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Brain MRI alterations, neurodevelopment, and visual outcomes in children and adults born preterm

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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«Visuopathy of prematurity»: *hjerneforandringer, nevroutvikling, og syn hos barn og voksne født for tidlig*

Barn som er født for tidlig (premature) har økt risiko for langvarige nevroutviklingsforstyrrelser og synsvansker. Vanskene ser ut til å være til stede selv uten cerebral skade eller prematuritetsretinopati som er karakterisert av unormal vekst av blodkar i netthinnen som resulterer i redusert syn. Det er derfor mulig at prematuritetsretinopati bare er toppen av et isfjell av synsvansker vi har betegnet som *«Visuopathy of prematurity» (VOP),* og som mulig involverer både hjerneforandringer og strukturelle endringer i netthinnen.

Vi undersøkte hjernesubstans, nevroutvikling, og syn hos barn født ekstremt for tidlig (gestasjonsalder ≤28 uker) og voksne født for tidlig med svært lav fødselsvekt (fødselsvekt ≤1500 g, very low birth weight: VLBW) i Midt-Norge. Vi undersøkte også om avbildning av netthinnen og hjernesubstans langs synsbanene kunne avdekke kliniske bildemarkører for synsvansker hos barn og voksne født for tidlig. Synsfunksjon ble testet i klinikken, netthinnen og hjernesubstans ble undersøkt ved avbildning, og synsbanene ble undersøkt ved registrering av elektrofysiologisk hjerneaktivitet. Vi vurderte også barnas nevroutvikling gjennom foreldrerapportering og nevropsykologisk testing.

Vi fant at barn som er født for tidlig har strukturelle endringer i netthinnen og nedsatt synsfunksjon som var assosiert med flere foreldrerapporterte utfordringer i skolealder innenfor motorikk, læring, persepsjon, og kognitiv funksjon. Gruppen med VLBW-voksne viste nedsatt synsfunksjon og strukturelle endringer i netthinnen sammenlignet med en kontroll-gruppe med voksne født til termin. VLBW-voksne hadde også endringer i hjernesubstans langs synsbanene som predikerte nedsatt synsfunksjon i denne gruppen.

Funnene i denne avhandlingen tyder på at en tverrfaglig tilnærming ved bruk av både kliniske bildemarkører og testing av synsfunksjon i klinikken, kan bidra til en større forståelse av mekanismene som underligger synsvansker hos barn og voksne født for tidlig. En slik tilnærming kan bidra til identifisering av årsaken og alvorlighetsgraden til synsvansker, og dermed forbedre oppfølgingen av barn og unge i denne gruppen.

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Abbreviations

AD	axial diffusivity
BCVA	best corrected visual acuity
BPD	bronchopulmonary dysplasia
BW	birth weight
CC	corpus callosum
CFT	central foveal thickness
CMT	central macular thickness
CP	cerebral palsy
cpd	cycles per degree
DTI	diffusion tensor imaging
ELBW	extremely low birth weight
ETDRS	early treatment diabetic retinopathy study
FA	fractional anisotropy
FAZ	foveal avascular zone
FFT	five to fifteen (questionnaire)
GA	gestational age
GM	grey matter
IFOF	inferior-fronto occipital fasciculus
IOP	intraocular pressure
IPGCL	inner plexiform ganglion cell layer
IVH	intraventricular haemorrhage
LBW	low birth weight
LGN	lateral geniculate nucleus
LogMAR	logarithm of the minimum angle of resolution
MD	mean diffusivity
MRI	magnetic resonance imaging
MVD	macular vascular density
MVF	macular vascular flow
NEC	necrotising enterocolitis
NICU	neonatal intensive care unit
NNK	Norwegian Neonatal Network (database)
NSI	neurosensory impairment
NTNU	Norwegian University of Science and Technology
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
OR	optic radiation

PR-VEP	patterned reversed visual evoked potential
pre-OL	preoligodendrocyte
RD	radial diffusivity
REK	Regional Committee for Medical and Health Research Ethics
RNFL	retinal nerve fibre layer
ROI	region of interest
ROP	retinopathy of prematurity
SD	standard deviation
SES	socioeconomic status
V1	primary visual cortex
VEP	visual evoked potential
VEGF	vascular endothelial growth factor
VLBW	very low birth weight
VOP	visuopathy of prematurity
WM	white matter
WMI	white matter injury

List of papers

The thesis is based on the following papers:

Paper I: Visual function correlates with neurodevelopment in a population cohort of school-aged children born extremely preterm

Sigrid Hegna Ingvaldsen, Tor Ivar Hansen, Asta Kristine Håberg, Viggo Moholdt, Kari Anne Indredavik Evensen, Olaf Dammann, Dordi Austeng, Tora Sund Morken

Acta Paediatrica (2023), 112(4): 753-761

Findings presented at the Nordic Congress of Ophthalmology (NOK) 2021, Oslo, Norway. Findings presented at the Pediatric Academic Societies (PAS) Meeting 2022, Denver, USA.

Paper II: Retinal structure and visual pathway function at school age in children born extremely preterm: A population-based study

Sigrid Hegna Ingvaldsen, Kyrre Moljord, Arnstein Grøtting, Petter Moe Omland, Dordi Austeng, Tora Sund Morken

BMC Ophthalmology (2023), 23(296): 1-10

Findings presented at the Nordic Congress of Ophthalmology (NOK) 2022, Reykjavik, Iceland.

Paper III: Visual outcomes and their association with grey and white matter microstructure in adults born preterm with very low birth weight

Sigrid Hegna Ingvaldsen, Anna Jørgensen, Arnstein Grøtting, Trond Sand, Live Eikenes, Asta Kristine Håberg, Marit Sæbø Indredavik, Stian Lydersen, Dordi Austeng, Tora Sund Morken, Kari Anne Indredavik Evensen

Under review in Scientific Reports (2023)

Findings presented at the NTNU Low Birth Weight Life study seminar 2022, Trondheim, Norway. Findings presented at the Norwegian Research School in Neuroscience (NRSN) PhD-Conference 2022, Stiklestad, Norway. Findings presented at the Pediatric Academic Societies (PAS) Meeting 2023, Washington D.C, USA.

List of papers not included in this thesis:

Visual function in adults born preterm with very low birth weight- A two-country birth cohort study

Maarit Kulmala, Anna Perregaard Munch Jørgensen, Kristina Anna Djupvik Aakvik, Laura Jussinniemi, Silje Dahl Benum, Sigrid Hegna Ingvaldsen, Dordi Austeng, Eero Kajantie, Kari Anne I. Evensen, Anna Majander, Tora Sund Morken

Acta Ophthalmologica (2023), 00: 1-9.

Forecasting migraine with machine learning based on mobile phone diary and wearable data

Anker Stubberud, Sigrid Hegna Ingvaldsen, Eiliv Brenner, Ingunn Winnberg, Alexander Olsen, Gøril Bruvik Gravdahl, Manjit Singh Matharu, Parashkev Nachev, Erling Tronvik

Cephalalgia (2023), 43(5): 1-10.

Visuopathy of prematurity: is retinopathy just the tip of the iceberg?

Sigrid Hegna Ingvaldsen, Tora Sund Morken, Dordi Austeng, Olaf Dammann

Pediatric Research (2021), 91: 1043-1048

A biofeedback app for migraine: Development and usability study

Sigrid Hegna Ingvaldsen, Erling Tronvik, Eiliv Brenner, Ingunn Winnberg, Alexander Olsen, Gøril Bruvik Gravdahl, Anker Stubberud

JMIR Formative Research (2021), 5(7): e23229

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Summary

Being born preterm increases the risk of long-term neurodevelopmental challenges and adverse visual outcomes, such as reduced visual function. The adverse outcomes seem to be present even without cerebral damage or severe eye disease, such as *retinopathy of prematurity* (ROP), characterized by abnormal blood vessel growth in the retina, causing reduced vision. Therefore, ROP might just be the tip of an iceberg of a larger entity termed *«Visuopathy of prematurity» (VOP*) which may involve brain alterations and altered retinal structure that could explain the adverse visual outcomes in individuals born preterm.

In this thesis, we aimed to assess brain matter, neurodevelopment, and visual outcomes in school-aged children born extremely preterm (gestational age ≤28 weeks) and adults born preterm with very low birth weight (VLBW; birth weight ≤1500 g) in Central Norway. We also aimed to explore whether imaging of retinal structure and brain matter microstructure along the visual pathway could reveal potential clinical imaging markers for adverse visual outcomes. Visual function was examined in the clinic, retinal structure and brain matter microstructure was assessed by imaging, and visual pathway function was recorded with electrophysiology. Also, we assessed neurodevelopmental challenges at school age with parent reports and neuropsychological testing.

We found an altered retinal structure in children born preterm and reduced visual function associated with a higher level of neurodevelopmental challenges within motor skills, learning, perception, and executive functions at school age. We also found altered retinal structure and reduced visual function in VLBW adults compared to a control group of adults born to term. Moreover, VLBW adults displayed brain matter alterations along the visual pathway that predicted reduced visual function. The findings of this thesis suggest that a multi-disciplinary approach using both clinical imaging markers and visual function testing could provide a more comprehensive understanding of the mechanisms underlying adverse visual outcomes in children and adults born preterm. In addition, a multi-disciplinary approach might contribute to identifying the cause and extent of the adverse visual outcomes, thereby improving the follow-up of individuals born preterm.

“The eyes are said by poets to be the windows to the soul, but they are also windows to the brain”- Henry Marsh (2014)

1 Introduction

1.1 Preterm birth

Approximately 15 million babies are born preterm every year (Walani 2020). Preterm birth can therefore be considered a global epidemic with different survival rates worldwide due to the expensive care that preterm infants need (Blencowe, Cousens et al. 2012). In the western part of the world, the rate of preterm births has increased over the last decades due to the increase in preterm survivors (Wilson-Costello, Friedman et al. 2005). Unfortunately, the infants who survive do so with several physical and neurodevelopmental challenges that may follow them into adulthood (Johnson and Marlow 2017).

Preterm birth is defined based on the number of completed weeks of pregnancy (gestational age; GA) or based on birth weight (World Health Organization 2023). The World Health Organization divides preterm birth by GA into three sub-categories: moderate to late preterm, defined as GA between 32 to 37 weeks; very preterm, defined as GA between 28 to 32 weeks; and extremely preterm, defined as GA before 28 weeks (Dbstet 1977). Adverse health outcomes with decreasing gestation at birth have been shown in both children (Boyle, Poulsen et al. 2012) and adolescents (Berry, Foster et al. 2018).

Birth weight is also used to define the degree of prematurity and may be the only available statistic regarding preterm birth in low-income countries (Dbstet 1977). Accordingly, birth weight is essential in cross-country research on the long-term consequences of preterm birth. Low birth weight is defined as ≤2500 g and further divided into two sub-categories: very low birth weight (VLBW), defined as birth weight below 1500 g; and extremely low birth weight (ELBW), defined as birth weight below 1000 g (Gomella, Cunningham et al. 2013). Very low birth weight has been associated with abnormal brain structure, lower IQ, increased risk of mental health problems and reduced physical function (Evensen, Aakvik et al. 2022).

1.1.1 Prenatal risk factors and postnatal consequences

Prenatal risk factors for preterm birth include intrauterine infection, malnutrition, hypertensive disorders, low pre-pregnancy body mass index, and adverse mental health of

the mother (Pusdekar, Patel et al. 2020). In addition, environmental factors such as low levels of education and low socioeconomic status may also increase the risk for preterm delivery (Delnord and Zeitlin 2019).

After preterm birth, infants have underdeveloped and fragile organ systems that are not yet mature enough to support them in the extrauterine environment, making them vulnerable to several complications after birth (Saigal and Doyle 2008). The complications include respiratory distress syndrome, bronchopulmonary dysplasia, hearing and visual impairment, cardiovascular disease, and neurological insults such as periventricular leukomalacia (Ream and Lehwald 2018).

It is also common that their fragile immune system is attacked by inflammatory responses (Humberg, Fortmann et al. 2020). In addition, preterm infants are often exposed to high oxygen due to breathing difficulties and have a limited antioxidant defence, which is important for protecting the cells against the harmful effect of oxidants. This dangerous combination of exposure to high oxygen and a limited antioxidant defence may lead to oxidative stress (Saugstad 2005). Several pathological consequences of immaturity at birth appear to be related to oxidative stress, such as retinopathy of prematurity and white matter injury (WMI) (Panfoli, Candiano et al. 2018).

1.2 The preterm brain

The brain's plasticity abilities makes it more vulnerable to stressful experiences, especially during weeks 20 to 40 of gestation, characterised by axon formation and myelinization processes critical for normal brain maturation (Cheong, Burnett et al. 2020). Major developmental events such as cerebral cortical dendritic development, synaptogenesis, populating of upper cortical layers, and lineage in cerebral white matter occur during weeks 32 to 40 of gestation (Volpe 2019). Preterm birth might disturb these processes and increases the risk of brain injury and adverse neurodevelopmental outcomes (Kelly, Shaul et al. 2023). Preterm brain injuries are often a combination of white matter and grey matter structure alterations, which have been coined *encephalopathy of prematurity* (Volpe 2009).

Preterm brain injuries, such as WMI, can be discovered by brain magnetic resonance imaging (MRI), and the degree of white matter abnormalities can be assessed by using diffusion tensor imaging (DTI), an MRI sequence that can measure the degree of white matter organization, myelination, and axon injury in the brain tissue (Corroenne, Arthuis et al. 2022). Periventricular leukomalacia, characterised by large regions of cystic necrosis deep in the white matter adjacent to the ventricular wall, is the most severe form of WMI in individuals born preterm (Back 2017) but is rarely seen today. Instead, diffuse WMI, characterized by a loss of white matter and abnormal white matter development, has become a common pathology in preterm infants (van Tilborg, Heijnen et al. 2016). This brain dysmaturation involves a cascade starting with inflammatory factors affecting preoligodendrocytes (pre-OLs), crucial myelin-producing cells for the development of normal white matter (van Tilborg, Heijnen et al. 2016). Moreover, pre-OLs are especially vulnerable to inflammation during the postnatal period, which is the period where infants also has the highest risk of WMI (Panfoli, Candiano et al. 2018).

From week 20 to 24 of gestation, there is a rapid increase in the number of oligodendroglia initiators developed; after 24 weeks, the oligodendroglia progenitor differentiation leads to pre-OLs emerging in the cerebral white matter, and the pre-OLs initiate myelinization ensheathment of the white matter axons (Volpe 2019). The pre-OLs account for about 90% of the lineage during this period, and from weeks 32 to 40, pre-OLs remain the predominant myelin-producing cell of oligodendroglia lineage in the brain´s white matter (Back, Luo et al. 2001, van Tilborg, Heijnen et al. 2016). Accordingly, the pre-OLs contribute to most of the white matter lineage in the gestational window of very preterm birth, when pre-OLs are vulnerable to inflammatory damage (Back, Luo et al. 2001). Indeed, the significant differences in white matter density that exist between children born preterm and their term-born peers (Ahn, Park et al. 2019, Dubner, Dodson et al. 2019) correspond with the time window of OL lineage maturation. Figure 1 shows the biological mechanisms of healthy and abnormal white matter development due to preterm birth.

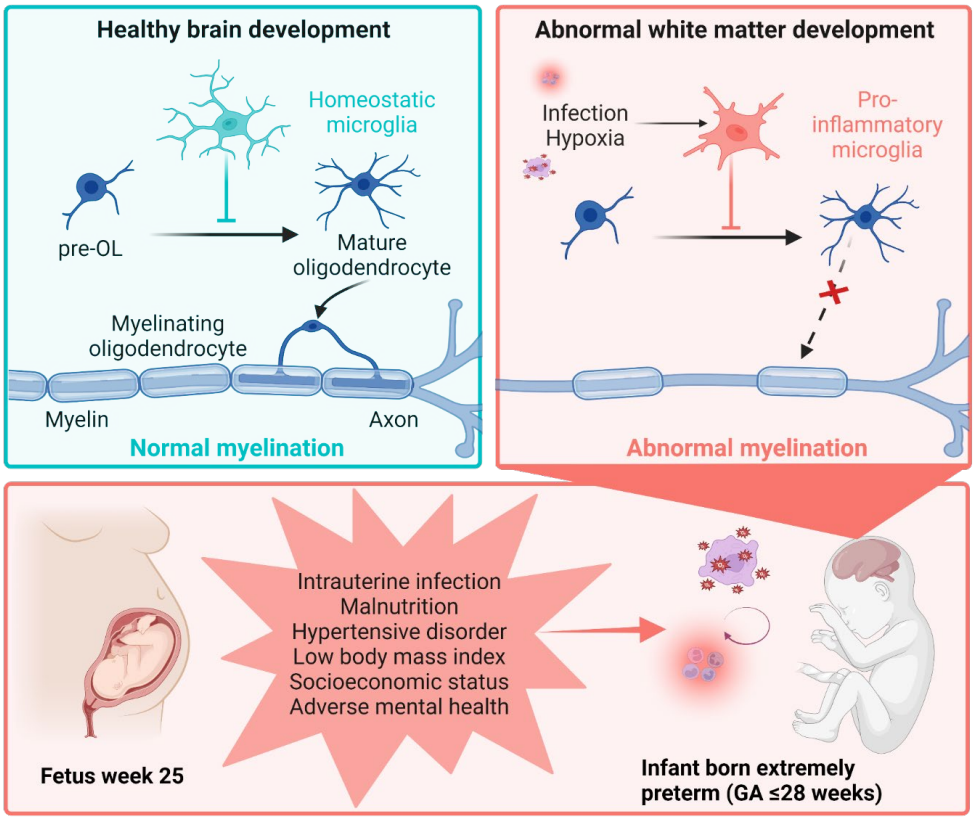

Figure 1. Biological mechanisms of white matter development

Top left: normal white matter myelinization starting with oligodendroglia progenitors' differentiation, leading to pre-OLs and myelinization of white matter axons. Bottom and top right: prenatal risk factors initiate preterm birth that causes postnatal stressors, such as oxidative stress and inflammation, leading to abnormal myelination of white matter axons which could result in diffuse white matter injury. ©Sigrid Hegna Ingvaldsen (2023)

1.2.2 Long-term neurodevelopmental consequences

The sensory and neurological impairments commonly seen in individuals born preterm are often accompanied by neurodevelopmental challenges that may persist into adulthood and are increasingly present in critical periods of life (Delnord and Zeitlin 2019). During early childhood, reduced motor skills become a major neurodevelopmental challenge, even in individuals without neonatal cerebral damage (Evensen, Ustad et al. 2020). Five-year-old

children born preterm show lower performance and a higher risk of developmental delays in visual-motor integration and fine motor skills than term-born peers (Dathe, Jaekel et al. 2020). Also, reduced motor skills at 12 months of corrected age have been associated with increased cognitive challenges and language difficulties at three years of age (Panceri, Silveira et al. 2022).

At school-age and early adolescence, increased responsibility, novel social scenes and the importance of social relationships outside the home can be triggering. As a result, challenges within executive functioning and learning skills could become noticeable in children vulnerable to these stressors (Delnord and Zeitlin 2019). Indeed, school-aged children born extremely preterm display a higher level of parent-reported developmental challenges within learning, planning, and memory (Burnett, Anderson et al. 2018) and lower performance in reading and solving mathematical problems (McBryde, Fitzallen et al. 2020).

The Norwegian University of Science and Technology (NTNU) Low Birth Weight (LBW) Life Study has followed individuals born preterm with VLBW and a term-born control group from infancy to adulthood with clinical assessment at several time points. The study has found that individuals born preterm with VLBW had lower IQs than term-born peers at 5, 14, and 19 years of age. At 19 years of age, participants born preterm with VLBW also displayed lower memory abilities, attention, and executive function scores (Evensen, Aakvik et al. 2022). The transitional phase from adolescence to adulthood, requiring a higher degree of independence, may also prompt mental health disorders, with anxiety and attention-deficit/hyperactivity disorder as two of the most common disorders at this time in individuals born preterm (Yates, Treyvaud et al. 2020). Indeed, psychiatric morbidity increased from 14 to 19 years of age and even more to 26 years of age in the NTNU LBW Life study, with anxiety disorders as the most prevalent challenge among the participants born preterm with VLBW. At 26 years of age, results from the same cohort also showed that fewer in the VLBW group completed high school, and one-fifth were unemployed or received disability benefits compared with term-born controls (Evensen, Aakvik et al. 2022).

Several studies have assessed the onset and potential causes of neurodevelopmental challenges. The neurological consequences of an underdeveloped brain caused by preterm birth have been associated with several neurodevelopmental challenges (Evensen, Aakvik et al. 2022). However, research on the association between neurodevelopment and the consequences of an immature visual system due to preterm birth is sparse.

