregnancy, the periventricular area in humans contains “crossroads areas”, through which growing

callosal cortico-cortical axons intersect. These crossroad areas are rich in guidance factors crucial for the spatial arrangement of axons (Judas et al., 2005). An injury in this region during the later half of pregnancy, or in the neonatal period for preterms, has the potential to severely disturb the midline crossing of callosal axons (Benjak et al., 2008,Deng and Elberger, 2001, Judas et al., 2005, Silver et al., 1982, Smith et al., 2006). Furthermore, preterm lesions in the subventricular zone and periventricular area may harm populations of future callosal cells directly (Gressens, 1992, Judas et al., 2005,Volpe, 1996). The vulnerability of the immature corpus callosum has also been shown in a rodent model of perinatal ischemic-hypoxic injury: severe axonal degeneration and deterioration of fibre orientation was seen in the corpus callosum as early as three hours after an ischemic-hypoxic event (Skoff et al., 2001).

The thinning of the splenium often encountered in very preterm children need not be casued by direct damage, such as described above, but could be a consequence of the general loss of periventricular white matter (Caldu et al., 2006, Nagy et al., 2003). Due to antero-and retrograde degeneration, injuries to *any* visual fibres destined to make interhemispheric connections will eventually converge in the splenium of the corpus callosum (Neil and Inder, 2006,Yoshida et al., 2004), thereby decreasing FA values in this area. However, in children born at term with unilateral perinatal periventricular white matter injury the corpus callosum is reported to be unaffected, although there may be significant changes in DTI fibre count on the lesional side, involving corticospinal tract, corticobulbar tract and superior thalamic radiation (Thomas et al., 2005). This is contrary to findings in *premature* children, where changes in the corpus callosum are often reported as equal or worse than those of general white matter (Caldu et al., 2006, Nagae et al., 2007, Skranes et al., 2007). This suggest that not all the damage seen in the corpus callosum of prematures is due

to antero- and retrograde degeneration. Neuronal perinatal preterm cerebral injury appears to be more harmful for callosal fibres than injury occurring at term.

In our study, axial diffusivity and radial diffusivity both correlated to visual acuity in the splenium of the VLBW subjects, indicating that both disturbed axonal growth, loss of axons and impaired myelination may contribute to the functional impairment (Song et al., 2005, Song et al., 2003, Song et al., 2002).

**Relationship between visual acuity and the corpus callosum**

It has been known for more than a century that the posterior part of the corpus callosum transfers visual information (Dejerine and Dejerine-Klumpke, 1895) and approximately 15 % of all fibres originating in the occipital lobes contribute to callosal pathways (Dougherty et al., 2005). With such large amount of neural capacity devoted to the transhemispheric access of visual data, it is not surprising to find a correlation between a visual function and the microstructure of the corpus callosum.

The functional importance of the splenium in transferring visual information from one hemisphere to centres (both visual and other) in the other hemisphere is well established, both through studies of patients with callosal pathology (Gazzaniga, 2000, Geschwind, 1965), and by fMRI and DTI studies in healthy volunteers (D'Arcy et al., 2006, Dougherty et al., 2005). Lesions of the splenium have been described to cause a range of visual problems; from pure alexia (the inability to read) (Binder and Mohr, 1992, Geschwind, 1965), to increased visual neglect in stroke patients (Bird et al., 2006) and topographical disorientation (Tamura et al., 2007).

**Visual acuity - a midline function**

One distinguishing trait of visual acuity is that it is very much a midline function. This is important, since midline information is particularly favoured for callosal transfer (Berardi et al., 1989, Innocenti and Fiore, 1976, Iwamura et al., 2001, Ptito, 2003). The highest visual acuity is achieved in the retinal fovea, defining the centre of the visual field. Here the concentration of cones is ten-to twentyfold higher than a few degrees peripherally (Hendrickson, 1994, Østerberg, 1935). In the optic chiasm information from both retinas, including the foveas, is split down the vertical midline, and each hemisphere receives a hemifield of visual information (Brysbaert, 2004, Leff, 2004). Integration of the two foveal visual hemifields therefore depends on some transhemispheric relay of information. If the connection, or "zipping up", of the two foveal hemifields is not optimal, the resolution could be reduced, leading to lower visual acuity. A compensatory strategy of fixating slightly to the side of the object of interest might be used, however, as the maximum resolution falls rapidly at any distance from the fovea, this will also lead to lower acuity (Anstis, 1974, Weiter et al., 1984). Thus structural integrity of the splenium can be presumed to be of importance in achieving good visual acuity.

**Timing of injury**

It is possible that the timing of callosal injury in prematurity is important for the visual outcome. In adults experiencing callosectomy, there are to our knowledge no reports on impairments of visual acuity, but one report on "normal visual acuity" after surgery (Afraz et al., 2003). In cats there is an early critical period in the first three weeks after birth, where a surgical section of the corpus callosum leads to deficits in visual acuity. Lesions after this period do not affect visual acuity

(Elberger, 1984). There is also evidence from rat studies that early interhemispheric communication is crucial for the functional development of visual cortex (Caleo et al., 2007). There may be a similar early sensitive period in humans, when callosal normality is particularly important for the development of good visual acuity.