1.3 Visual development and function

The eye acts like a camera by projecting small images of the outside world onto the light-sensitive retina in the back of the eye (Kandel, Schwartz et al. 2000). The retina is a thin sheet of neurons consisting of several retinal layers, with the fovea in the middle facilitating light to access foveolar photoreceptors and enabling sharp vision (Jabroun, AlWattar et al. 2021). During foetal development, the fovea is formed by the centrifugal movement of inner retinal layers to the periphery and migration of the outer photoreceptor layers towards the centre of the foveola (Åkerblom, Larsson et al. 2011, Bringmann, Syrbe et al. 2018). The movement of inner retinal layers allows light to pass through and be absorbed by photoreceptors for further processing. This process occurs during late gestation- consequently, the development of retinal vasculature and the low-level processing of visual information in the retina are vulnerable to prenatal and postnatal consequences of preterm birth (He, Pettenkofer et al. 2022).

The cells in the photoreceptor layers absorb light and convert it into a neural signal (Kandel, Schwartz et al. 2000). This signal is further transmitted via the axons of ganglion cells in the retinal nerve fibre layer and inner plexiform ganglion cell layer that form the optic nerve (Yazdankhah, Shang et al. 2021). Visual signals travel through the optic nerve, and information from both eyes merges at the optic chiasm (Kandel, Schwartz et al. 2000). From here, the optic tract conveys the information to the lateral geniculate nucleus, where the axons synapse. The axons of the lateral geniculate nucleus fan out through the brain's white matter as optic radiations, and the information is transmitted to the primary visual cortex via the inferior-frontal occipital fasciculus (Raz and Levin 2014). In addition, the occipital-callosal fibre tract connects the two occipital lobes via the corpus callosum, ensuring visual information

flow between the two hemispheres (Bartolomeo and Thiebaut de Schotten 2016). Figure 2 shows an overview of the areas along the visual pathway involved in processing visual stimuli.

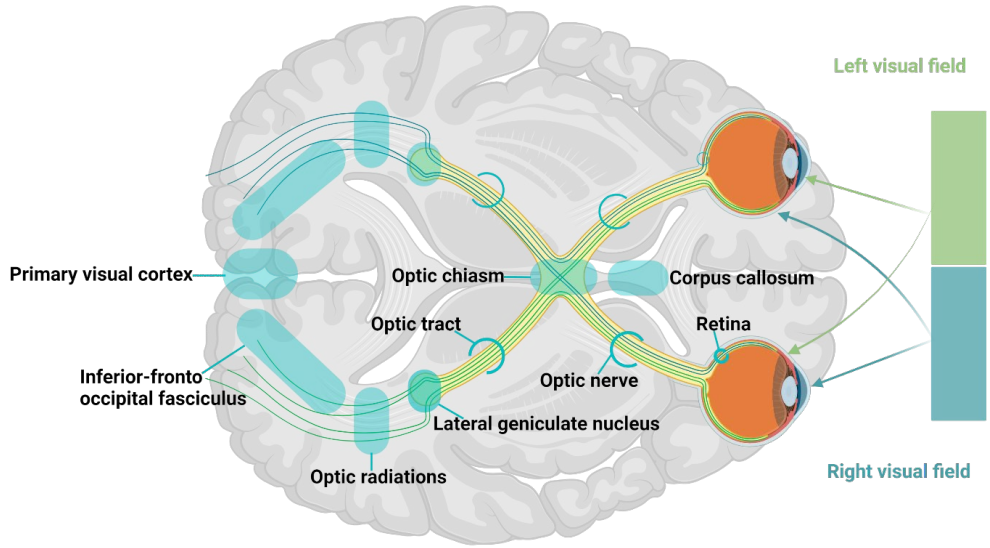

Figure 2. Illustration of the visual pathway

Illustration of the visual pathway starting in the retina with visual information travelling via the optic nerve, crossing in the optic chiasm, and being conveyed to the primary visual cortex for processing. ©Sigrid Hegna Ingvaldsen (2023)

Visual function refers to how well the visual system detects and processes visual stimuli (Bennett, Bex et al. 2019). Visual acuity measures sharp vision and is the most frequently used visual function test in the clinic (Roark and Stringham 2019) and reduced visual acuity among children born preterm seems to persist into adulthood (Pétursdóttir, Holmström et al. 2020), regardless of any history of retinopathy of prematurity (Jain, Sim et al. 2022). Contrast sensitivity measures the threshold required to detect contrast in daily life (Dönmez, Özcan et al. 2020). Studies have shown reduced contrast sensitivity in children (Larsson, Rydberg et al. 2006) and adults born preterm compared with term-born peers (Kulmala, Jørgensen et al. 2023).

With visual evoked potentials (VEPs), we can assess the speed (latency) and strength (amplitude) of the visual signal travelling through the optic nerve for higher-order visual

processing by presenting visual stimuli (Markand 2020). When we use alternating patterns, such as an alternating checkboard on a screen, VEPs give us information about visual maturation (Ruberto, Angeli et al. 2014). Longer VEP latencies indicate slower visual processing, and this pattern has been found in children born preterm (Feng, Xu et al. 2011).

1.4 Retinopathy of prematurity- the tip of the iceberg

Retinopathy of prematurity (ROP) is a disease of abnormal neovascularization of the retina that occurs predominantly among very preterm infants and might be caused by the risk factors that follow preterm birth, such as postnatal infection, sustained systemic inflammation and high oxygen supply (Hartnett and Penn 2012, Dammann, Hartnett et al. 2022). Preterm infants are regularly screened for ROP postnatally in the NICU by visualizing the fundus manually or in images (Dammann, Hartnett et al. 2022). Neonatal screening has improved over the years, and modern systematic ROP screening identifies individuals that need treatment early in the postnatal period. Therefore, end-stage ROP is rarely seen in high-income countries (Sabri, Ells et al. 2022). However, screening guidelines differ worldwide and even between national regions due to geographical variations and socioeconomic differences in healthcare systems (Bujoreanu Bezman, Tiutiuca et al. 2023). The ROP diagnosis is made by clinically observed pathological neovascularization of the retina during early development (Hellström, Smith et al. 2013). At St. Olavs Hospital in Trondheim, all infants born with GA <32 weeks have their first ROP examination at five weeks postnatal age, while infants born extremely preterm (GA ≤28 weeks) have their first ROP examination at 31 weeks postmenstrual age (Klingenberg, Austeng et al. 2022).

The first phase of ROP is characterised by delayed vascularization and disruption of blood vessel growth due to a loss of growth factors and nutrients (hyperoxia). In some eyes, blood vessel growth stabilizes after this phase and the ROP regress spontaneously. However, if the ROP progresses to the second phase, the disease can result in retinal detachment at its end stage, causing visual impairment if not treated. In this second phase, vascular development becomes reactivated by vessel growth and increasing nutrient demands (hypoxia), leading to vascularization of the remaining avascular parts of the retina. In severe ROP, the second phase

is characterised by abnormal vascularization growing out of the retina and further into the vitreous (Dammann, Hartnett et al. 2022).

To classify ROP disease, the level of neovascularization in the retina is defined by five ROP stages. In stage 1, a white demarcation line is present at the junction of the vascular and avascular retina. In stage 2, the disease develops into an elevated ridge at the intersection, to a vascularized ridge (stage 3), partial retinal detachment (stage 4), and complete retinal detachment and consequently blindness if the ROP progresses to stage 5 (Dammann, Hartnett et al. 2022, Sabri, Ells et al. 2022). Three zones illustrate the anatomical location of the vascularization. In addition, severe ROP is often associated with dilation of the posterior retinal vessels, called plus disease.

Therefore, the ROP stage, zone and the presence of plus disease determines whether the ROP needs to be treated (Chiang, Quinn et al. 2021). Type I ROP is characterized by either plus disease in zone 1, stage 3 ROP in zone 1, or stage 2 or 3 ROP with plus disease in zone 2. Type II ROP is characterized by either stage 1 or 2 ROP in zone 1 or stage 3 ROP in zone 2 (Klingenberg, Austeng et al. 2022). Type II ROP requires close monitoring, while Type I ROP is more severe and requires treatment. Figure 3 show the consequences of preterm birth causing neovascularization of the retina in ROP pathogenesis.

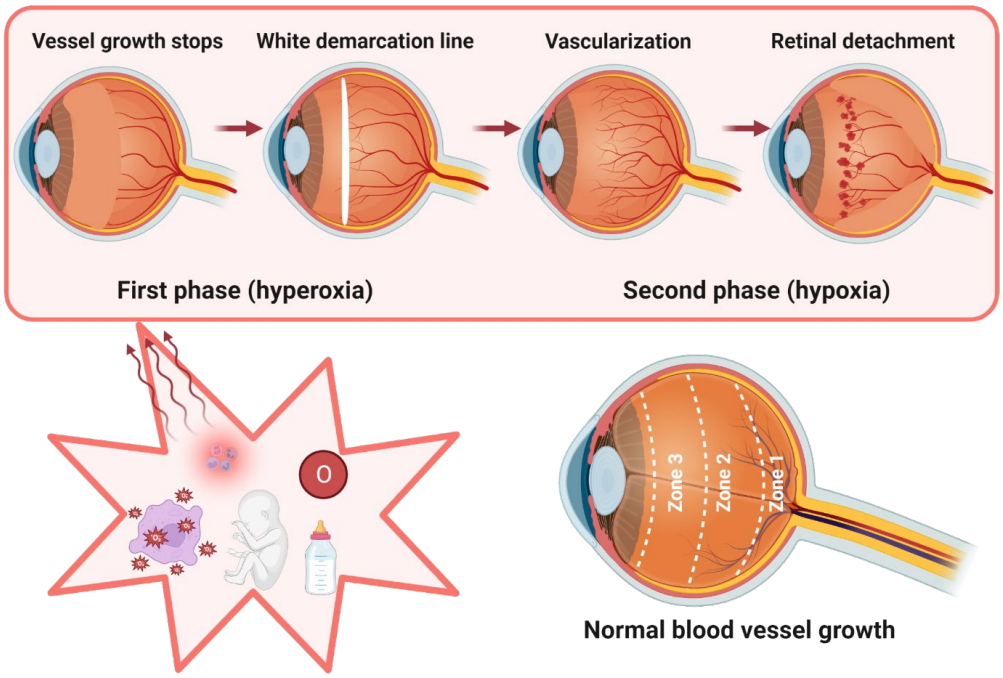

Figure 3. Pathogenesis of retinopathy of prematurity

Top: the first phase of ROP pathogenesis with delayed vascularization (hyperoxia), and the second phase with increased blood vessel growth in the retina (hypoxia) causing neovascularization. Bottom left: postnatal risk factors for ROP, including oxidative stress, inflammation, oxygen fluctuations, malnutrition, and early gestational age. Bottom right: healthy retina with normal blood vessel growth divided into retinal zones. ©Sigrid Hegna Ingvaldsen (2023)

Cryotherapy, involving freezing the sclera, choroid and avascular retina, was the earliest treatment of ROP, but this treatment was time-consuming and had high rates of unfavourable outcomes (Sabri, Ells et al. 2022). Therefore, in the 2000s, laser treatment which aims at reducing the avascular retina with photocoagulation became the standard treatment of ROP due to its reduction in unfavourable outcomes (Bujoreanu Bezman, Tiutiuca et al. 2023).

One of the major triggers of ROP is an imbalance of the amount of vascular endothelial growth factor (VEGF) (Dammann, Hartnett et al. 2022). Even though VEGF is important for normal blood vessel and neural growth in the eye, changes in the oxygenation of retina caused by the postnatal consequences of immature at birth can lead to high levels of VEGF and uncontrolled blood vessel growth (Fu, Sun et al. 2020). Therefore, to balance the VEGF, a treatment goal

will often be to down-regulate the impact of VEGF with anti-VEGF agents, such as bevacizumab, and a shift to the anti-VEGF treatment of ROP has been seen worldwide (Bujoreanu Bezman, Tiutiuca et al. 2023).

Although there have been improvements in neonatal care over the decades, ROP remains one of the most serious consequences of preterm birth (Dammann, Hartnett et al. 2022). In the US, the incidence of diagnosed ROP increased from 4.4% in 2003 to 8.1% in 2019 (Bhatnagar, Skrehot et al. 2023). In Norway, the incidence of ROP among individuals born extremely preterm (GA ≤28 weeks) was 40% from 2009-2017 (Grottenberg, Korseth et al. 2021). In addition, the ROP incidence seems to increase with reduced gestational age and birth weight (Hellström, Smith et al. 2013). Indeed, a study of ROP incidence in Sweden revealed that the risk of ROP declined by 50% for every week's gestation increase (Austeng, Källen et al. 2009).

Over the years, findings in both children and adults born preterm have revealed that individuals born preterm show adverse visual outcomes, especially in individuals with a history of ROP (Åkerblom, Andreasson et al. 2014, Pétursdóttir, Holmström et al. 2020). However, studies report that visual outcomes are also impaired in individuals with regressed ROP (Darlow, Elder et al. 2018, Bowl, Lorenz et al. 2019) and even in individuals with no history of ROP (Larsson, Martin et al. 2004).

1.5 Visuopathy of prematurity- the iceberg

Vascularization of the retina due to ROP might not be the only explanation for adverse visual outcomes in individuals born preterm. Instead, ROP might just be the tip of an iceberg of a larger entity termed *Visuopathy of prematurity (VOP)* (Ingvaldsen, Morken et al. 2021), presented in Figure 4. The VOP entity may involve brain alterations and altered retinal structure that could cause the long-term adverse visual outcomes observed in individuals born preterm, even without a history of ROP (Morken, Dammann et al. 2019).

Moreover, clinical imaging markers assessed with real-time imaging of retinal structure (using optical coherence tomography) and diffusion tensor imaging (with magnetic resonance imaging) along the brain´s visual pathway may shed light on the source and degree of the brain alterations and altered retinal structure (Ingvaldsen, Morken et al. 2021).

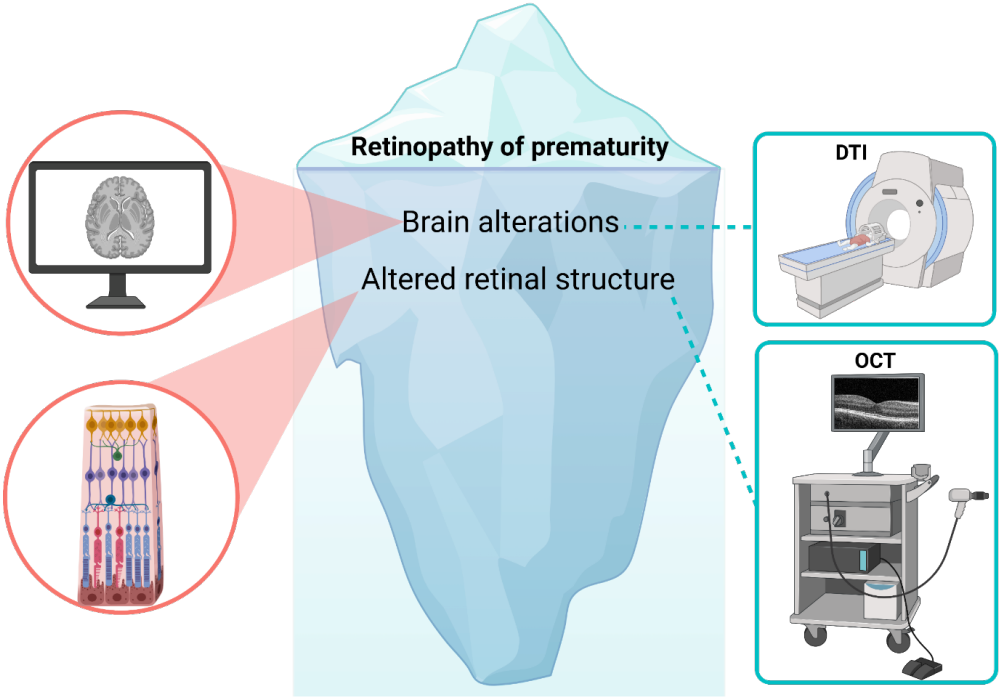

Figure 4. Visuopathy of prematurity

DTI= diffusion tensor imaging; OCT= optical coherence tomography. The visuopathy of prematurity entity illustrates that retinopathy of prematurity is just the tip of an iceberg of a larger entity of adverse visual outcomes that could be explained by brain alterations and altered retinal structure (left). Right: DTI with magnetic resonance imaging and retinal imaging with OCT might reveal clinical imaging markers for the adverse visual outcomes. ©Sigrid Hegna Ingvaldsen (2023)

2 Aims of the thesis

Overall, this thesis aimed to assess brain MRI alterations, neurodevelopment, visual function, and retinal structure in children and adults born preterm. Moreover, the thesis explored whether imaging of altered retinal structure and white and grey matter microstructure along the visual pathway could reveal clinical imaging markers for the adverse visual outcomes.

The aims of each paper were:

Paper I

To assess visual function and neurodevelopment in a geographically defined population of school-aged children born extremely preterm (GA ≤28 weeks) with and without a history of ROP. Moreover, we wanted to explore associations between visual acuity and contrast sensitivity with parent-reported neurodevelopmental outcomes and neuropsychological testing.

Paper II

To explore the retinal structure, visual pathway function, and the associations between these outcomes in a geographically defined population of school-aged children born extremely preterm with and without a history of ROP.

Paper III

To assess whether visual function and retinal structure differed between adults born preterm with VLBW and term-born controls. Furthermore, we wanted to explore whether white and grey matter microstructure along the visual pathway could predict their visual outcomes.

3 Design and methods

3.1 Study design

The study population assessed in Papers I and II consisted of children residing in Central Norway who were born extremely preterm (GA ≤28 weeks) between 2006-2011. They were identified via the Norwegian Neonatal Network (NNK) database, a national medical quality registry collecting data on all newborns admitted to Norway's neonatal intensive care units (NICUs). The information from NNK was cross-checked with medical health records to identify all eligible children and the Norwegian National Population Register was accessed to obtain parental addresses. In addition, a parent-reported questionnaire, ophthalmological assessments, and brain MRI were completed at St. Olavs Hospital over two consecutive days, while a neuropsychological test battery was completed at home between March 3 and September 2, 2021.

The study population assessed in Paper III were part of a large longitudinal hospital-based follow-up study, the NTNU LBW Life Study, including individuals with VLBW (birth weight ≤1500 g) and a term-born control group (gestational age ≥37 weeks with a birth weight >10th percentile) (Bakketeig, Jacobsen et al. 1993). Participants in the VLBW group were born in 1986-1988 and admitted to the Neonatal Intensive Care Unit at St. Olavs Hospital, Trondheim University Hospital, in Norway. Participants in the control group were born to mothers recruited from the Trondheim area during pregnancy in the same years. The participants have been invited for several clinical assessments from infancy to adulthood (Evensen, Aakvik et al. 2022). In this study, we included participants with DTI from a brain MRI assessment at 26 years of age and visual data from a clinical assessment at 32 years of age, carried out between 2019 and 2021.

3.2 Study populations

School-aged children born extremely preterm (Papers I and II)

Sixty-nine children born extremely preterm were invited via a mailed letter containing information about the study. Two participants did not meet for the clinical visual assessment, and one could not complete the clinical visual assessment due to movement artefacts from cerebral palsy. The same participant with cerebral palsy could not complete the neuropsychological Memoro test, and the child´s parents did not complete the parent-reported questionnaire. One participant had missing data from optical coherence tomography (OCT) due to movement artefacts, while two had missing OCT data due to nystagmus. The same two participants with nystagmus also had missing data from the pattern-reversal visual evoked potentials (PR-VEP) recording, while one participant had missing PR-VEP data due to movement artefacts causing no reliable components to be identified in the data. Three participants did not meet for the brain MRI. The non-participants consisted of individuals who did not consent to participate or could not be reached. Figure 5 presents the flow of participants.

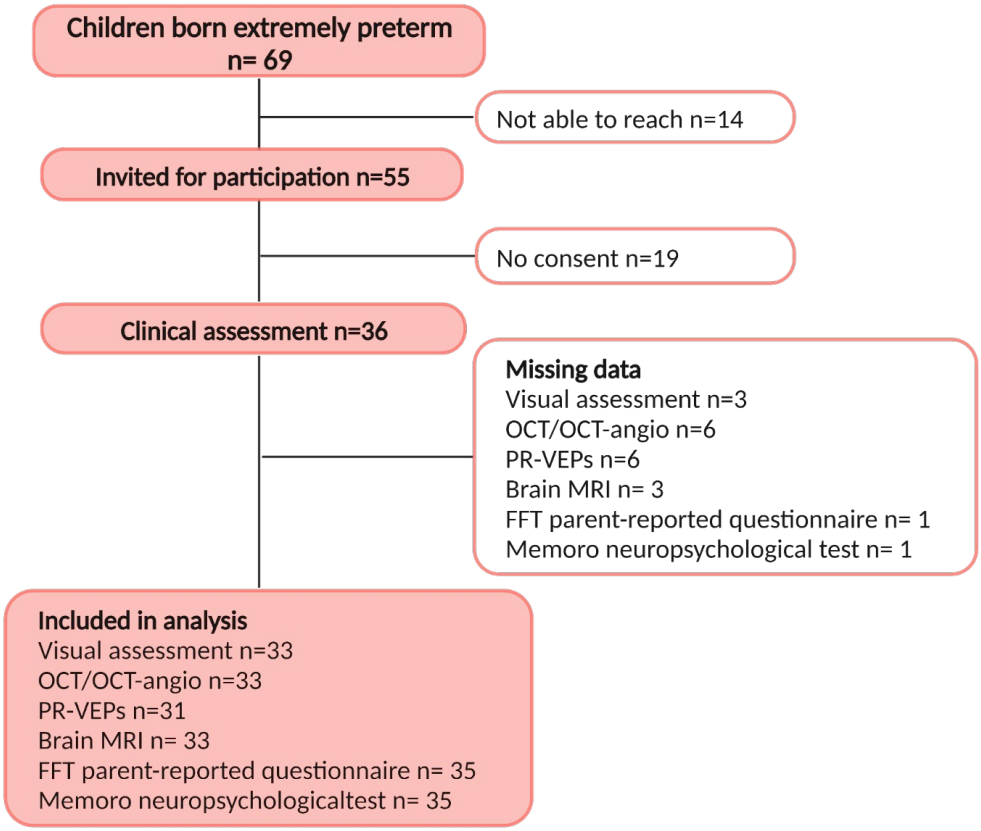

Figure 5. The flow of school-aged children born extremely preterm (Papers I and II)

FFT= five to fifteen; MRI= magnetic resonance imaging; OCT= optical coherence tomography; PR-VEPs= pattern-reversal visual evoked potentials.

Adults born preterm with very low birth weight and term-born controls (Paper III)

The VLBW group consisted of 121 individuals, and the control group originally consisted of 120 individuals. The non-participants included individuals who did not consent to participation, were not clinically assessed at 32 years of age (some only answered questionnaires because they could not attend the clinical assessment) or did not have DTI from brain MRI at 26 years of age. Figure 6 presents the flow of participants.

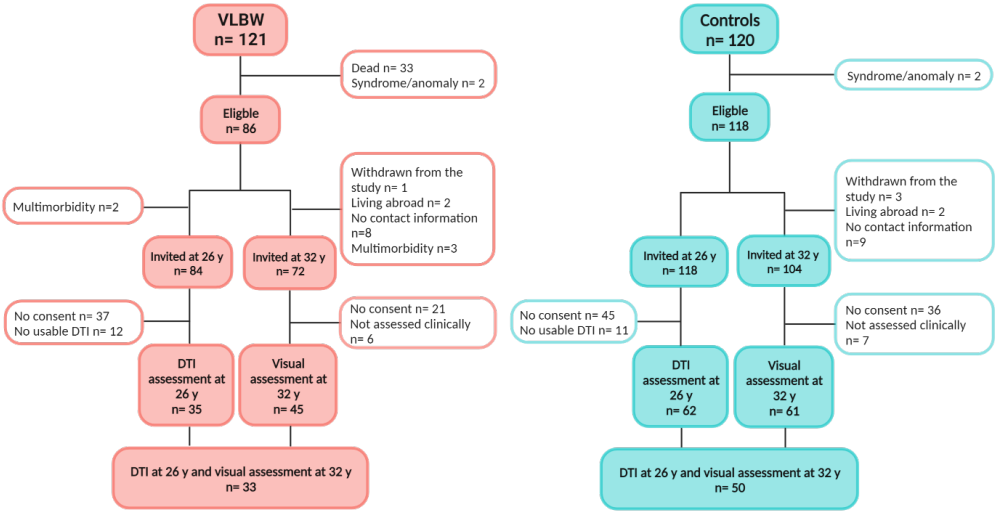

Figure 6. The flow of participants in the VLBW and control group (Paper III)

DTI= diffusion tensor imaging; VLBW= very low birth weight; y= years.

3.3 Methods and assessments

Several assessments and methods were used in this thesis. They are summarised and grouped by study population in Table 1. A detailed description of all methods follows in this section. During assessments and analysis, all examiners were blinded for group status (children born extremely preterm with ROP or without ROP and VLBW or control).

The better eye of the participants was defined as the eye with the highest best corrected visual acuity measured with the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (described in more detail in the subsequent section). The right eye was chosen if the BCVA ETDRS letter score was equal in both eyes. The better eye was used in all analyses with visual data (retinal structure measures, best corrected visual acuity, contrast sensitivity, visual evoked potentials).

Diffusion tensor imaging metrics were extracted to explore the microstructure of white and cortical grey matter. The mean value of the right and left hemispheres was used for all metrics (fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity) in all analyses.

Table 1. Overview of methods and assessment used in this thesis

Type of assessment	Papers	Outcomes	Name of the assessment tool	References
Background data	I	Apgar score, BPD, BW, CP, ductus treatment, GA, IVH, NEC syndrome, ROP status and treatment	Norwegian Neonatal Network	(Norwegian Institute of Public Health 2005)
	III	Apgar scores, BW, GA, head circumference, IVH, maternal age, NSI, parental SES	Medical health records	
Visual assessments	I	Intraocular pressure	iCare device	
	I, II, III	Best corrected visual acuity	Early Treatment Diabetic Retinopathy Study Chart	(Brown, Kaiser et al. 2006) (Rosenfeld, Brown et al. 2006)
	I, III	Contrast sensitivity thresholds (cpd 3, 6, 12, 18)	CSV 1000E chart	(Kelly, Pang et al. 2012)
	II	CFT, CMT, FAZ, central MVD and MVF Circumpapillary RNFL thickness Peri-foveal IPGCL thickness	OCT (-A) (Zeiss Cirrus 6000)	(Akiyama, Saito et al. 2022)
	III	Central RNFL thickness	OCT (Heidelberg)	(Early Treatment Diabetic Retinopathy Study Research Group)
	II, III	PR-VEPs (16', 66', and 33' check size)	Keypoint Neurolite software	(Odom, Bach et al. 2016)
Brain MRI	I, II, III	T1- and T2- weighted images Diffusion tensor imaging	Siemens Skyra 3 Tesla system	
Neurodevelopment	I	Neuropsychological testing	Memoro test battery	(Hansen, Haferstrom et al. 2015, Hansen, Lehn et al. 2016, Hansen, Olsen et al. 2017)
		Development and behaviour	Parent-reported Five-to-Fifteen questionnaire	(Korkman, Jaakkola et al. 2004) (Lambek and Trillingsgaard 2015)

BPD= bronchopulmonary dysplasia; BW= birth weight; CFT= central foveal thickness; CMT= central macular thickness; CP= cerebral palsy; FAZ= foveal avascular zone; GA= gestational age; IPGCL= inner plexiform ganglion cell layer; IVH= intraventricular haemorrhage; MVD= macular vascular density; MVF= macular vascular flow; MRI= magnetic resonance imaging; NEC= necrotising enterocolitis; OCT= optical coherence tomography; PR-VEPs= pattern-reversal visual evoked potentials; RNFL= retinal nerve fibre layer; ROP= retinopathy of prematurity; SES= socioeconomic status.

3.3.1 Background characteristics (Papers I and III)

Background characteristics for both study populations included birth weight, gestational age, Apgar scores, sex, and intraventricular haemorrhage (IVH).

Background characteristics for children born extremely preterm (Papers I and II) also included ROP status and treatment, cerebral palsy, bronchopulmonary dysplasia, necrotising enterocolitis, and information about both medical and surgical treated ductus. In addition, intraocular pressure was measured with an iCare device (IC100 Tonometer, Centervue SpA., California, USA), and ocular medical history (use of glasses/lenses, eye disease/surgery and amblyopia treatment) was obtained for all participants.

Background characteristics for adults born with VLBW (Paper III) additionally included information about parental socioeconomic status (SES), head circumference at birth, maternal age, and the presence of neurosensory impairment (NSI). Parental SES was calculated according to Hollingshead´s Two Factor Index of Social Position, based on parental education and occupation information (Hollingshead 1957). The score ranges from 1 (low) to 5 (high). Parental SES was collected at the 14 years assessment and supplemented at the 19 years assessment. The presence of NSI was defined as blindness, use of a hearing aid, cerebral palsy diagnosed by a paediatrician at the 14-year follow-up or self-reported at the 32-year follow-up, and/or IQ score below 70 assessed by a psychologist with versions of the Wechsler Intelligence Scale at 19, 14, and 5 years (Yule, Gold et al. 1982, Wechsler 1999, Tulsky, Saklofske et al. 2003).

3.3.2 Best corrected visual acuity (Papers I, II, and III)

The best corrected visual acuity (BCVA) tests the sharpness of your vision and how well you can see from a certain distance with best-corrected vision. Following subjective refraction under standardised light conditions, BCVA was measured at a 4 m distance according to the standardised Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (Brown, Kaiser et al. 2006, Rosenfeld, Brown et al. 2006). The ETDRS chart is presented in Figure 7. Participants are told to read the letters on each line from the left and as far down as possible as the letters get smaller. How many letters they can read determines their BCVA ETDRS letter score.

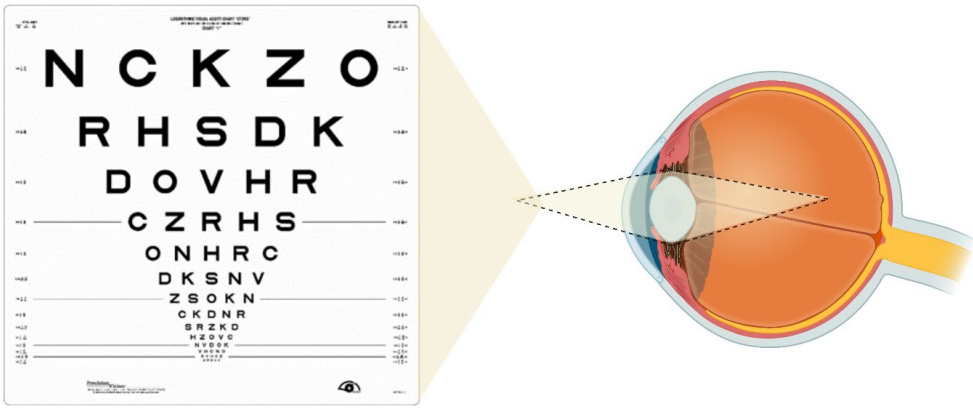

Figure 7. Testing of visual acuity with the ETDRS chart (Papers I, II, and III)

Best corrected visual acuity assessment with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart from PrecisionVision, testing how sharp the participants' vision was at a 4 m distance. ©Sigrid Hegna Ingvaldsen (2023)

3.3.3 Contrast sensitivity (Papers I and III)

Contrast sensitivity thresholds are also a measure of visual function that measures different levels of contrast in several spatial frequencies. Contrast sensitivity was tested with the best-refracted correction at a constant mean luminance of 85cd/m2 (no glare) using the CSV 1000E chart (VectorVision, Ohio, USA) at a 2.5 m distance (Kelly, Pang et al. 2012). The chart consists of four rows with different spatial frequencies (3, 6, 12, and 18 cycles per degree; cpd) with two circles of sine-wave gratings presented below each other in eight columns of declining contrast levels (Figure 8). Participants were asked to identify which of the two circles they could see a grating pattern shown as vertical lines. The lowest level of contrast the participants could see in each spatial frequency was the contrast sensitivity threshold (on a scale from 0-8, where eight is the nest contrast sensitivity threshold that showed the lowest level of contrast) and was used for analyses.

All spatial frequencies (3, 6, 12, and 18 cpd) were used for analysis in Paper I, while only 6 cpd was used as the contrast sensitivity measure in Paper III.

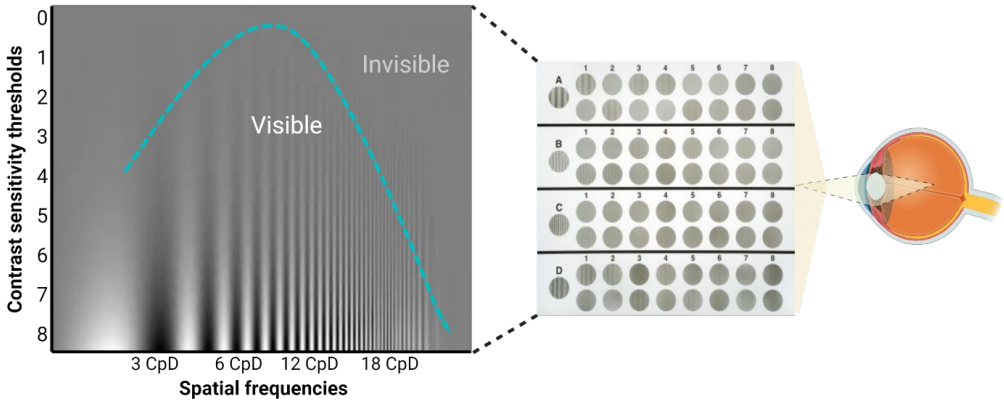

Figure 8. CSV 1000E chart and contrast sensitivity curve (Papers I and III)

*Left: the contrast sensitivity curve with contrast sensitivity thresholds on the y-axis and spatial frequencies on the x-axis, illustrating what is visible for the participants in higher spatial frequencies. Right: CVS 1000E chart from Vector Vision with contrast sensitivity thresholds in columns from left to right (1-8) and spatial frequencies 3-18 cycles per degree (*cpd*) in rows from top to bottom (A-D).* ©Sigrid Hegna Ingvaldsen (2023)

3.3.4 Optical coherence tomography (Papers II and III)

Optical coherence tomography (OCT) imaging is a reliable and useful tool for measuring retinal microstructure due to its non-invasive, real-time cross-sectional imaging of live tissue (Morken, Dammann et al. 2019). While OCT images measure the anatomical structure of the retina, OCT-angio (OCT-A) images measure the retina's vascular structure (Vinekar, Sinha et al. 2021).

In Paper II, retinal structure measures were obtained with the Zeiss Cirrus 6000 (Carl Zeiss Meditec, Inc., California, USA). The retinal areas in the OCT and OCT-A are presented by the ETDRS grid presented in the OCT-A image in Figure 10. The ETDRS grid divides the retina into the central retina (A1 area), which measures 1 mm in diameter, the inner retina (A2-A5 areas), measuring 3 mm in diameter and the outer retina (A6-A9 areas), measuring 6 mm in diameter. Figure 10 presents an OCT B-scan where you can see all segmented layers of the retina in the centre (1 mm), inner retina (3 mm), and outer retina (6 mm). The OCT-A parameters included macular vascular density (mm/mm^2) and macular vascular flow (%) in the superficial central

area of A1, the foveal avascular zone (FAZ) area (mm^2), FAZ circularity and mean central macular thickness (µm) in A1. Peri-foveal inner plexiform ganglion cell layer thickness (IPGCL; µm) was measured as the average of the inner (A2-A5) and outer (A6-A9) layers of the macula. Circumpapillary retinal nerve fibre layer thickness (RNFL; µm) was automatically quantified by the software as the average of all papillary sectors surrounding the optic nerve. Central retinal thickness was measured manually from the inner limiting membrane to the outer limit of the retinal pigment epithelium.

In Paper III, a Heidelberg Spectralis machine (Heidelberg, Germany) was used to obtain central RNFL thickness from the A1 area. Figures 9 and 10 presents the OCT measures used in this thesis.

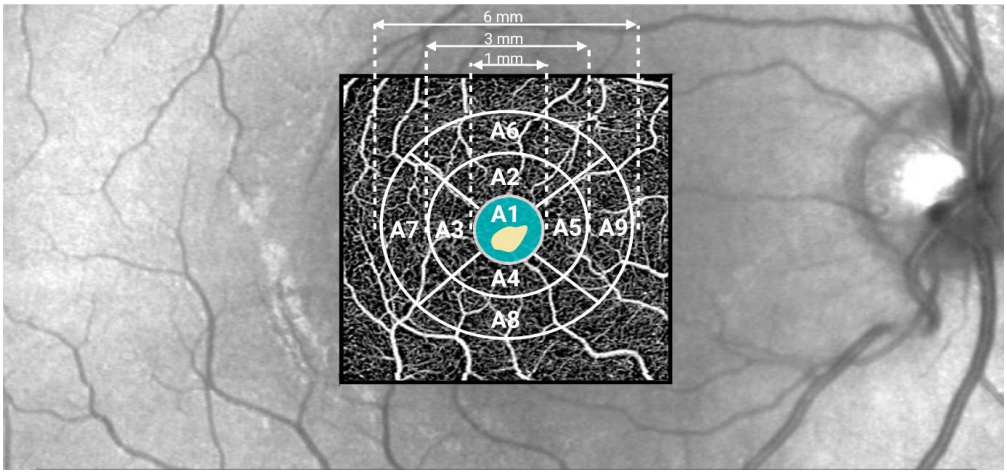

Figure 9. OCT-A image of the macula with the ETDRS grid (A1-A9) (Paper II)

ETDRS= Early Treatment Diabetic Retinopathy Study; OCT-A= optical coherence tomography angiography. The ETDRS grid with the centre (1 mm in diameter; A1), inner retinal layers (3 mm; A2-A5) and outer retinal layers (6 mm; A6-A9). The foveal avascular zone is in yellow (Paper II). The mean central macular thickness, vascular density and vascular flow were obtained from the A1 ETDRS area (blue) (Paper II). ©Sigrid Hegna Ingvaldsen (2023)

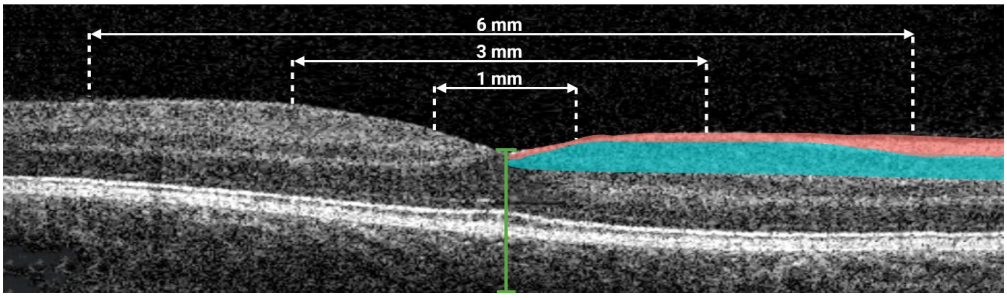

Figure 10. OCT B-scan of the retinal layers assessed in this thesis (Papers II and III)

OCT= optical coherence tomography. A cross-sectional OCT image (B-scan) of the retina presenting the OCT measures used in this thesis. The retinal nerve fibre layer thickness (pink area) was measured circumpapillary in Paper II and within the 1 mm A1 of the ETDRS grid in Paper III. The inner plexiform ganglion cell layer thickness (blue area) consists of the inner plexiform and ganglion cell layers and was measured peri-foveal (the average thickness of A2-A9 ETDRS areas) in Paper II. The central retinal thickness (green line) was measured from the dip to the retinal pigment epithelium (Paper II). ©Sigrid Hegna Ingvaldsen (2023)

3.3.5 Pattern-reversal visual evoked potentials (Papers II and III)

Pattern-reversal visual evoked potentials (PR-VEPs) provide information about visual pathway function, making PR-VEP recordings a good tool for exploring the visual pathway from the macula to subcortical brain areas. Visual evoked potentials are electrophysiological responses elicited by several discrete visual stimuli that activate the visual cortex. For the studies included in this thesis, pattern-reversal stimuli were chosen so that PR-VEPs could provide an index of visual maturation and reveal visual pathway function in preterm participants (Ruberto, Angeli et al. 2014, Markand 2020).

Figure 11 show the PR-VEP assessment and the quantitative electrophysiological presentation of the components that are extracted; the visual stimuli's strength (amplitude) and speed (latency). The N70 and P100 latency (ms) and peak-to-peak N70-P100 amplitude (µV) were obtained for analysis in Papers II, and the P100 latency was obtained for analysis in Paper III. Latencies were measured from stimulus onset to the peak of the N70 and P100 waves, and amplitude was measured between the N70 and P100 peaks. The P100 peak represents the first positive electrophysiological signal reaching the visual cortex approximately 100 ms after stimulus onset. A P100 latency of more than 100 ms indicates delayed processing of the visual stimuli.

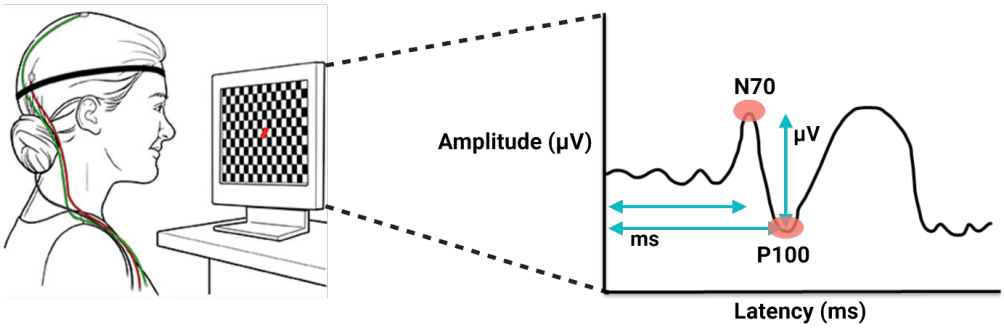

Figure 11. Pattern-reversal visual evoked potentials task (Papers II and III)

Left: illustration of the pattern-reversal visual evoked potential task. Right: the recorded electrophysiological signal where the amplitude (measured in µV) is presented on the y-axis, and latency (measured in milliseconds) is presented on the x-axis. The first negative peak (N70) and the first positive peak (P100) used in this thesis are marked with red boxes. ©Sigrid Hegna Ingvaldsen (2023)

The PR-VEPs were recorded on a Keypoint computer (Keypoint, Neurolite Software, Natus, Switzerland) from the occipital midline (Oz) and referred to the mid-frontal electrode (Fz) according to the ISCEV standards (Odom, Bach et al. 2016). The subjects were seated and relaxed in a chair with neck support in a dark room. One eye was covered with an eyepatch while looking at the monitor. The monitor showed high-contrast black-and-white checks with a red fixation point in the middle of the checkboard that the participants fixated on in each run. In Paper II, PR-VEPs were recorded in one eye at a time with 66' (12x16) (large checks) and 16' (48x64) (small checks). In Paper III, PR-VEPs were recorded in one eye at a time with a 33' (24x32) check size.