**Function and cerebral (micro-)structure**

To our knowledge, this is the first study to show a correlation between visual acuity and FA values of the splenium. However, it is not the first time general visual ability or other cerebral functions have been shown to correlate with callosal structure and integrity.

Smaller (posterior) corpus callosum midsagittal areas, in subjects born preterm, have been associated with impaired verbal IQ (Nosarti et al., 2004), IQ and memory (Caldu et al., 2006), as well as visual motor integration (Rademaker et al., 2004). Using fMRI and conventional MRI, Santhouse and coworkers (Santhouse et al., 2002) have shown different cerebral activation during visual tasks demanding callosal transfer in prematurely born young adults with callosal thinning, compared to both premature and term born control subjects without such injury. Correlations between visual ability/activity and FA values in the optic radiations have also been published: Bassi and coworkers have reported correlations between visually guided behaviour and FA values in the optic radiations at term in premature babies (Bassi et al., 2008). FA values of the optic radiations have been found to correlate significantly with fMRI measures of visual cortex activity (Toosy et al., 2004).

In our study no correlation was seen between FA values of the splenium and visual acuity in the control group, possibly indicating that the microstructure in a normal splenium is not a limiting factor for the development of optimal visual acuity.

**MD values occipital periventricular white matter in the VLBW group**

There was a negative correlation between visual acuity and MD values of the occipital periventricular white matter in the VLBW group. The optic radiations traverse this area, and the correlation may be explained by focal periventricular leucomalacia, or a more diffuse white matter involvement, resulting in increased MD values and reduced vision. Increased MD values have been reported in areas of white matter with MRI abnormality in preterm children (Counsell et al., 2003). However, the results may well be confounded by partial volume effects: subjects with enlarged ventricles, with more cerebrospinal fluid and less white matter in the periventricular voxels, will have higher MD values. Dilated ventricles are part of the typical MRI findings of periventricular leukomalacia, and are known to correlate to impaired visual function (Serdaroglu et al., 2004). Many of the VLBW children in our study had dilatation of the posterior horns of the lateral ventricles (Skranes et al., 2005), and the correlation may therefore be between lower visual acuity and large ventricles rather than abberant microstructure in the periventricular posterior white matter. However, although a partial volume effect is likely, the correlation is still of interest, as a loss of periventricular white matter (a probable cause of increase in ventricular volume) is at least as serious as a change of microstructure.

**MD values in the superior colliculi (control group)**

The correlation between good visual acuity and higher MD values in the superior colliculi of the control group is interesting. Although the correlation was seen only at the level uncorrected for multiple comparisons, we find it worthwhile to report these findings.

The superior colliculi have retinotopic organization (Schneider and Kastner, 2005) , and are important for saccades and visual attention (Awh et al., 2006, Krauzlis et

al., 2004, Pierrot-Deseilligny et al., 1991). Functional MRI has shown the superior colliculi to be of primary importance in visual search (Himmelbach et al., 2007). Variation in the ability to perform visual search and maintain foveal fixation seems likely to influence visual acuity.

However, our findings must be regarded with caution due to the small size of the superior colliculi compared to the voxel size in the DTI study.

**Methodological limitations**

In this study a voxel-wise regression analysis comparing the FA values in the whole brain of VLBW adolescents with visual test scores was performed. A potential confounding factor in this study is inaccuracies in the spatial normalisation of the diffusion images which can lead to spurious results. We have attempted to minimise inaccuracies in the spatial normalisation by using a custom template based on all subjects in the study. We further applied a threshold on the FA values that confined the analysis to white matter. We have also repeated the regression analysis in a region of interest, individually placed in each VLBW subject's splenium, thus ensuring that only voxels in the splenium were included in the analyses. The results from this test confirm that there is a significant correlation between visual acuity and FA values in this area in the VLBW group.

Partial volume effect may influence the correlations between MD values and visual acuity, as discussed above, and those results must be regarded with caution.

The results have been corrected for multiple comparisons with an FDR corrected threshold of 0.05 (Benjamin and Hochberg, 1995), reducing the risk that a chance finding has been incorrectly accepted as real. Although the method has limitations which should not be ignored, voxel based morphometry is a commonly used

method, well suited to study neuroanatomical correlates to neurological function and dysfunction (Ashburner and Friston, 2001,Ridgway et al., 2008).

**Conclusion**

Our findings indicate that subnormal visual acuity in VLBW adolescents may be related to changes in the microstructure of the splenium part of the corpus callosum. The splenium is particularly prone to injury in prematurity. It constitutes the route for transhemispherical relay of visual information and favours foveal data. A normal splenium may contribute more to the development of optimal visual acuity than previously acknowledged.

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