3.3.6 Magnetic resonance imaging (Papers I and III)

Magnetic resonance imaging (MRI) is a well-established and powerful tool for exploring brain anatomy and long-term brain development in vivo. The principle of MRI is based on the spinning motion of specific nuclei present in biological tissue. The nuclei are characterised by their tendency to align their axis of rotation to an applied magnetic field, and they have unequal atom numbers, such as hydrogen (^{1}H). Hydrogen atoms (protons) can be manipulated when placed in a magnetic field and used to discriminate between biological

tissue or demonstrate the contrast between normal anatomical features and pathology (Westbrook and Talbot 2019). In the studies included in this thesis, brain MRI was performed on a Siemens Skyra 3 with a scan time of approximately 20 minutes.

Structural imaging (Paper I)

One of the main advantages of MRI is its excellent tissue contrast, making it a good tool for evaluating atypical brain development (Giedd and Rapoport 2010, Tocchio, Kline-Fath et al. 2015). The contrast characteristics of the MRI images depend on many variables that can be altered to highlight fat or water in brain tissue, which can help identify pathology or brain atrophy in MRI images. Structural MRI imaging often uses specific sequences to obtain T1- and T2-weighted images. In general, T1-weighted images increase the signal of fat and suppress the signal of water, while T2-weighted images increase the signal of water and suppress the signal of fat in brain tissue (Westbrook and Talbot 2019). An example of the difference between a T1- and T2-weighted MRI image is presented in Figure 12.

In Papers I and II, a 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence and a 3D T2 spin echo (SPACE) sequence was used for the brain imaging of the children born extremely preterm. The images were read by a consultant in neuroradiology using a standardised protocol, including an assessment of the ventricular system, brain surface, the posterior fossa, and craniocervical junction. A thorough evaluation of potential white matter abnormalities and tissue atrophy was performed, in addition to the thickness of the corpus callosum, hippocampus volume, cerebellum size and other pathological findings. The thickness of the optic nerve and chiasma was also evaluated.

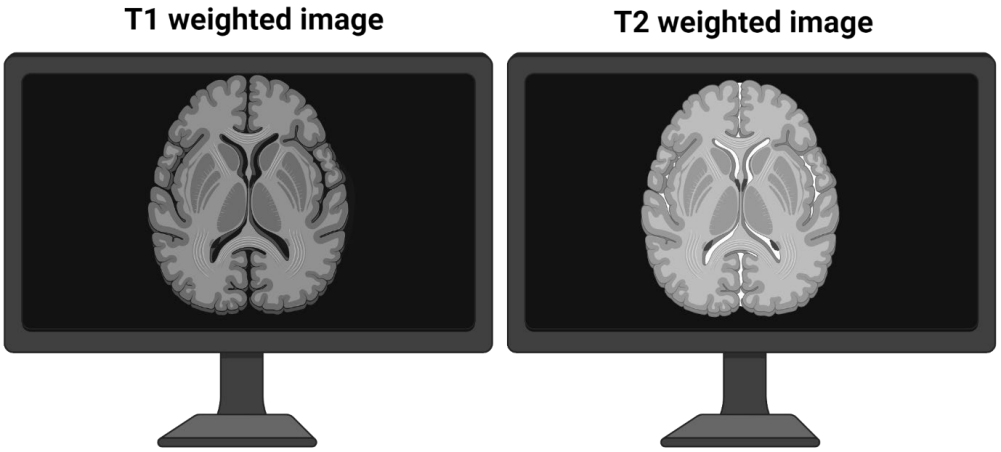

Figure 12. T1- and T2-weighted images (Paper I)

Diffusion tensor imaging (Paper III)

White matter (WM) and cortical grey matter (GM) microstructure alterations can be seen with diffusion tensor imaging (DTI), an MRI technique for exploring white matter organization and connectivity. The axons and their myelin sheet act as barriers to the free and random motion (or diffusion) of water molecules in brain tissue. Imaging with DTI can measure the water molecules' net displacement by calculating their diffusion degree and direction (Wycoco, Shroff et al. 2013). If water molecules are not obstructed in the short diffusion time frame, they may travel freely, and the MRI signal will be approximately the same in all directions, such as in the case of cerebrospinal fluid. However, if water molecules are hindered by axons within a white matter tract, the MRI signal will be altered depending on the direction of the diffusion gradients relative to the direction of the tissue (Curran, Emsell et al. 2016).

Quantitative DTI metrics allow us to calculate parameters that can tell us about the diffusion direction of water molecules and, thereby, the organization of WM and GM microstructure, voxel by voxel in the brain. For example, fractional anisotropy (FA) measure the degree of directionality of the diffusion in the WM fibres from 0 (isotropic indicating disorganized white matter) to 1 (anisotropic movement indicating good white matter organization) (Alexander, Lee et al. 2007, Bouyssi-Kobar, Brossard-Racine et al. 2018), while mean diffusivity (MD)

characterises the overall diffusivity in a particular voxel (Curran, Emsell et al. 2016, Rimol, Botellero et al. 2019). Axial diffusivity (AD) represents diffusion parallel to the WM tracts, and radial diffusivity (RD) represents diffusion perpendicular to the WM tracts. The AD and RD metrics can indicate whether low FA and high MD that characterises the preterm brain are more related to axon injury and poor fibre organisation (lower AD) or impaired myelination and axon packing (higher RD) (Hollund, Olsen et al. 2018, Pascoe, Melzer et al. 2019). The DTI metrics and their relationship with each other can be visualized as an ellipsoid with three tensors (λ1, λ2, and λ3) indicating the diffusion direction and orientation, as illustrated in Figure 13.

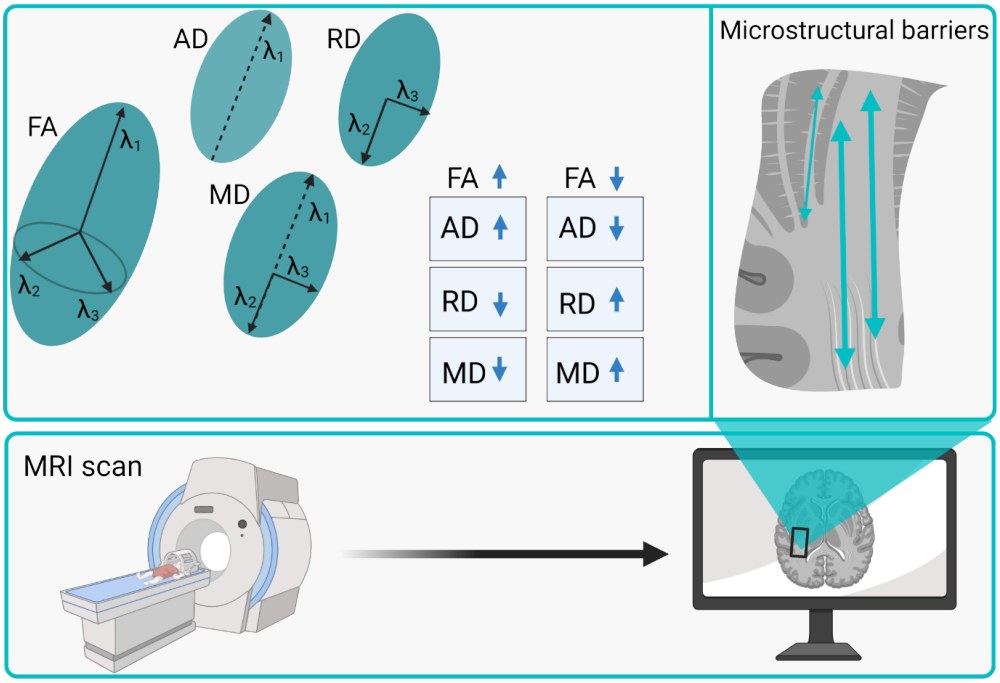

Figure 13. Diffusion tensor imaging (Paper III)

AD= axial diffusivity; FA= fractional anisotropy; MD= mean diffusivity; MRI= magnetic resonance imaging; RD= radial diffusivity. Top left: FA, AD, RD, and MD presented as ellipsoids with tensors. Top centre: the characteristic pattern of relationships between the DTI metrics. Top right: illustration of the diffusion in white matter microstructure. Bottom: MRI machine and horizontal view of an MRI image.

In Paper III, DTI from the 26-year-old adults born preterm with VLBW was acquired, and voxel-wise maps of FA, MD, AD (λ1), and RD (λ2+ λ3)/2) were calculated for the VLBW and control group. In addition, regions of interest in white matter tracts and primary visual cortex were manually created based on masks from the John Hopkins University white-matter labels atlas (Mori, Wakana et al. 2005) and the Jülich histological atlas in FSL (Bürgel, Schormann et al. 1999, Bürgel, Amunts et al. 2006) (Figure 14).

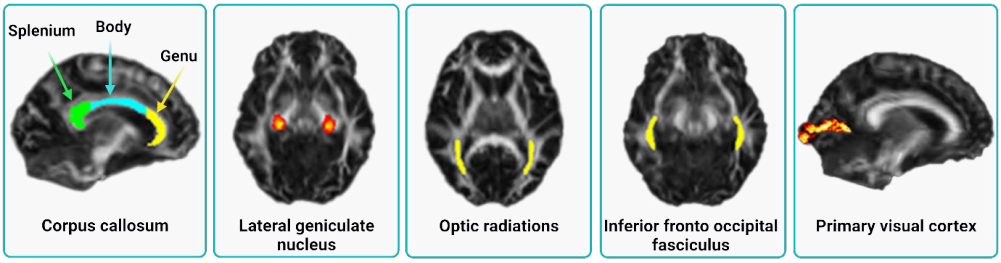

Figure 14. Regions of interest along the visual pathway (Paper III)

From the left: corpus callosum (including the splenium, body, and genu), lateral geniculate nucleus optic radiations, inferior-fronto occipital fasciculus, and primary visual cortex. ©Sigrid Hegna Ingvaldsen (2023)

3.3.7 Neuropsychological testing- Memoro test battery (Paper I)

Neuropsychological testing was performed with the self-administered web-based test battery Memoro (https://memoro.no), a validated and reliable tool for neuropsychological testing (Hansen, Haferstrom et al. 2015, Hansen, Lehn et al. 2016, Hansen, Moskowitz et al. 2017). The test duration was approximately 20 minutes and tested reaction time, executive function, working memory, processing speed, visual memory and pattern separation. A detailed description of the tasks is included in the supplementals of Paper I.

3.3.8 Development and behaviour- Five to Fifteen questionnaire (Paper I)

Parent-reported neurodevelopmental challenges were assessed with the Five-to-Fifteen (FFT) questionnaire. The FFT is a reliable and validated standardised Nordic questionnaire for evaluating the development and behaviour of children and adolescents aged 5-15 years (Korkman, Jaakkola et al. 2004, Lambek and Trillingsgaard 2015). The questionnaire covers

several neurodevelopmental domains, such as motor skills, executive functions, perception, memory, language and communication, learning skills, social skills, and mental health problems. Statements related to learning, executive function, motor skills and perception were assessed in Paper I. Scores, where a higher value means a higher level of challenges, were compared with a 90th percentile score from a normative population sample matched by sex and age (Lambek and Trillingsgaard 2015). The FFT questionnaire and 90th percentile scores are included in the supplementals of Paper I.

3.4 Statistical analysis

All statistical analyses in the thesis were conducted using the SPSS software 27.0 (IBM, New York, USA) and RStudio 4.2 (PBC, Boston, MA). Two-sided p-values <0.05 was regarded as statistical significance. Histograms and Q-Q plots were visually inspected to assess the normality of the data distributions, and statistical analysis was chosen as suited. Independent two-sample *t*-tests and chi-square tests were applied to test for differences in background characteristics between participants and non-participants (Paper I). In all Papers, a subnormal visual acuity was defined as a BCVA ETDRS letter score of <85 (equivalent to 20/20 Snellen and LogMAR 0.0; clinically regarded as normal vision). In Papers I and II, the percentage of participants with subnormal contrast sensitivity and OCT measures were calculated based on cut-off scores from reference populations. Cut-off scores for subnormal PR-VEPs (Paper II) were defined as 2 or 3 SD from the mean based on a reference population. The cut-offs for subnormal scores are presented in Table 2.

In Paper I, Memoro scores were converted into z-scores using data from 51 healthy individuals (59% females) with a mean age of 14 years (range 13 to 14 years) from the Memoro normative database. Independent two-sample t-tests with p-values adjusted for unequal variances and chi-square tests were used to assess for differences between participants with ROP and participants without ROP on all outcome variables. In addition, Pearson´s correlation analysis was conducted to explore associations between visual function (BCVA and contrast sensitivity) and neurodevelopmental outcomes (FFT scores and Memoro z-scores). For significant associations, a separate correlation analysis for participants with ROP and without

ROP was performed, and a z-score for the differences between within-group associations was calculated with Fisher's z transformation.

In Paper II, independent two-sample t-tests with p-values adjusted for unequal variances were performed to assess differences in OCT- and PR-VEP outcomes between participants with and without ROP. Next, a partial Pearson's correlation analysis, controlling for the effect of age, was performed to explore the association between PR-VEP outcomes and RNFL and IPGCL thickness.

In Paper III, we assessed differences in visual outcomes and DTI metrics for each region of interest (ROI; one at a time) between groups (VLBW and control group) using linear regression with age at assessment and sex entered as covariates. Next, we explored whether DTI metrics could predict visual outcomes using linear regression with one visual outcome at a time as the dependent variable. Age at 32 years, sex, MD for V1 and FA for each remaining region of interest (one at a time), group and the interaction between group and FA/MD in ROIs were entered as independent variables. Finally, to explore potential causes for associations between FA and MD in regions along the visual pathway with reduced visual outcomes, the same linear regression analysis was repeated with AD and RD as DTI metrics.

Table 2. Cut-offs for subnormal scores based on term-born reference populations

Paper	Outcome	Age	Subnormal cut-off score	Assessment tool	Reference
I	3 cpd	11-19 years	<6 threshold	CSV 1000E chart	(VectorVision 2004)
I	6 cpd	11-19 years	<7 threshold		
I	12 cpd	11-19 years	<7 threshold		
I	18 cpd	11-19 years	<7 threshold		
II	FAZ area	6-8 years	<0.3 mm/mm^2	PlexElite 9000	(Rezar-Dreindl, Eibenberger et al. 2021)
II	FAZ circularity	6-8 years	<0.7		
II	RNFL thickness	6-15 years	<83 µm	Zeiss Cirrus	(Larsson, Molnar et al. 2018)
II	IPGCL thickness	8 years	<99 µm		(Pueyo, González et al. 2015)
II	CMT	6-15 years	>255 µm		(Molnar, Holmström et al. 2015)
II	P100 latency (small checks)	Adults	≥113.5 ms (+2 SD) ≥119.3 ms (+3 SD)	Keypoint software	Local values were obtained at the Department of Neurology Section of Clinical Neurophysiology at St.Olavs Hospital, Trondheim, Norway
II	P100 latency (large checks)	Adults	≥109.4 ms (+2 SD) ≥114.8 ms (+3 SD)		
II	N70-P100 amplitude (small checks)	Adults	≤3.9 µV (-2 SD) ≤2.5 µV (-3 SD)		
II	N70-P100 amplitude (large checks)	Adults	≤2.7 µV (-2 SD) ≤1.5 µV (-3 SD)		

CMT= central macular thickness; cpd= *cycles per degree; ETDRS= Early Treatment Diabetic Retinopathy Study; FAZ= foveal avascular zone; IPGCL= inner plexiform ganglion cell layer; ms= milli seconds; RNFL= retinal nerve fibre layer; SD= standard deviation; µm= micrometre; µV= amplitude.*

3.5 Ethics

The studies included in this thesis were conducted following the principles of the Declaration of Helsinki, and the methods used were non-invasive and did not inflict pain. All participants were referred to a medical specialist if indicated by assessments. The Regional Committee for Medical and Health Research Ethics (REK) in Central Norway approved the study involving school-aged children born extremely preterm (registration number: 100434, Paper I and II) and adults born preterm with VLBW and term-born controls (registration number: 23879, Paper III).

In the study involving school-aged children born extremely preterm, written informed consent was obtained from both parents before enrolment, and the participants received financial compensation by gift card (NOK 300) for attendance. In the study involving adults born preterm with VLBW and term-born controls, written informed consent was obtained from all participants, and they received financial compensation of NOK 1000 for attendance.

4 Results

4.1 Background characteristics of the study populations

School-aged children born extremely preterm (Papers I and II)

Two participants (6%) had nystagmus, five (14%) had been treated for amblyopia, and 15 (42%) used glasses or lenses. Nearly half (49%) of the participants scored lower than a BCVA ETDRS letter score of <85, equivalent to LogMAR 0.0, in their better eye and 67% scored lower in their worse eye. The prevalence of ROP was 19%. Of the seven participants with ROP, two developed Type I and were treated. One participant had Type II that regressed, and four had mild ROP (stage 2). Table 3 shows the background characteristics of the participants. There were no significant differences between participants and non-participants (results are presented in Paper I).

Table 3. Background characteristics for school-aged children born extremely preterm

Variable	Participants (n= 36)	
	Mean	**(SD)**
Gestational age (weeks)	26.2	(1.3)
Birth weight (grams)	848.8	(224.2)
Apgar score after 5 min	8.03	(1.7)
Age (years)	12.8	(1.6)
	n	**(%)**
Males	11	(30.6)
Preeclampsia; yes	9	(26.5)
Antenatal steroids	25	(71.4)
ROP status	7	(19.4)
Type I	2	(0.06)
Type II	1	(0.03)
stage 2	4	(11.1)
Cerebral palsy	1	(2.8)
BPD; yes	16	(45.7)
IVH; yes	4	(11.1)
NEC syndrome; yes	1	(2.9)
Surgically treated ductus; yes	11	(30.6)
Medically treated ductus; yes	16	(44.4)

BPD= bronchopulmonary dysplasia; IVH= intraventricular haemorrhage; NEC= necrotising enterocolitis; ROP= retinopathy of prematurity; SD= standard deviation.

Adults born preterm with very low birth weight and term-born controls (Paper III)

Table 4 shows the background characteristics of the VLBW and control group. For the VLBW group, 24% scored lower than a BCVA ETDRS letter score of <85, equivalent to LogMAR 0.0, in their better eye and 64% scored lower in their worse eye. For the control group, 18% scored lower than a BCVA ETDRS letter score of <85 in their better eye and 40% scored lower in their worse eye. No participants had been treated for ROP. Three participants in the VLBW group had intraventricular haemorrhage and four had neurosensory impairment.

There were few differences between the participants and non-participants (results are presented in supplementals of Paper III). However, for the VLBW group, non-participants had slightly lower gestational age, birth weight, Apgar score after 1 min, and maternal age at delivery than the participants. There were also fewer males among the participants compared with non-participants. For the control group, non-participants had slightly lower gestational age and maternal age at delivery than participants.

Table 4. Background characteristics for the VLBW and control group

Variable	VLBW group (n= 33)		Control group (n= 50)	
	Mean	**(SD)**	**Mean**	**(SD)**
Maternal age[a]	30.0	(5.3)	31.3	(4.5)
Parental SES (1-5)[b]	3.3	(1.3)	3.9	(1.1)
Birth weight (grams)	1274.7	(203.6)	3736.1	(472.4)
Gestational age (weeks)	29.6	(2.8)	40.0	(1.2)
Birth head circumference (cm)[c]	27.5	(2.2)	35.6	(1.1)
Apgar score after 1 min[d]	7.1	(1.7)	8.9	(0.4)
Apgar score after 5 min[d]	8.8	(1.1)	9.9	(0.4)
Age at brain MRI (26 years)	26.2	(0.7)	26.5	(0.4)
Age at clinical assessment (32 years)	32.4	(0.8)	32.5	(0.5)
	n	**(%)**	**n**	**(%)**
Males	13	(39)	21	(42)
Intraventricular haemorrhage; yes[e]	3	(9)	0	*NA*
Neurosensory impairment; yes	4	(12)	0	*NA*

MRI= magnetic resonance imaging; SD= standard deviation; SES= socioeconomic status 1-5, where five is highest; VLBW= very low birth weight.

[a] Data missing for one control participant

[b] Data missing for two VLBW participants and eight control participants

[c] Data missing for five VLBW participants and three control participants

[d] Data missing for one VLBW participant and three control participants

[e] Data missing for one VLBW participant

4.2 Main findings of the papers included in this thesis

Paper I: ***Visual function correlates with neurodevelopment in a population cohort of school-aged children born extremely preterm***

We found that over half of the participants scored lower than cut-offs for subnormal contrast sensitivity scores in all spatial frequencies. Nearly half (49%) of the participants scored lower than a normal visual acuity letter score of 85 in their better eye, and 67% scored lower than normal in their worse eye. The median BCVA ETDRS letter score for the better eye was 82 in participants with ROP and 85 in participants without ROP. Moreover, results revealed a pattern of increased visual acuity with higher gestational age.

Approximately half of the participants showed higher levels of parent-reported neurodevelopmental challenges >90th percentile in all domains (learning, executive functions, motor skills, and perception). The lowest performance for neuropsychological testing with Memoro (presented as z-scores) was found in reaction time (-1.9 SD), executive functions (-2.3 SD), and processing speed (-1.2 SD). Visual acuity correlated negatively with parent-reported learning, executive functions, motor skills, and perception. Contrast sensitivity correlated negatively with perception (3 cpd and 12 cpd) and motor skills (3 cpd). There were no associations between visual function and Memoro z-scores. The findings indicate that school-aged children born extremely preterm display lower performance on tasks related to visual processing compared with term-born peers. Moreover, they display subnormal visual function which is correlated with increased parent-reported neurodevelopmental challenges.

Paper II: ***Retinal structure and visual pathway function at school age in children born extremely preterm: A population-based study***

The participants generally displayed altered retinal structure compared with cut-offs for subnormal scores. Their foveal avascular zone was smaller, the circumpapillary retinal nerve fibre layer (RNFL) and peri-foveal inner plexiform ganglion cell layer (IPGCL) were thinner, and central macular thickness was increased. The altered retinal structure was more pronounced in participants with ROP.

Moreover, 39% of participants displayed longer P100 latencies in small checks (small checks/large checks)123/117.1 ms) compared with participants without ROP (110/102 ms)Finally, we found a negative correlation between P100 latency in large checks and circumpapillary RNFL and peri-foveal IPGCL thickness. The finding suggests that school-aged children born extremely preterm have altered retinal structure and that there is a relationship between thinner RNFL and IPGCL thickness with delayed visual pathway signalling in this group.

Paper III: ***Visual outcomes and their association with grey and white matter microstructure in adults born preterm with very low birth weight***

We found that the VLBW group displayed lower contrast sensitivity and a thicker central RNFL than the control group. The VLBW group also showed higher axial and radial diffusivity in the genu of the corpus callosum (CC) and higher radial diffusivity in the optic radiations (ORs) compared with the control group.

Moreover, prediction analyses with linear regression revealed an interaction effect between group and fractional anisotropy (FA) in regions within the CC and mean diffusivity (MD) in primary visual cortex (V1) on visual acuity, contrast sensitivity, and P100 latency. Within the VLBW group, higher FA in CC regions, ORs and lateral geniculate nucleus (LGNs), and lower MD in V1 predicted better visual acuity; higher FA in body of CC, ORs, and inferior-fronto occipital fasciculus, and lower MD in V1 predicted better contrast sensitivity; and higher FA in splenium of CC and ORs predicted a P100 latency closer to 100 ms. These associations were not observed within the control group. After performing sensitivity analyses excluding participants with neurosensory impairments, there was no longer a significant interaction effect between group and FA/MD in regions along the visual pathway on visual outcomes. However, higher FA in LGNs still predicted better visual acuity; and higher FA in the body of CC and ORs still predicted better contrast sensitivity within the VLBW group. The findings suggest that DTI metrics in regions along the visual pathway could predict visual function outcomes in adults born preterm with VLBW.

5 Discussion

5.1 Methodological considerations

5.1.1 Outcome measures and assessments

We measured visual function and structure to assess visual outcomes in this thesis and used the better eye for all analyses. The better eye was defined as the eye with the best corrected visual acuity, measured by BCVA ETDRS letter scores. There are some disagreements in the ophthalmological field on whether the better eye or both eyes should be used in clinical research. Including both eyes in the analysis will increase the data points and the study's statistical power. However, if data from the right and left eye are used, the correlation between eyes should be assessed (Sainani 2010), and if the correlation is strong, some choices of statistical analysis will be lost because most statistical procedures assume that observations are independent of each other (Armstrong 2013).

Using both eyes in the analysis may also distort the BCVA ETDRS letter score due to potential non-central nervous system injury, such as amblyopia or strabismus, which could affect the visual acuity in the worse eye (Larsson, Rydberg et al. 2006). The better eye will be the preferred eye for participants and therefore a more accurate measure of visual function in daily life, which is the primary visual outcome in this thesis. Thus, even though the statistical power would perhaps be increased by including both eyes in analyses, we chose to use the better eye to improve the clinical impact of our findings and remove the potential confounding influence of the worse eye.

The adults born preterm with VLBW assessed in Paper III were born in the 1980s before data from systematic ROP screening was available to the extent that allows for analysis. We, therefore, lack information regarding the ROP status in this group. However, none of the participants had been treated for ROP, so it is unlikely that the results were largely affected by an unknown severe ROP diagnosis.

To assess neurodevelopmental outcomes in children born extremely preterm (Paper I), a parent-reported Nordic questionnaire called Five-to-Fifteen and a self-administered web-based neuropsychological test battery called Memoro were used. Even though the Five-to-

Fifteen questionnaire has been validated in several Nordic populations (Korkman, Jaakkola et al. 2004, Lambek and Trillingsgaard 2015), the results cannot, with high confidence, be generalized to populations outside the Nordic countries because parent-reporting of neurodevelopmental challenges in children is subjective and may be affected by cultural differences. Also, the Memoro test battery used for neuropsychological testing was developed in Norway and has only been validated in Norwegian populations (Hansen, Lehn et al. 2016). Still, the tasks included in Memoro are based on well-known neuropsychological tests (Stark, Yassa et al. 2013, Evensmoen, Rimol et al. 2021). Furthermore, the tasks are mainly visual and, therefore, to a smaller degree, affected by language- and cultural differences.

In Paper I, T1- and T2-weighted images were read to assess whether the school-aged children had any cerebral or diffuse white matter injury, but diffusion tensor imaging (DTI) analyses were not performed. A DTI sequence was added to the brain MRI assessment. But unfortunately, several participants had braces which interfered with the image reliability due to image distortion and signal reduction caused by the metal. The susceptibility artefacts are commonly seen in the presence of braces when using echo-planar imaging of the head region (Miao, Wu et al. 2020). Consequently, few participants had any usable DTI data, making it difficult to perform any analysis.

In Paper III, we used DTI to measure white matter alterations in ROIs along the visual pathway and grey matter alterations in the primary visual cortex. Although DTI is a non-invasive technique which does not require contrast agents or chemical tracers (Corroenne, Arthuis et al. 2022), the MRI method has some methodological limitations that should be mentioned. Even though DTI has good reliability due to its sensitivity to tissue structure, it cannot account for cortical variation and is affected by various confounding tissue properties (Chen, Wang et al. 2023). Moreover, DTI cannot characterize complex diffusion in the presence of white matter crossing fibres due to the multimodality of diffusion orientation (Figley, Uddin et al. 2022). Previous findings have shown that fractional anisotropy will decrease when the axon diameter is large or when there is a fibre intersection which affects the white matter integrity in the voxels (Eikenes, Løhaugen et al. 2011, Chen, Wang et al. 2023). Consequently, DTI

cannot model more than one dominant orientation for each voxel, affecting its ability as a reliable tool for clinical imaging markers. Moreover, the limitations underline the importance of assessing axial diffusivity and radial diffusivity together with fractional anisotropy and mean diffusivity to characterize the diffusion and its clinical impact in more detail.

Some novel and advanced diffusion MRI techniques can overcome these limitations by increasing the specificity of certain microstructural properties (Martinez-Heras, Grussu et al. 2021). One of these techniques is high angular resolution diffusion imaging, a sequence using a larger number of unique diffusion-weighting gradient directions to capture more features of the diffusion orientation in voxels (Tournier, Mori et al. 2011). This sequence was tried in pilots of earlier brain MRI assessments in the NTNU LBW Life Study. However, the sequence made the scan time too long, consequently enhancing imaging artefacts, and was not included in the brain MRI study protocol for the NTNU LBW Life study.

5.1.2 Sample size and bias

A large sample size is every researcher's dream because it means a smaller margin of error, further increasing the study's statistical power and the reliability and generalizability of your findings (Armstrong 2019). However, when examining rare diseases and small populations, the recruitment of participants will be restricted, and the sample size will likely have a statistical power below the recommended 80%, consequently decreasing the validity of the results (Partington, Cro et al. 2022). Our population-based study in Central Norway assessing children born from 2006-2011 with and without ROP (Papers I and II) had a small sample size due to the small study population of children born extremely preterm in this geographical area, especially children with ROP. Even though it is known that ROP prevalence varies greatly within Norway, with up to a fivefold difference in odds of severe ROP between health regions, we expected the prevalence to be around 40-50% based on the prevalence of severe ROP in Norway from 2009 to 2017 (Grottenberg, Korseth et al. 2021). However, in our study including individuals born between 2006 and 2011, only 19% had ROP, suggesting that Central Norway is amongst the regions in Norway with the lowest prevalence of ROP.

In the longitudinal NTNU LBW Life follow-up study (Paper III), the loss to follow-up is inevitable. Of the adults invited for the study, the participation rate was 39% (VLBW group) and 46% (control group) in the 26-year brain MRI assessment and 42% (VLBW group) and 48% (control group) in the 32-year clinical assessment of visual outcomes. These participation rates are slightly lower than 50-80%, considered acceptable in cohort studies (Fewtrell, Kennedy et al. 2008). Additionally, the 32-year assessment was partially completed during the covid-19 pandemic, which affected the participation rate.

The studies included in this thesis were geographically or hospital-based within a specific period, thereby minimizing the risk of selection bias since all participants were born within the same period. Moreover, analysis between the children born extremely preterm that participated in the study and individuals that declined to participate (non-participants) did not reveal any significant differences in background characteristics (Paper I). Also, there were no clinically important differences in background characteristics between participants and non-participants in the VLBW or control group (Paper III). It is, therefore, unlikely that the results in this thesis have been affected by attrition bias due to systematic differences between participants and non-participants (Nunan, Aronson et al. 2018).

The internal validity (concerning the study's credibility) of cohort studies with two comparable groups can also be affected by misclassification bias (Miroshnychenko, Zeraatkar et al. 2022). Misclassification bias is an information bias that can affect the data if the researcher is exposed to group status during data collection or analysis (Tripepi, Jager et al. 2010). In this thesis, all researchers that collected, processed, and analysed the data were unaware of group status (children born extremely preterm with ROP or without ROP, and VLBW or control group) until the last level of the analysis. It is, therefore, unlikely that information bias has affected the results in this thesis.

5.1.3 Study design and confounding factors

A confounder is a variable distributed differently between study groups (such as gender or age) and is associated with the intervention or outcome (Yan, Karmur et al. 2020). In clinical

cohort studies with limited sample sizes and unbalanced sample ratio in study groups, there is always a risk of confounding factors affecting the results.

The small sample size in Papers I and II reduced our statistical power to some degree. Consequently, the significant differences between the participants with ROP and without ROP should be interpreted cautiously. Moreover, the participants with ROP were heterogeneous regarding their ROP diagnoses (two received treatment, four had mild ROP, and one had ROP that regressed). The small heterogenous group of participants with ROP could have caused the large variability in visual outcomes scores, consequently affecting the results. In addition, the findings of no significant difference between the VLBW and control group (Paper III) on some of the outcomes measures in this paper should also be interpreted with caution because the wide confidence intervals (as a result of relatively small sample size and large variability in the data) may include smaller clinical important effects between the groups (Hazra 2017, Schober, Bossers et al. 2018).

Including a control group in Papers I and II would have increased the validity of our results by reducing the effects of potential confounding factors and increasing the statistical power of the findings. To compensate for the lack of a control group and the potential bias that follows, we used cut-off values for subnormal scores based on data from age-matched term-born reference populations that were assessed using similar equipment and methods as presented in this thesis.

To minimize confounders affecting the analyses, we used adjustment for covariates, excluded extreme scores that could affect the results due to reasons other than low/high outcome scores, and performed sensitivity analyses. In Papers I and II, extreme scores (>2 SD from the mean) due to nystagmus, blindness, amblyopia, or technical difficulties (due to concentration difficulties during tests or electrophysiological noise during PR-VEP assessments) were removed from the final analysis. In addition, analysis with PR-VEP outcomes was adjusted for age in Paper II. In Paper III, all analyses were adjusted for sex and age, and sensitivity analysis excluding four participants with neurosensory impairments was performed for all regression analyses. The exclusion of participants with neurosensory impairments made the results

weaker, but indicated the same pattern of lower FA, higher MD and RD with reduced visual outcomes. These mentioned countermeasures, in addition to using the better eye in all analyses (thus, avoiding potential confounding from the worse eye), increased the study's internal validity.

No adjustments for multiple comparisons were made in the correlation- and regression analyses in Paper I-III. Partially because we were interested in several neurodevelopmental outcomes, DTI metrics, and visual outcomes, and some of these measures were likely correlated. Because of the small sample size and explorative nature of the studies, a p-value adjustment would reduce the chance of Type I error at the expense of increasing the likelihood of Type II errors (Rothman 2014).

5.1.4 Generalizability of results

Both studies in this thesis recruited preterm populations within a predefined period with no clinically significant differences between participants and non-participants. We can therefore conclude that the study groups are representative of the study populations of school-aged children born extremely preterm and adults born preterm with VLBW in Central Norway. The NTNU LBW Life Study participants were born in the 1980s, and one can debate whether the findings apply to individuals born preterm today. However, as the cohort study of children born from 2006-2011 showed, contrast sensitivity has not improved in later birth cohorts.

The findings of adverse visual outcomes in the participants included in this thesis cover a range of ages (children and adults), born in different periods (the 1980s and 2000s), with two different definitions of being preterm (based on birth weight and gestational age). The findings of reduced contrast sensitivity, longer P100 latencies, and altered retinal structure in both study populations increase the generalizability of findings to individuals born preterm across ages, and indicate that the thesis have high external validity (Carlson and Morrison 2009).

5.2 Interpretation of results

5.2.1 Visual function in children and adults born preterm

The children and adults born preterm showed close to normal BCVA, defined as a BCVA ETDRS letter score of ≥85, clinically regarded as normal vision. Moreover, only three letters separated the mean BCVA ETDRS letter score for the better and worse eye of the participants in Papers I and II. Studies that have assessed better visual acuity in school-aged children born extremely preterm are sparse. However, our findings coincide with a study of 10-year-old children born preterm with a birth weight of ≤1500 g that found no difference in visual acuity compared to controls (Larsson, Rydberg et al. 2006). Another study, including children born very preterm (GA ≤32 weeks) at 6 to 10 years of age with no history of ROP, found that they had slightly poorer BCVA in one eye compared with controls (Yassin, Al-Dawood et al. 2019). Also, a study of children born extremely preterm with a history of ROP (4 to 12 years of age) showed significantly lower BCVA in children with treated ROP and spontaneously regressed ROP compared with controls (Lee, Park et al. 2023)

In Paper III, there were no significant differences in mean BCVA ETDRS letter score between the VLBW and control group. A recent two-country birth cohort study including VLBW adults and term-born controls from the NTNU LBW Life Study and the Helsinki Study of Very Low Birth Weight Adults (HeSVA) found lower BCVA ETDRS letter score in the better and worse eye in the VLBW group compared with the control group (Kulmala, Jørgensen et al. 2023). The discrepancy in visual acuity from this study and Paper III could perhaps be caused by lower visual acuity in the VLBW adults from the HeSVA study. Also, it could be due to the larger sample size in the study of Kulmala et al. (2023). Indeed, the standard deviation in Paper III indicated large variability in scores within the groups, which makes it more difficult to detect a statistically significant difference when the sample size is relatively small (Field 2018).

Research on visual acuity in other cohorts of adults born preterm is sparse, but the EPICure study has reported significantly lower BCVA in young adults born extremely preterm with and without a history of ROP (Balasubramanian, Beckmann et al. 2019, Jain, Sim et al. 2022). Also, a follow-up study from New Zealand found that VLBW adults (27 to 29 years of age) with a history of ROP had significantly lower BCVA than adults without ROP and term-born controls

(Darlow, Elder et al. 2018). In the same study, visual impairment did not differ between the VLBW adults and controls but was seen more often in VLBW adults with a history of ROP (Darlow, Elder et al. 2018).

The discrepancy in findings between the EPICure and New Zealand studies and Paper III could indicate that ROP has a large effect on visual acuity since the EPICure and New Zealand studies (Darlow, Elder et al. 2018, Jain, Sim et al. 2022) included participants with ROP while it is unlikely that the VLBW adults in Paper III had a history of severe ROP that would have affected the results. On the other hand, we included children born extremely preterm with ROP in Paper I and found approximately normal BCVA regardless of ROP status. However, only two of these children had severe ROP. In addition, findings from Paper I also showed that participants born with gestational age (GA) ≤24 weeks had a larger variability in BCVA ETDRS letter scores, with lower scores than participants born with GA ≥27 weeks. These patterns in the data might indicate that GA and ROP status impact visual acuity, especially in individuals with severe ROP and GA <27 weeks.

Even though visual acuity is the clinic's most used visual function measure, testing of contrast levels in a range of spatial frequencies might be a more sensitive and correct reflection of day-to-day visual function than visual acuity. Visual acuity only consists of high-contrast stimuli and various levels of contrast, and not only high-contrast vision reaches cortical neurons for processing (Shamsi, Liu et al. 2022). Impaired contrast sensitivity can provide information on optical qualities, retinal layers, and higher-level visual processing (Shamsi, Liu et al. 2022) and will give a more comprehensive description of visual function than visual acuity alone. For instance, a study of children with complete recovery of visual acuity following amblyopia treatment showed that contrast sensitivity remained impaired (Jia, Ye et al. 2022). Also, one study found that contrast sensitivity was superior to visual acuity in identifying optic neuritis in multiple sclerosis (Fernandez and Villa 2022). In Paper I, the children born extremely preterm generally showed lower contrast sensitivity compared with cut-offs for subnormal scores, and participants with ROP had a lower contrast sensitivity threshold in the highest spatial frequencies (12 cpd and 18 cpd) compared with participants without ROP. The findings corroborate results from a Swedish cohort that found lower contrast sensitivity in children

born preterm with VLBW compared with controls, even when excluding children with a history of ROP (Larsson, Rydberg et al. 2006). In Paper III, VBLW adults showed reduced contrast sensitivity in the low spatial frequencies of 6 cpd. Similar findings have previously been demonstrated in the NTNU LBW Life Study at 14 years (Lindqvist, Vik et al. 2007). Moreover, the results are consistent with a Swedish cohort that found lower contrast sensitivity in VLBW adults (29 years of age) compared with controls (Pétursdóttir, Holmström et al. 2020). Hence, the findings from this thesis suggest that reduced contrast sensitivity in children born preterm might persist into adulthood.

Another interesting finding of this thesis is that participants born preterm also showed slightly longer P100 latencies at school age and in adulthood compared with reference populations and controls born to term. In Paper II, several participants displayed longer (+2 SD) P100 latencies in small checks (16') and some in large checks (66'). Also, Paper III showed that VLBW adults displayed slightly longer P100 latencies than the control group in a check size of 33'. Few have studied PR-VEPs in adults born preterm, and there are no studies of children born extremely preterm using the same method and check sizes as in this thesis. However, one study of 12-year-old children born moderate to late preterm (GA 32 to 36 weeks) found lower PR-VEP P100 amplitudes in a check size of 60' but no differences in latencies compared with a group of term-born controls (Raffa, Nilsson et al. 2017). Another study of 11-year-old children born preterm (mean GA of 30 weeks) found longer P100 latencies and lower P100 amplitudes in check sizes of 60' and 15' compared with controls (Michalczuk, Urban et al. 2015). Moreover, the same study also found a negative correlation between P100 latencies and GA indicating longer P100 latencies and lower amplitude with reduced GA (Michalczuk, Urban et al. 2015). Also, a study of 4-to-6-years old children born preterm with VLBW (birth weight ≤1500 g and GA ≤32 weeks) found longer P100 latencies in check sizes of 7', 13', 27', 54', and 108' compared with term-born controls. The same study also showed a pattern of longer P100 latencies with reduced check size and increased spatial frequency (Feng, Xu et al. 2011).

The inconsistency in P100 latency findings between the study of Raffa et al. (2017) with our results and others (Feng, Xu et al. 2011, Michalczuk, Urban et al. 2015) could be attributed to

the differences in GA at birth. The study of Raffa et al. (2017) included children with GA 32 to 36 weeks, while the other studies only had children with a GA ≤32 weeks (Feng, Xu et al. 2011, Michalczuk, Urban et al. 2015), and our participants were born with GA ≤28 weeks. The discrepancies might suggest that GA is an important risk factor for delays in visual pathway signalling. Indeed, Michalczuk et al. (2015) found that longer P100 latencies were associated with lower GA and a pattern of longer P100 latency with reduced GA was also observed in our study (Paper II).

Longer P100 latencies could indicate delayed visual pathway function in the two major visual pathways that the check sizes reflect, namely the magnocellular and parvocellular pathways. The magnocellular pathway responds to the low spatial resolution and high luminance contrast sensitivity that are presented by large checks, and the parvocellular pathway responds to the high spatial resolution and low luminance contrast sensitivity that is presented by the small checks (Fujita, Yamasaki et al. 2011, Tremblay, Vannasing et al. 2014). The magnocellular pathway is thought to convey input to the dorsal stream through dorsal areas of the visual cortex and to the parietal lobe, while the parvocellular pathway conveys information to the ventral regions of the visual cortex and the temporal lobe (Leung, Thompson et al. 2018). The findings of longer P100 latencies in both large and small check sizes of 16', 66' (Paper II), and 33' (Paper III) could suggest delayed visual pathway function in both the dorsal and ventral streams in individuals born preterm.

5.2.2 The association between visual function and neurodevelopment at school-age

Neurodevelopmental challenges in children born preterm without serious cerebral damage at birth may not become apparent until school-age. During this rapid developmental period, more complex cognitive and social skills are required to succeed in classroom- and social situations.

In Paper I, we found that school-aged children born extremely preterm score lower on neuropsychological tests than peers born to term, especially in tasks involving reaction time, processing speed, and executive functions. Even though low performance in these tasks did not show any significant association with visual function, the tasks provide information on

how fast participants transform visuospatial information into motor parameters and may reflect dorsal stream function (Van Braeckel, Butcher et al. 2008). Poorer performance on similar tests of visuomotor integration has been found in adults born preterm with VLBW compared with controls (Pétursdóttir, Holmström et al. 2021), suggesting that lower neuropsychological performance observed at school age could indicate delayed processing in the dorsal stream that might persist into adulthood. The parent reports of neurodevelopmental challenges indicated that the children born extremely preterm experienced learning, perception, and motor skills difficulties. These findings coincide with similar studies of children born preterm that found challenges with executive function (Doyle, Spittle et al. 2021), reading and mathematical problems (McBryde, Fitzallen et al. 2020) and perception skills (Butcher, Bouma et al. 2012) at school age compared with term-born peers.

Few studies have assessed whether or how visual function is associated with neurodevelopmental challenges. One study found a correlation between visual function at one year and neurodevelopmental testing within motor skills, social competencies and visual-motor coordination at two years (Ricci, Lucibello et al. 2020). In addition, visual function and perception have previously been associated with academic achievement in school-aged children born extremely preterm (Molloy, Di Battista et al. 2017). The findings of an association between reduced visual acuity and contrast sensitivity and higher levels of parent-reported neurodevelopmental challenges in this thesis could suggest that neurodevelopmental challenges following preterm birth become more apparent at school-age, especially in cases of complex visual scenes requiring fast visual processing of visual stimuli with various spatial frequencies.

5.2.3 Retinal structure as a clinical marker of visual function

Retinal imaging using OCT is a reliable tool for identifying pathological changes in the retina´s microstructure, as it provides real-time cross-sectional imaging of the live retinal tissue and is comparable with histological resolution (Vajzovic, Hendrickson et al. 2012). Imaging using OCT should, therefore, also be a good candidate for assessing clinical markers for the adverse visual outcomes observed in individuals born preterm. For example, the children born extremely preterm in Paper II showed signs of an altered retinal structure characterised by a

small foveal avascular zone (FAZ), thinner circumpapillary RNFL, thinner perifoveal IPGCL, and an increased central macular thickness. These findings are consistent with several other studies describing thicker inner retinal layers and thinner outer and circumpapillary layers in children born preterm with a history of ROP (Pueyo, González et al. 2015, Bowl, Stieger et al. 2016, Chen, Chen et al. 2019) and without ROP (Jabroun, AlWattar et al. 2021, Maleita, Serras-Pereira et al. 2021). Furthermore, Paper III showed that the VLBW group had a significantly thicker central RNFL than controls. This finding corroborates with the EPICure study that found thicker central RNFL in 19-year-old adults born preterm with VLBW compared with controls (Balasubramanian, Beckmann et al. 2019) and coincides with findings of thicker inner retinal layers in 5-16-year-old children born preterm (Åkerblom, Larsson et al. 2011).

The RNFL and IPGCL are perhaps the most relevant layers to assess for clinical markers of visual function due to the high amount of myelinated axons from these layers reaching the length of the optic nerve (Lam 2015, Yazdankhah, Shang et al. 2021). Indeed, studies have found the ganglion cell layer to be an independent predictor of visual function in adults born extremely preterm compared with other retinal layers (Balasubramanian, Jain et al. 2019), and circumpapillary RNFL is thinner in children born preterm (Fieß, Christian et al. 2017, Maleita, Serras-Pereira et al. 2021) independent of the effect of ROP. Moreover, circumpapillary RNFL correlates with BCVA in children born preterm with a history of ROP (Lee, Park et al. 2023).

The IPGCL and RNFL both contain retinal ganglion cell layers. Thus, thinner layers in that part of the retina could represent shrinkage or loss of retinal ganglion cells (Kupersmith, Garvin et al. 2016), causing decreased axonal density (Rothman, Sevilla et al. 2015). Furthermore, the altered retinal structure observed in this thesis may be caused by the disruption of the centrifugal retinal migration due to preterm birth, which further affects optic nerve development (Balasubramanian, Jain et al. 2019). The close anatomical connections between retinal ganglion cell layers and the optic nerve could explain the association between thinner IPGCL and RNFL delayed P100 latency in Paper II.

The immaturity of photoreceptors in individuals born preterm could also offer insight into the association of thinner RNFL and IPGCL with delayed PR-VEPs. The retina contains approximately 100 million rods and 6 million cones (Kandel, Schwartz et al. 2000), and these photoreceptors are the first stop for processing visual information by light absorption. They are also primarily responsible for conveying the information to the retinal ganglion cells in the RNFL and IPGCL that make synaptic connections with the optic nerve. While the rod photoreceptors are sensitive to light and responsible for vision under low luminance, the cone photoreceptors are solely responsible for vision in daylight and the fovea are packed with cones photoreceptors that set the limit of our visual acuity and colour vision (Kandel, Schwartz et al. 2000). Several studies have found reduced cone function in children born preterm (Ecsedy, Varsányi et al. 2011, Molnar, Andreasson et al. 2017), most likely due to delayed photoreceptor development as a consequence of preterm birth (Vajzovic, Rothman et al. 2015). Moreover, Masri et al. (2020) found a close synaptic connection between immature photoreceptors and delayed processing in the parvocellular and magnocellular pathways (Masri, Grünert et al. 2020). Decreased cone-mediated pupillary response to photopic stimuli has also been shown in children born preterm with macular developmental arrest, characterized by significantly reduced outer nuclear layer to inner retinal layer ratio in the fovea (Bowl, Lorenz et al. 2019, Bowl, Raoof et al. 2019).

The close anatomical relationship between retinal structure and visual pathway functioning shown by the reliable real-time cross-sectional imaging of the easily accessible OCT tool suggests that OCT is a good candidate for exploring clinical markers of adverse visual outcomes. The findings of thicker inner retinal layers and thinner outer retinal layers with OCT-imaging and an association of thinner RNFL and IPGCL with delayed visual pathway signalling in the participants born preterm in this thesis supports this notion.

5.2.4 White and grey matter alterations as a clinical marker for visual outcomes

The eye is an anatomical extension of the brain via the optic nerve, and several parallels can be seen between the neurons and vasculature (Nguyen, Acosta et al. 2021). For example, injury to the optic nerve and brain results in the same insults, such as degeneration of axons, scar formation, myelin destruction, and neurotoxic environments involving inflammation

(London, Benhar et al. 2013). It is, therefore, conceivable that indications of altered white and grey matter microstructure by assessing DTI metrics could serve as a helpful tool in locating the cause and degree of adverse visual outcomes with a neural origin. In Paper III, we found that altered white and grey matter microstructure, indicated by decreased fractional anisotropy (FA) and increased radial diffusivity (RD) and mean diffusivity (MD) in the visual cortex and corpus callosum at 26 years of age, predicted reduced visual function at 32 years of age within the VLBW group. The findings support DTI as a candidate for exploring clinical markers for adverse visual outcomes that cannot be explained by ROP alone because of other neural components. Indeed, inflammation as a consequence of preterm birth might induce damage to preoligodendrocytes which further leads to impaired development of myelination in the brain tissue that may result in altered white and grey matter microstructure.

Indeed, we did observe higher axial diffusivity (AD) and RD in the genu of corpus callosum (CC) and higher RD in the optic radiations (ORs) in the VLBW group compared with the control group. Low AD indicates axonal injury in white matter (Winklewski, Sabisz et al. 2018), which was not observed in the VLBW group. Instead, the VLBW group showed higher AD than controls, which might indicate that altered WM microstructure is not caused by axonal injury or poor fibre organization within the voxels in this group. Rather, impaired myelination may be the primary source of the altered white and grey matter microstructure associated with adverse visual outcomes, as indicated by higher RD (Pascoe, Melzer et al. 2019) in the genu of CC and ORs in the VLBW group compared with the control group. Indeed, higher RD (indicating impaired myelination) in the body of CC predicted reduced BCVA and contrast sensitivity function, and higher RD in LGNs and V1 predicted reduced BCVA within the VLBW group.

The DTI findings in this thesis also emphasize the importance of interpreting FA values together with AD and RD to interpret better what might cause white and grey matter alterations. However, as previously mentioned, DTI has some methodological issues limiting its reliability in analysing the cause of high or low DTI metrics due to its dependence on several factors such as fibre density, myelination, and axon diameter (Figley, Uddin et al. 2022). Therefore, it is important to conduct large-scale studies to further explore DTI metrics as

clinical markers for white and grey matter alterations associated with adverse visual outcomes in individuals born preterm.

Few studies have assessed the association of visual function and DTI metrics in individuals born preterm with VLBW. However, some studies have explored the possibility of retinal layers as clinical markers for neurodegenerative disorders (Mauschitz, Lohner et al. 2022) and severity of white matter lesions (Peng, Kwapong et al. 2020). In our study, DTI metrics were associated with visual function outcomes. These results coincide with earlier findings in the NTNU LBW Life Study of better visual acuity with higher FA in the CC in adolescents (Lindqvist, Skranes et al. 2011).

This study showed no significant associations between central RNFL thickness and DTI metrics in VLBW adults or term-born controls. Central RNFL thickness was measured in the A1 area of the ETDRS grid, which corresponds to the foveal area of the retina. Even though foveal development is crucial for visual function, there might be other measures of RNFL that would be more interesting to assess when exploring the associations with white and grey matter microstructure along regions in the visual pathway. In this case, circumpapillary RNFL thickness, used as the retinal structure measure in Paper II, has closer anatomical connections with the cortical processing of visual information because of its close synaptic connections with the optic nerve. Therefore, DTI metrics could be stronger associated with retinal structure that is more closely anatomically connected with higher cortical visual information processing, such as circumpapillary RNFL.

6 Concluding remarks and clinical implications

This thesis assessed visual function and retinal structure in school-aged children and adults born preterm and explored the association between neurodevelopmental challenges and visual function at school age. Moreover, the thesis explored clinical imaging markers for the brain MRI alterations (using diffusion tensor imaging; DTI) and altered retinal structure (using optical coherence tomography; OCT) included in the VOP entity that might explain the adverse visual outcomes observed in children and adults born preterm.

In general, we found that participants born preterm have reduced contrast sensitivity and altered retinal structure at school age that seems to persist into adulthood. In addition, the children performed poorer on neuropsychological tasks than their term-born peers, perhaps reflecting reduced processing abilities in complex visual scenes. Moreover, we found a relationship between reduced visual function and increased levels of parent-reported neurodevelopmental challenges at school age.

In addition, OCT imaging of retinal structure in children born extremely preterm revealed an association between thinner circumpapillary retinal nerve fibre layer (RNFL) thickness and perifoveal inner plexiform ganglion cell layer (IPGCL) thickness with longer P100 latencies in the large checks task. This association could indicate delayed visual pathway function due to reduced synaptic connections between the retina and optic nerve in school-aged children born preterm. Finally, diffusion tensor imaging revealed altered white and grey matter microstructure (which could be caused by impaired myelination) in regions along the visual pathway that predicted reduced visual acuity, contrast sensitivity, and longer P100 latencies in adults born preterm with VLBW but not in term-born controls.

From a clinical perspective, the findings from this thesis suggest that contrast sensitivity testing might be a better indicator of adverse visual outcomes than visual acuity alone, perhaps due to its better reflection of day-to-day visual function. Indeed, this thesis showed that contrast sensitivity was the visual function outcome with the largest difference between the VLBW and control group contrast sensitivity showed the strongest association with

parent-reported neurodevelopmental challenges in children born extremely preterm at school age.

Thinner RNFL and IPGCL in the retina and a combination of lower FA values and higher MD and RD values in white and grey matter microstructure along the visual pathway, could be potential clinical imaging markers for adverse visual outcomes that have a neural origin. However, since an OCT machine is more easily accessible in the clinic than an MRI machine, it may be that OCT imaging is a better tool for exploring clinical imaging markers in the follow-up of individuals born preterm. Parameters from DTI could add to this knowledge by locating which regions that show altered microstructure with impaired myelination, as indicated by low FA values and high MD and RD values. Rapid advances in artificial intelligence and machine learning present exciting opportunities for future research to look more closely at clinical markers with both DTI and OCT in larger preterm populations (Li, Fan et al. 2021).

The findings of this thesis suggest that children and adults born preterm have adverse visual outcomes that cannot solely be explained by ROP. Instead, the adverse visual outcomes might have a neural origin and be part of the larger entity of VOP, which includes brain MRI alterations and altered retinal structure that could explain the adverse visual outcomes in the participants included in this thesis. A multidisciplinary approach to ophthalmological follow-up of individuals born preterm, using both visual function testing (including visual acuity and contrast sensitivity assessment) and clinical imaging markers (using OCT and DTI), can help identify the cause and extent of VOP.

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9 Papers I-III

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ORIGINAL ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Visual function correlates with neurodevelopment in a population cohort of school-aged children born extremely preterm

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Abstract

Aim: To investigate visual function and neurodevelopment in a geographically defined population cohort of school-aged children born extremely preterm.

Methods: All children born extremely preterm in Central Norway between 2006 and 2011 (n=65) were identified, and 36 (median age, min/max: 13, 10/16) were included. Best-corrected visual acuity (BCVA), contrast sensitivity (four spatial frequencies), parent-reported challenges and neuropsychological testing in learning, executive functions, motor skills, perception, reaction time, working and visual memory, processing speed, and pattern separation were measured. Brain MRI (3T) was acquired and read by a neuroradiologist.

Results: Median (min/max) BCVA letter score was 85 (35/91) in the better and 82 (13/89) in the worse eye. ROP participants (n=7) had lower contrast sensitivity in the two highest spatial frequencies (p =0.024 and p =0.004). Parent-reported challenges correlated negatively with BCVA (learning: p =0.014; executive functions: p =0.002; motor skills: p =0.000; and perception: p =0.001), while motor skills correlated negatively with one (p =0.010) and perception with two (p =0.003 and p =0.009) of four spatial frequencies. Neuropsychological tests were reduced relative to norms. None had MRI-verified preterm brain injury.

Conclusion: Visual function was subnormal and correlated with parent-reported challenges in a small cohort of extremely preterm school-aged children, indicating that visual function may be a marker of neurodevelopmental outcomes.

KEYWORDS
contrast sensitivity, extremely preterm, neurodevelopment, visual acuity

Abbreviations: GA, Gestational age; ROP, Retinopathy of prematurity; VOP, Visuopathy of prematurity; BCVA, Best corrected visual acuity; ETDRS, Early treatments of diabetic retinopathy study; CS, Contrast sensitivity; CpD, Cycles per degree; IOP, Intraocular pressure; FFT, Five to fifteen; BW, Birth weight; VLBW, Very low birth weight.

1 | INTRODUCTION

Individuals born extremely preterm (gestational age (GA) <28 completed weeks) have an increased risk of visual impairments that are not fully explained by sequelae from neonatal retinopathy of prematurity (ROP).[1–3] Pathological neovascularisation of the retina in the neonatal period may lead to retinal detachment and blindness. However, ROP is usually identified and treated thanks to improvements in neonatal care.[4] The disease regression usually spares the part of the retina that enables sharp vision, the fovea, and should, therefore, theoretically not impact visual function. Nevertheless, several studies report that visual function is indeed impaired in individuals with regressed neonatal ROP[5] and that visual function may be impaired in the absence of ROP among children[1] and adults[3] born preterm. It is conceivable that ROP and other adverse exposures associated with preterm birth induce injury to other components of the visual axis that form vision. Indeed, severe ROP is associated with an increased risk for visual processing difficulties in adolescence[6] and cerebral dysfunction in adulthood.[7] It has been proposed that ROP should no longer only be considered a vascular illness but a disease that also impacts neural tissue.[8] Furthermore, retinal and brain pathologies in extremely preterm infants may be different expressions of neurovascular disease.[7] ROP appears to be the tip of an iceberg of a broader entity of visual problems rooted in neurovascular tissue injury of the retina and brain that we call "visuopathy of prematurity".[9]

In this exploratory study, we wanted to examine the relationship between visual acuity and contrast sensitivity and parent-reported neurodevelopmental problems, neuropsychological testing, and brain MRI in a geographically defined population of school-aged children born extremely preterm in Central Norway. We hypothesized that (1) visual function is subnormal in the whole group and lower in those with ROP, (2) levels of neurodevelopmental challenges are higher compared with average population mean scores, and (3) lower visual function is associated with atypical neurodevelopment.

Key notes

- This study explores the association between visual acuity and contrast sensitivity and neurodevelopmental outcomes among school-aged children born extremely preterm
- The study found subnormal visual function which correlated with parent-reported neurodevelopmental challenges
- The findings support the hypothesis that there exists a larger entity of visual problems among preterms that cannot be fully explained by ROP and that may be associated with neurodevelopmental outcomes

2 | METHODS

2.1 | Study design and participants

All children residing in Norway who were born extremely preterm between 2006 and 2011 in the geographical area of Central Norway were identified via the Norwegian Neonatal Network (NNK), a national medical quality registry that collects data of all newborns admitted to neonatal units in Norway. The study had no exclusion criteria. Information from NNK was cross-checked with medical health records to identify all eligible children and the Norwegian National Population Register to obtain parental addresses. Access to health records was made via the electronic medical record system Doculive (Norsk e-helse AS). Sixty-five children were invited via a mailed letter containing information about the study. Parents were contacted by phone for consent; 14 could not be reached. Of the remaining 51, 36 (25 girls) consented and were enrolled in the study between March 3rd and September 2nd, 2021. Background neonatal data were obtained from NNK and cross-checked in medical records for participants and non-participants (declined to participate, n=15; could not be reached, n=14; Table 1).

2.2 | Ophthalmological examination

Best-corrected visual acuity (BCVA) was obtained monocularly following subjective refraction at a 4 m distance according to the Early Treatment Diabetic Retinopathy Study (ETDRS) on the examination day.[10,11] A subnormal BCVA was defined as <85 ETDRS letter score (equivalent to 20/20 Snellen and LogMAR 0.0; clinically regarded as normal vision). Best corrected contrast sensitivity (CS) thresholds were tested with the CSV 1000E chart (VectorVision) at a 2.5 m distance. The chart applies four rows, and eight columns of sine-wave gratings of four spatial frequencies (3, 6, 12, and 18 Cycles per Degree; CpD) presented below each other in rows of declining levels of contrast. Participants were asked to identify the grating pattern in two circles presented in columns, and the lowest correctly was recorded as the CS threshold. The cut-off score for a lower CS threshold compared to norms was based on values from age-matched controls born to term (11–19 years old)[12] and calculated as a percentage of participants with CS thresholds < average value. Both BCVA and CS were assessed under standardized light conditions. An ocular slit-lamp examination was performed, and abnormal findings in the anterior or posterior segments were noted. Testing was performed on both eyes separately by an ophthalmologist blinded for ROP status. The eye with the best BCVA was used in all analyses. Intraocular pressure (IOP) was measured with an iCare device (IC100 Tonometer, Centervue SpA). Medical ocular history (use of glasses/lenses, eye disease/surgery and amblyopia treatment) was obtained.

2.3 | Parent-reported neurodevelopmental outcomes

Parent-reported neurodevelopmental outcomes were assessed with the Five-to-Fifteen questionnaire (FFT; in Appendix S1), developed

TABLE 1 Background data of children born extremely preterm in Central Norway between 2006 and 2011.

Variable	Participants (n = 0 36)	Non-participants (n = o 29)	p-Value
Age; years (median (min/max))	13 (10/16)	12 (10/15)	0.466
Sex; F (n (%))	25 (69.4)	17 (58.6)	0.438
Preeclampsia; Yes (n (%))	9 (26.5)		
Antenatal steroids; Yes (n (%))	25 (71.4)		
Gestational age; weeks (median (min/max))	26.5 (23.6/27.6)	26.0 (23.2/27.6)	0.406
Birth weight; grams (median (min/max))	838 (525/1320)	860.0 (470/1190)	0.572
5-min APGAR score (median (min/max))	8 (3/10)		
ROP (n (%))	7 (19.4)	9 (31)	0.387
stage 1 (n (%))	0	1 (3.4)	
stage 2 (n (%))	4 (11.1)	3 (10.3)	
stage 3 (n (%))	3 (8.3)	3 (10.3)	
stage 5 (n (%))	0 (0)	1 (3.4)	
Cerebral palsy (n (%))	1 (2.8)		
Bronchopulmonary dysplasia; Yes (n (%))	16 (45.7)		
IVH; Yes/No (n (%))	4 (11.1)		
NEC syndrome; Yes (n (%))	1 (2.9)		
Surgically treated ductus; Yes (n (%))	11 (30.6)		
Medical treated ductus; Yes (n (%))	16 (44.4)		

Abbreviations: IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

to assess symptoms of neurodevelopmental disorders in children and adolescents.[13,14] FFT was mailed to the parents and completed either at home or on-site. Statements related to learning, executive function, motor skills, and perception were assessed. Scores, where a higher value means a higher level of challenges, were compared to a 90th percentile score from a normative population sample matched by sex and age,[14] and the percentage of participants with scores >90th percentile was calculated for each domain (90th percentiles are presented in Appendix S2).

2.4 | Neuropsychological testing

Neuropsychological testing was performed with the self-administered web-based test platform Memoro (https://memoro.no), a validated and reliable tool for cognitive testing.[15–17] Instructions and login credentials were sent by email to the participants, and the test was completed at home before or after the examination day. The test duration was approximately 20 min and tested reaction time, executive function, working memory, processing speed, visual memory and pattern separation. Outcome scores were converted into z-scores using data from 51 healthy individuals (59% females) from the same geographical region with a mean age of 13.7 years (range 13–14) from the Memoro normative database. A negative z-score indicates lower performance than healthy peers (test task descriptions in Appendix S3).

2.5 | Brain MRI

MRI was performed on a Siemens Skyra 3 Tesla system (Siemens Medical Solution) using a 32-channel head coil. The scan time was approximately 20 minutes. The 3D T1 mprage and 3D T2 space were read using a standardized protocol by a consultant in neuroradiology blinded for ROP status. The symmetry of the ventricular system, the surface of the brain, the posterior fossa, and the craniocervical junction was assessed. A thorough investigation of potential white matter abnormalities, focal or general tissue loss/atrophy, the thickness of the corpus callosum, volume of the hippocampus, size of the cerebellum, structural abnormalities of the cortex, and other pathological findings was performed. In addition, the thickness of the optic nerves and chiasma was evaluated.

2.6 | Statistical analyses

Statistical analyses were conducted using the SPSS software 28.0 (IBM) and RStudio 4.1.2 (PBC). Histograms and Q-Q plots of residuals were visually inspected for normality. Independent two-sample t-test and chi-square test were applied to test for participant and ROP status differences. For study outcomes with a significant difference by ROP status, correlation analyses by ROP status were performed, and a z-score for the differences was calculated with

Fisher's z transformation. In addition, Pearson correlations were performed to explore associations between visual function and neurodevelopmental outcomes. Results are reported with median (min/max) unless stated otherwise.

2.7 | Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Regional Committee for Medical and Health Research Ethics in Norway (2020/100434). Written informed consent was obtained from both parents before enrollment in the study.

3 | RESULTS

3.1 | Background data

There were no differences between participants and non-participants regarding age, sex, GA, birthweight (BW), or ROP status (Table 1). The prevalence of any ROP in the population was 23%. Twenty-six participants had no history of ROP, while 7 participants (19%) had neonatal ROP. Four (11%) with ROP stage 2 and three (8%) with ROP stage 3. Of the participants with ROP stage 3, two had received treatment: one with laser, and one with intravitreal injection of vascular endothelial growth factor inhibitor.

3.2 | Brain MRI

No abnormalities were found when assessing the symmetry of the ventricular system, the brain surface, the posterior fossa, the craniocervical junction, potential white matter abnormalities, focal or general tissue loss/atrophy, corpus callosum thickness, hippocampal volume, cerebellar size, cortical structural abnormalities. In addition, the thickness of the optic nerve and chiasma was normal in the obtained MRI images.

3.3 | Ophthalmological examination

Two participants (6%) had nystagmus, five (14%) had been treated for amblyopia, and 15 (42%) used glasses or lenses. Median intraocular pressure was 17 (11/26) mmHg for the better eye and 17 (9/23) for the worse eye (normal range of IOP 6-21 mmHg).

The median (min/max) BCVA ETDRS letter score in the better and worse eye was 85 (35/91) and 82 (13/89), respectively. Nearly half (49%) of the participants scored lower than the ETDRS letter score <85, equivalent to LogMAR 0.0, in the better eye and two-thirds (67%) in their worse eye (Table 2). The median spherical equivalent was 0.50 (-2/-8.5) in the better and .25 (-2.8/-8.8) in the worse eye. The median BCVA in the better eye was 82 (35/91) in participants with ROP compared with 85 (73/90) in participants without ROP ($p = 0.097$). There was a pattern of better BCVA in higher gestational ages (Table 2).

Contrast sensitivity was lower in the highest spatial frequencies in those with ROP than those without, CpD 12 ($p = 0.024$, effect size $r = 0.48$) and CpD 18 ($p = 0.004$, effect size $r = 0.58$; Figure 1). Moreover, over half of the participants scored lower than the cut-off on all spatial frequencies in both eyes, and it was a pattern of poorer contrast sensitivity in the lowest spatial frequency with lower GA (Table 2).

3.4 | Parent-reported neurodevelopmental outcomes

Approximately half the participants showed a higher level of parent-reported challenges. In the learning domain, 51% of the participants scored >90th percentile, 37% in the executive function, 40% in the motor skills and 43% in the perception domain. In addition, 57% of participants born in GA week ≤24 had a symptom score above the 90th percentile in all domains (Table 3).

3.5 | Neuropsychological testing

In several domains, the extremely preterm cohort showed lower performance than peers from the Memoro normative database. The lowest performance was found in reaction time (-1.9 SD), executive function (-2.3 SD), and processing speed (-1.2 SD; Table 4). There was also a considerably lower performance in working memory span (forward= -0.60 SD, backwards= -0.57 SD). However, the preterm participants had performance scores within the normal range in visual memory (-0.16 SD) and pattern separation (-0.35 SD). Participants ≤24 GA week showed a more considerable reduction in executive functions and reaction time than those born closer to term relative to the norms (Table 4).

3.6 | Associations between visual function and neurodevelopmental outcomes

BCVA correlated negatively with all FFT domains; learning ($r = -0.43$, $p = 0.014$), executive functions ($r = -0.52$, $p = 0.002$), motor skills ($r = -0.63$, $p = 0.000$), and perception ($r = -0.57$, $p = 0.001$; Figure 2). This indicates that in participants with lower BCVA, parents more often reported that the child had problems. Two contrast sensitivity thresholds were also correlated with parent-reported neurodevelopmental outcomes. CpD 3 ($r = -0.59$, $p = 0.003$) and CpD 12 ($r = -0.38$, $p = 0.009$) were negatively correlated with perception, while CpD 3 ($r = -0.40$, $p = 0.010$) was negatively correlated with motor skills, meaning that those with lower contrast sensitivity in these spatial frequencies had higher levels of challenges in perception and motor skills. There were no significant correlations between neuropsychological test performance and visual function.

TABLE 2 Visual outcome and age distribution in school-aged children born extremely preterm in Central Norway between 2006–2011 by gestational age.

Gestational age (weeks)					
	≤24	25	26	27	Total<28
Outcomes	(*n* = 6)	(*n* = 5)	(*n* = 7)	(*n* = 15)	(*n* = 33)
Age	12 (11/15)	14 (12/16)	11 (10/15)	13 (10/14)	13 (10/16)
BCVA and contrast sensitivity thresholds in the better eye					
BCVA	84 (35/88)	82 (78/86)	85 (68/91)	86 (73/90)	85 (35/91)
<85 (*n*(%))[a]	4 (67)	4 (80)	3 (43)	5 (33)	16 (49)
CpD 3[b]	4 (1/6)	5 (4/8)	5 (3/8)	6 (3/8)	5 (1/8)
<6 (*n*(%))	5 (83)	3 (60)	3 (43)	6 (40)	17 (52)
CpD 6[b]	5 (0/6)	7 (2/8)	5 (0/8)	6 (4/8)	6 (0/8)
<7 (*n*(%))	6 (100)	2 (40)	5 (71)	8 (53)	21 (64)
CpD 12[b]	6 (0/6)	5 (2/8)	5 (0/8)	7 (2/8)	6 (0/8)
<7 (*n*(%))	6 (100)	4 (80)	6 (86)	6 (40)	22 (67)
CpD 18[b]	6 (0/8)	6 (0/8)	4 (0/7)	7 (2/8)	6 (0/8)
<7 (*n*(%))	5 (67)	4 (80)	6 (86)	5 (33)	19 (58)
BCVA and contrast sensitivity thresholds in the worse eye					
BCVA	83 (13/87)	75 (56/83)	83 (62/89)	83 (71/88)	82 (13/89)
<85 (n(%))[a]	4 (67)	5 (100)	4 (57)	11 (73)	24 (67)
CpD 3	5 (3/6)	5 (1/6)	3 (2/6)	6 (4/8)	6 (1/8)
<6 (*n*(%))[b]	5 (100)	5 (100)	5 (100)	5 (100)	32 (100)
CpD 6	5 (3/8)	2 (0/8)	5 (1/7)	6 (4/8)	6 (0/8)
<7 (*n*(%))[b]	4 (80)	3 (60)	6 (86)	9 (60)	22 (69)
CpD 12	5 (5/6)	3 (0/8)	5 (0/7)	7 (4/8)	5 (0/8)
<7 (*n*(%))[b]	5 (100)	4 (80)	6 (86)	7 (47)	22 (69)
CpD 18	67 (4/8)	1 (0/8)	6 (2/8)	6 (2/8)	5 (0/8)
<7 (*n*(%))[b]	4 (80)	3 (60)	4 (57)	10 (67)	21 (66)

Abbreviations: BCVA, best-corrected visual acuity; CpD, cycles per degree. Data are presented as median (min/max).

[a]Participants with a score <85 (equivalent to 20/20 vision and LogMAR 0.0).

[b]Cut-off scores for contrast sensitivity based on <average value for 11–19 years of age.[12]

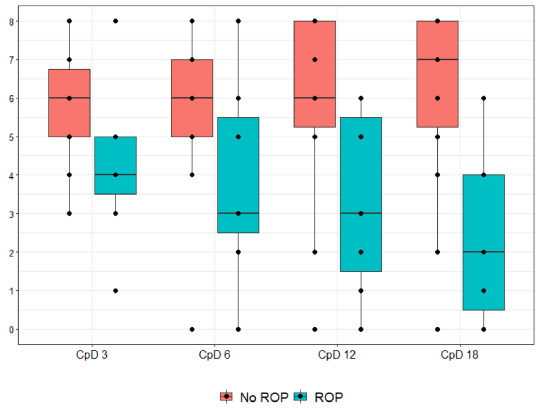

FIGURE 1 Boxplot with median and range of contrast sensitivity thresholds in extremely preterm school-aged children born in Central Norway between 2006 and 2011 with ROP (*n* = 7) and no ROP (*n* = 26) in the neonatal period. CpD, cycles per degree; ROP, retinopathy of prematurity.

4 | DISCUSSION

In this geographically defined population of school-aged children born extremely preterm with regressed or no ROP and no MRI-defined preterm brain abnormalities, visual acuity and contrast sensitivity scores were lower, and participants displayed higher levels of developmental challenges and lower performance on neuropsychological tests compared to norms. Furthermore, those with ROP had poorer contrast sensitivity than those without in the highest spatial frequencies. Both best corrected visual acuity and contrast sensitivity correlated with parent-reported levels of neurodevelopmental challenges, regardless of ROP status, with more challenges in individuals with lower visual function.

A strength of this study is the geographically defined population-based design, inviting all children born extremely preterm in Central Norway during a specific period. Moreover, background data on non-participants indicated that the study population is representative of the extremely preterm population of Norway. Furthermore, visual data were obtained by the same ophthalmologist applying

TABLE 3 Parent-reported neurodevelopmental challenges in a cohort of school-aged children born extremely preterm in Central Norway between 2006 and 2011 by gestational age at birth.

Gestational age (weeks)					
	≤24	25	26	27	Total <28
	(*n* = 6)	(*n* = 5)	(*n* = 7)	(*n* = 15)	(*n* = 33)
Learning	.83 (.19/1.6)	.70 (.41/1.1)	.22 (.11/1.3)	.41 (.00/1.4)	.56 (.00/1.6)
>90 percentile (*n* (%))	5 (71)	4 (80)	2 (29)	7 (44)	18 (51)
Executive functions	.86 (.12/1.7)	.44 (.12/.76)	.28 (.12/.92)	.48 (.00/1.2)	.44 (.00/1.7)
>90 percentile (*n* (%))	4 (57)	2 (40)	2 (29)	5 (31)	13 (37)
Motor skills	.30 (.12/1.5)	.12 (.00/.47)	.18 (.00/.47)	.24 (.00/.56)	.18 (.00/1.5)
>90 percentile (*n* (%))	4 (57)	1 (20)	1 (14)	8 (50)	14 (40)
Perception	.28 (.00/.89)	.11 (.00/.50)	.06 (.00/.39)	.17 (.00/.78)	.17 (.00/.89)
>90 percentile (*n* (%))	4 (57)	2 (40)	2 (29)	7 (44)	15 (43)

Note: Parent-reported neurodevelopmental challenges outcomes presented as score median (min/max) and n (%) of the present cohort that scored >90 percentile for scores on the domains from a normative sample matched to the sex and age of the participants by gestational age at birth.

TABLE 4 Results from a neuropsychological test in school-aged children born extremely preterm in Central Norway between 2006 and 2011 by gestational age at birth.

Gestational age (weeks)					
	≤24	25	26	27	Total <28
	(*n* = 6)	(*n* = 5)	(*n* = 7)	(*n* = 15)	(*n* = 33)
VM	.20 (-2.1/.32)	.24 (-1.1/.33)	-.06 (-.75/.30)	-.02 (-1.6/.33)	.08 (-2.1/.33)
PS	-.22 (-1.2/.89)	-.14 (-.18/.27)	-.60 (-1.5/1.4)	-.67 (-2.0/1.1)	-.23 (-2.0/1.4)
PRS	-1.9 (-2.6/-.13)	-1.5 (-2.0/-.10)	-.94 (-4.5/.80)	-.94 (-1.9/.10)	-1.0 (-4.5/.79)
EF	-.39 (-24.1/1.2)	-.39 (-.39/.88)	-.71 (-6.7/.46)	-1.2 (-13.3/.88)	-.39 (-24.1/1.2)
RT	-2.4 (-7.5/-.61)	-.34 (-17.9/-.30)	-.56 (-4.1/2.3)	-.95 (-3.8/1.4)	-1.0 (-17.9/2.3)
MSF	-.98 (-2.7/.69)	-.15 (-2.7/-.15)	-.98 (-2.7/.69)	-.15(-1.8/2.4)	-.98 (-2.7/2.4)
MSB	-.04 (-1.0/.40)	-1.0 (-1.7/-.31)	-1.0 (-1.7/1.1)	-.30 (-2.5/1.1)	-.31 (-2.5/1.1)

Abbreviations: EF, executive functions; PS, pattern separation; PRS, processing speed; MSF, memory span forward; MSB, memory span backwards; VM, visual memory; RT, reaction time.

Note: Z-scores for neuropsychological test performance obtained in peers from the same geographical region presented as median (min/max).

standardized tests. Neurodevelopmental outcomes were assessed with both objective testing and parent reports, which may detect differential aspects of neurodevelopmental problems. A limitation is the small number of participants and the small number of participants with ROP compared to those without ROP. In addition, the neuropsychological z-scores were derived from a relatively small general population sample. A limitation is also that both the parent-reported FFT questionnaire and the Memoro web-based neuropsychological test are developed and validated in Nordic settings and populations, which may decrease the translational value of results to other populations.

To the best of our knowledge, this is the first study to assess both BCVA and contrast sensitivity from low to high spatial frequencies in extremely preterm-born children. The findings indicate that visual function is indeed impaired long-term, and more so at lower contrast in high spatial frequencies, especially for those with a history of ROP. These findings are consistent with the idea that ROP is not only a vascular disease but that the neuroretina and possibly the cerebral part of the visual axis may also be affected.[5] Photoreceptor function in the central macula of school-aged children born extremely preterm is better with higher GA.[18] It is conceivable that extremely preterm birth interrupts the normal development of the neuroretina that would usually happen in the latter part of gestation, contributing to lower BCVA and contrast sensitivity long-term in the child.

Moreover, visual function, both BCVA, which measures high contrast acuity of letter optotypes of low spatial frequency and contrast sensitivity testing of varying contrast levels of the total spatial frequency span, were found to be associated with parent-reported neurodevelopmental difficulties. This is intriguing and may indicate that vision could be a marker of atypical neurodevelopment in preterm-born children. Neuropsychological test performance did not correlate with visual function. Possibly, real life is more visually demanding than a test situation where the child can concentrate on a sole task at a time, which may explain the discrepancy between the parent-reported difficulties and neuropsychological test outcome. This theory is in line with the hypothesis of dorsal stream

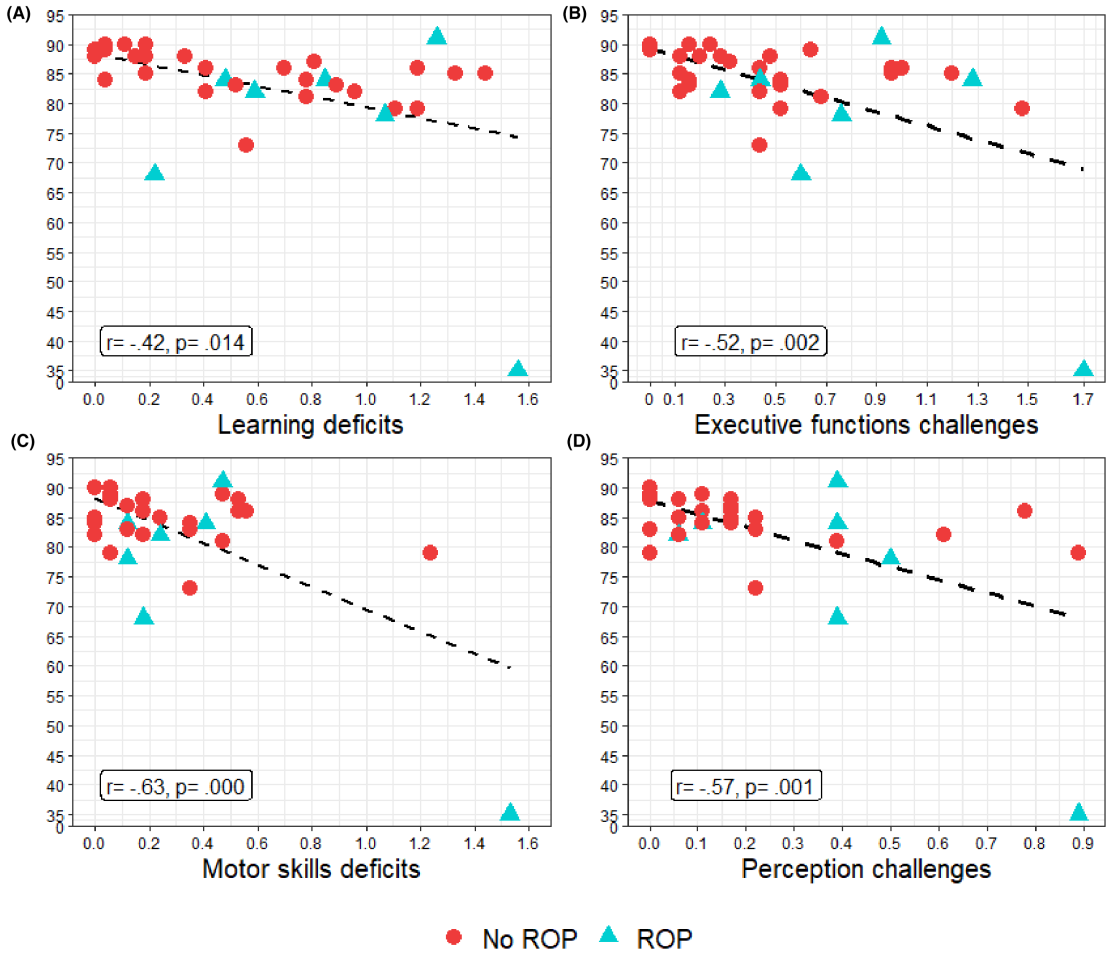

FIGURE 2 Scatterplots of correlations between best-corrected visual acuity (BCVA) and parent-reported challenges in extremely preterm born school-aged children born in Central Norway between 2006 and 2011 with ROP ($n = 7$) and without ROP ($n = 26$) in the neonatal period. r, Pearson's correlation coefficient; ROP, retinopathy of prematurity; BCVA, best-corrected visual acuity. The association between scores on parent-reported challenges (x-axis) and best-corrected visual acuity (y-axis) for all participants with correlation coefficient and a regression line (dashed line) is presented (A: learning challenges, B: executive functions challenges, C: motor skills challenges, D: perception challenges).

dysfunction[19] which includes difficulties in handling the complexity of visual scenes. Indeed, dorsal stream dysfunction has been hypothesized to explain perceptual challenges among preterms.[20]

The prevalence of ROP in this cohort from 2006 to 2011 in central Norway of 23% was lower than the prevalence in Norway for the years 2009–2017 of 40%,[4] and for the prevalence in Sweden in the EXPRESS study of 73%.[21] The EXPRESS study included children with a lower GA < week 27, which explains the higher prevalence of ROP in that population compared to ours, which included children <28 GA weeks. It is known that ROP prevalence varies greatly within Norway, with an up to fivefold difference in odds of severe ROP between health regions.[4] The present study suggests that Central Norway is among the regions in Norway with the lowest prevalence of ROP.

Lower contrast sensitivity was especially apparent in those with ROP and may represent a real-life functional impairment. Even though best-corrected visual acuity is considered the defining clinical measure of vision, it only measures the acuity of high contrast objects at a high spatial frequency. In real life, visual stimuli consist of various levels of contrast and spatial frequencies, and it is levels of contrast and not the high-contrast vision that reaches cortical neurons for processing, with some degree of contrast processing even taking place in the retina.[22] Impaired contrast sensitivity may be limited by optical qualities of the eye, retinal processing, or higher-level cortical processing. Testing of various spatial frequencies and declining levels of contrast are therefore considered a more sensitive measure of day-to-day vision in various ocular and

neural diseases. For instance, in children with complete recovery of visual acuity following amblyopia treatment, contrast sensitivity remained impaired[23] and contrast sensitivity was superior to visual acuity in identifying optic neuritis in multiple sclerosis.[24] It is conceivable that in individuals born extremely preterm, contrast sensitivity testing may be a more precise tool than BCVA to reflect the real-life vision.

Neuropsychological test scores might indicate that the participants performed worse than age-matched controls with measures of processing speed, reaction time and executive functions showing the greatest differences. Slow processing speed has been related to working memory and academic attainment,[25] and may conceivably impact several aspects of cognitive function. Indeed, studies of young adults born with very low birth weight (VLBW; <1500g) have found that processing speed, and working memory are reduced[26] and correlate with a reduced cortical surface area on MRI. Even though standard clinical MRI did not reveal signs of preterm brain injury sequelae in this cohort, subtle white matter abnormalities contributing to lower visual function and reduced neuropsychological performance may be present and should be investigated further. Interestingly, neurodevelopmental challenges in early school-age have been shown to persist when comparing cohorts over several timepoints from the 1990s to 2005,[27] with a trend of increasing executive dysfunction in children born in the most recent cohorts.[28] These studies highlight the importance of more knowledge regarding what causes these neurodevelopmental challenges to develop from infancy and persist through adulthood, even in the modern area of newborn medicine. The VOP paradigm could narrow the knowledge gap.[9]

5 | CONCLUSION

In a geographically defined population of 13-year-old school-aged children born extremely preterm without apparent brain abnormalities, visual function was subnormal, and contrast sensitivity was poorer in high spatial frequencies in those with regressed ROP. Furthermore, visual function correlated with parent-reported neurodevelopmental problems, regardless of ROP status. These findings support the hypothesis that factors associated with extremely preterm birth and ROP affect the visual system from the retina to the brain in ways that deserve further study.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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5-15R

QUESTIONNAIRE FOR EVALUATION OF DEVELOPMENT AND BEHAVIOUR

Parent questionnaire

To the parents: This questionnaire, for children and adolescents age 5 to 17, contains statements concerning the skills and behaviours of your child in various domains of development. Children are individuals. This means that their skills and behaviours vary from one child to another, and according to age.

The statements in the questionnaire are followed by boxes marked **Does not apply – Applies sometimes/to some extent – Applies.** Tick the box that contains the statement that you think best corresponds to your child's functioning in everyday situations, compared to children of their own age. Have in mind the child's present functioning, i.e. within the last 6 months. To get the most correct picture of your child's functioning, it is important that you complete the whole questionnaire.

You will be asked if the child's functioning in various domains leads to problems in daily living. Please consider whether or not these problems affect the child and others at home, in school and among friends. These questions are followed by four options: **No – A little – A great deal – Very much**.

To the professional applying this questionnaire: The questionnaire aims at elucidating the parent's views on their child's strengths and weaknesses in several developmental domains. It is not meant to serve as the sole basis for diagnostic decisions. The use of this questionnaire requires knowledge about normal and atypical child development as well as basic knowledge in psychometrics. Guidelines for professional use, administration and scoring are found in the MANUAL.

A teacher edition of the questionnaire is also available.

Reference for this questionnaire: Kadesjö, B., Janols. L-O, Korkman, M., Mickelsson, K., Strand, G., Trillingsgaard, A., Lambek, R., Øgrim, G., Bredesen, A. M., & Gillberg, C. (2017). Five-To-Fifteen-Revised (5-15R). Available at www.5-15.org

File name: 515_en-GB.pdf
File version: 2021.p.2.2
File date: 2021-11-16

Statement of consent to process given information electronically

The purpose of the 5-15R questionnaire and evaluation system is to evaluate the child's functioning in different areas of everyday life.

The responses will be compared to a large group of responses for children of the same age and gender.

The evaluation can identify areas where the child's functioning will be subject of interest of further evaluation or intervention.

The results from this evaluation are never used alone as basis for conclusions about the child or its environment.

The collected information will be entered and stored in a database without any identification of the child or the informant. These data are deleted no later than 6 months after the collection.

This statement of consent can later be withdrawn by contacting the person or institution that is inviting you give this statement.

I consent to the collection, storage and processing of data for the purpose described above.

Signature: ..... Date: .....

Your relation to the child: ☐ Parent ☐ Foster parent/guardian Other: .....

Your child's name: ..... Date of birth: .....

	Does not apply	Applies sometimes/ to some extent	Applies
Motor skills - gross motor skills; the child´s use of his/her body in various activities			
1. Difficulty acquiring new motor skills, such as learning how to ride a bike, skate, swim	☐	☐	☐
2. Difficulty throwing and catching a ball	☐	☐	☐
3. Difficulty running fast	☐	☐	☐
4. Has difficulties or does not like to participate in game sports such as soccer/football, land hockey, basketball	☐	☐	☐
5. Balance problems; for instance, has difficulty standing on one leg	☐	☐	☐
6. Often stumbles and falls	☐	☐	☐
7. Clumsy or awkward movements	☐	☐	☐
Motor skills - fine motor skills; the child's use of his/her hands:			
8. Does not like to draw, has difficulties drawing figures that represent something	☐	☐	☐
9. Difficulty handling, assembling and manipulating small objects	☐	☐	☐
10. Difficulty pouring water into a glass without spilling	☐	☐	☐
11. Often spills food onto clothes or table when eating	☐	☐	☐
12. Difficulty using knife and fork	☐	☐	☐
13. Difficulty buttoning or tying shoe-laces	☐	☐	☐
14. Difficulty using a pen (e.g., presses too hard, hand is shaking)	☐	☐	☐
15. Has not developed clear hand preference, i.e., is neither clearly right-handed nor left-handed	☐	☐	☐
16. Writing is slow and laborious	☐	☐	☐
17. Immature pencil-grip, holds the pen in an unusual manner	☐	☐	☐

Do problems with motor function interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Attention and concentration: the child's ability to pay attention and to concentrate on various tasks and activities:			
18. Often fails to pay close attention to details or makes careless mistakes	☐	☐	☐
19. Often has difficulty sustaining attention in tasks or play activities	☐	☐	☐
20. Often does not seem to listen when spoken to directly	☐	☐	☐
21. Problems following instructions and fails to finish schoolwork, chores, or duties	☐	☐	☐
22. Often has difficulty organizing tasks and activities	☐	☐	☐
23. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as homework)	☐	☐	☐
24. Often loses things necessary for tasks or activities (e.g., toys, school equipment, pencils, books, or tools)	☐	☐	☐
25. Is often easily distracted by extraneous stimuli (e.g., irrelevant sounds like other people talking, cars driving by)	☐	☐	☐
26. Is often forgetful in daily activities	☐	☐	☐

	Does not apply	Applies sometimes/ to some extent	Applies
Overactivity and impulsivity; the child's tendency to be too active or impulsive:			
27. In constant motion (fidgets with fingers, plucks at things etc)	☐	☐	☐
28. Difficulty remaining seated (squirms in seat, gets up and moves about)	☐	☐	☐
29. Often runs about or climbs excessively in situations in which is inappropriate	☐	☐	☐
30. Difficulty playing calmly and quietly	☐	☐	☐
31. Is often "on the go" or often acts as if "driven by a motor"	☐	☐	☐
32. Often talks excessively	☐	☐	☐
33. Often blurts out answers before the question has been completed	☐	☐	☐
34. Difficulty awaiting turns (in games, during meals etc)	☐	☐	☐
35. Often interrupts or intrudes on others (e.g., butts into conversations or games)	☐	☐	☐

Do problems with attention, concentration, over-activity or impulsivity interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Passivity/inactivity: the child's inactivity or tendency to be too passive			
36. Difficulty getting started on tasks/activities	☐	☐	☐
37. Difficulty completing a task/activity, does not get things done like the rest of the group	☐	☐	☐
38. Often "in own world" or daydreaming	☐	☐	☐
39. Seems slow, inert, or lacking energy	☐	☐	☐

Does passivity or inactivity interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Planning/organizing; the child's ability to plan or organise activities			
40. Difficulty understanding consequences of own actions (e.g., climbs in dangerous places, careless in traffic)	☐	☐	☐
41. Difficulty planning and preparing for tasks (e.g., collecting equipment needed for an outing or for school)	☐	☐	☐
42. Difficulty completing sequential tasks (e.g., young children: getting dressed in the morning without constant reminders; older children: completing home work without constant reminders)	☐	☐	☐

Do problems with planning/organising interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

	Does not apply	Applies sometimes/ to some extent	Applies
Perception of space and directions; the child's perception of space and directions in the physical world:			
43. Difficulty finding his/her way around (even in well known places)	☐	☐	☐
44. Seems disturbed by height differences (even slight) such as in connection with climbing stairs etc.	☐	☐	☐
45. Difficulty judging distance or size	☐	☐	☐
46. Difficulty comprehending orientation and spatial directions (young children turning clothes back to front, older children confusing letters such as b, p, d, or digits such as 6, 9)	☐	☐	☐
47. Bumps into other people, especially in narrow places	☐	☐	☐
Concepts of time; the child´s ability to understand concepts of time:			
48. Poor concepts of time, e.g., does not have an intuitive feeling for how long "five minutes" or "one hour" take or is uncertain about how long ago something happened	☐	☐	☐
49. Has only a vague idea about what time it is, whether it is morning or afternoon, whether it is time or not to go to school	☐	☐	☐
50. Repeatedly asks about when something is going to happen, e.g., how much time is left before an outing or before it is time to go to school	☐	☐	☐
51. Can read the clock mechanically but does not understand the actual time concept	☐	☐	☐
Perception of own body; the child's perception of his/her own body and sensory impressions:			
52. Does not have a sense of how clothes fit, does not straighten socks or trousers that have slid down	☐	☐	☐
53. Surprisingly poor perception of cold, pain etc	☐	☐	☐
54. Poor body awareness (uncertain of size of own body in relation to the environment, e.g., bumps into or tumbles over things without intention to do so)	☐	☐	☐
55. Oversensitive to touch (is irritated by tight clothing, perceives soft touch as rough etc)	☐	☐	☐
56. Difficulty imitating other people's movements	☐	☐	☐
Perception of visual forms and figures; the child's ability to perceive forms and figures:			
57. Tends to misinterpret pictures; e.g., may perceive a picture of a fried egg as that of a flower	☐	☐	☐
58. Difficulty noticing small differences in shapes, figures, words and patterns that look alike	☐	☐	☐
59. Difficulty drawing pictures such as that of a car, a house etc (compared with children of similar age)	☐	☐	☐
60. Difficulty with jigsaw puzzles	☐	☐	☐

Do problems with perception of space and directions, time, own body, or forms and figures interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

	Does not apply	Applies sometimes/ to some extent	Applies
Memory; the child's ability to remember facts or what he/she has experienced			
61. Difficulty remembering information about personal data, such as date of birth, home address etc	☐	☐	☐
62. Difficulty remembering the names of other people (e.g., name of teacher, school peers)	☐	☐	☐
63. Difficulty remembering the names of weekdays, months and seasons	☐	☐	☐
64. Difficulty remembering non-personal facts learned at school (e.g., historic events, chemical formulas etc)	☐	☐	☐
65. Difficulty remembering what has occurred recently, as who has phoned or, what he/she ate a few hours ago etc	☐	☐	☐
66. Difficulty remembering events that occurred some time ago, such as what happened on a trip, what Christmas presents he/she got etc	☐	☐	☐
67. Difficulty remembering where he/she put things	☐	☐	☐
68. Difficulty remembering appointments with peers or what home-work he/she has got	☐	☐	☐
69. Difficulty learning rhymes, songs, multiplication tables etc by heart	☐	☐	☐
70. Difficulty remembering long or multiple-step instructions	☐	☐	☐
71. Difficulty acquiring new skills, such as rules of new play or games	☐	☐	☐

Do problems with memory interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Comprehension of spoken language; the child's ability to understand language and speech:			
72. Difficulty understanding explanations and instructions	☐	☐	☐
73. Difficulty following stories read aloud	☐	☐	☐
74. Difficulty perceiving what other people say (often says "what?", "what do you mean?")	☐	☐	☐
75. Difficulty with abstract concepts such as "the day after tomorrow", "in the right order"	☐	☐	☐
76. Tends to misinterpret what is said	☐	☐	☐
Expressive language; the child's ability of language expression and to pronounce words:			
77. Uncertain of speech sounds and tends to misarticulate words	☐	☐	☐
78. Difficulty learning the names of colours, people, letters etc	☐	☐	☐
79. Difficulty finding words or explaining to other people, says: "the, the, the ..."	☐	☐	☐
80. Tends to remember words incorrectly, says "armbow" instead of "elbow", refers to "pointer" instead of "index" etc	☐	☐	☐
81. Difficulty explaining what he/she wants	☐	☐	☐
82. Difficulty speaking fluently without any breaks	☐	☐	☐
83. Difficulty expressing him/herself in whole sentences, in grammatically correct sentences, or inflecting words	☐	☐	☐

	Does not apply	Applies sometimes/ to some extent	Applies
84. Pronounces specific sounds incorrectly (has a lisp, difficulty pronouncing the sound of "r", nasal voice etc)	☐	☐	☐
85. Difficulty pronouncing complex words such as "electric", "screwdriver" etc	☐	☐	☐
86. Has a hoarse voice	☐	☐	☐
87. Stutters	☐	☐	☐
88. Speaks so rapidly that it is difficult to comprehend what he/she is saying	☐	☐	☐
89. Has a muddled speech	☐	☐	☐

Verbal communication; the child's ability to use language and ability to communicate with others:

90. Difficulty telling about experiences or situations so that the listener understands (e.g., what happened during the day or during the summer vacation)	☐	☐	☐
91. Difficulty keeping "on track" when telling other people something	☐	☐	☐
92. Difficulty taking part in a conversation, e.g., problems shifting from listening to talking	☐	☐	☐

Do problems with understanding of language, use of language, or verbal communication interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Acquisition of academic skills; if the child is under 8 years of age, move to item 122

Questions relating to children's learning can be difficult for parents without information from the child's teacher. Nevertheless, please try to respond to the following questions based on what you know or what you have heard from the child's teacher.

Reading, writing, arithmetic (only children 8 years or above):

93. Acquiring reading skills is more difficult than expected considering his/her ability to learn other things	☐	☐	☐
94. Has difficulties to understand what he/she is reading	☐	☐	☐
95. Difficulty reading aloud at normal speed (reads too slowly, too quickly, or fails to read fluently)	☐	☐	☐
96. Does not like reading (e.g., avoids reading books)	☐	☐	☐
97. Makes guesses while reading	☐	☐	☐
98. Difficulty spelling	☐	☐	☐
99. Has difficulties shaping letters and to write neatly	☐	☐	☐
100. Difficulty formulating him/herself in writing	☐	☐	☐
101. Difficulty acquiring basic math skills (addition, subtraction; i.e., plus, minus)	☐	☐	☐
102. Difficulty with math problems given in written form	☐	☐	☐
103. Difficulty learning and applying various mathematical rules	☐	☐	☐
104. Difficulty learning and use multiplication tables	☐	☐	☐
105. Difficulty with mental arithmetic	☐	☐	☐

	Does not apply	Applies sometimes/ to some extent	Applies

Learning new things and applying knowledge in school (only children 8 years or above):

106. Difficulty understanding verbal instructions	☐	☐	☐
107. Difficulty understanding or using abstract terms, e.g., terms relating to size, volume, spatial directions	☐	☐	☐
108. Difficulty participating in discussions with other children	☐	☐	☐
109. Difficulty learning facts or acquiring knowledge about the surrounding world.	☐	☐	☐
110. Exceptional knowledge or skills in some area	☐	☐	☐
111. Is good at artistic or practical things (playing an instrument, drawing, painting, construction work)	☐	☐	☐

Problem solving in school and approach to new learning situations (only children 8 years or above):

112. Difficulty planning and organising activities, (e.g., the order in which things should be done, how much time is needed to manage a specific task)	☐	☐	☐
113. Difficulty shifting plan or strategy when this is required (e.g., when the initial approach failed)	☐	☐	☐
114. Difficulty comprehending explanations and following instructions given by adults	☐	☐	☐
115. Difficulty solving abstract tasks (i.e., is dependent on learning material that can be seen or touched)	☐	☐	☐
116. Difficulty keeping on trying and completing tasks, often leaves them half finished	☐	☐	☐
117. Unmotivated for school work or comparable learning situations	☐	☐	☐
118. Learning is slow and laborious	☐	☐	☐
119. Does things too quickly, hastily, or in a hurry	☐	☐	☐
120. Can/will not take responsibility for own actions, needs a lot of supervision	☐	☐	☐
121. Very much in need of support, wants to know whether he/she is performing well	☐	☐	☐

Do academic problems or learning difficulties interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Social skills; the child's capacity to participate in social settings and interact with others

122. Does not understand other people's social cues, e.g., facial expressions, gestures, tone of voice, or body language	☐	☐	☐
123. Difficulty understanding the feelings of other people	☐	☐	☐
124. Difficulty responding to the needs of other people	☐	☐	☐
125. Difficulty verbally explaining emotions when feeling lonely, being bored etc	☐	☐	☐
126. Speaks with a monotonous or strange voice	☐	☐	☐
127. Difficulty expressing emotions and reactions with facial gestures or body language	☐	☐	☐

	Does not apply	Applies sometimes/ to some extent	Applies
128. Markedly "old fashioned" style?	☐	☐	☐
129. Difficulty behaving as expected by peers	☐	☐	☐
130. Difficulty realising how to behave in different social situations, such as when visiting relatives together with parents, when visiting friends, seeing a doctor, going to the cinema, etc.	☐	☐	☐
131. Is perceived by peers as different, odd, or eccentric	☐	☐	☐
132. Unintentionally makes a fool of himself so that parents feel embarrassed or peers start laughing	☐	☐	☐
133. Often seems to lack common sense	☐	☐	☐
134. Has a weak sense of humour	☐	☐	☐
135. Blurts out socially inappropriate comments	☐	☐	☐
136. Difficulty comprehending rules or prohibitions	☐	☐	☐
137. Often quarrels with peers	☐	☐	☐
138. Difficulty understanding and respecting other people's rights, for example, that younger children need more help than older ones, and that parents should be left alone when they demand it, etc.	☐	☐	☐
139. Difficulty in group or team activities or games, invents new rules for own benefit	☐	☐	☐
140. Difficulty making friends	☐	☐	☐
141. Does not often interact with peers	☐	☐	☐
142. Difficulty to participate in group activities	☐	☐	☐
143. Not accepted by other children to participate in their games	☐	☐	☐
144. Does not care for physical contact such as hugs	☐	☐	☐
145. Has one or a few interests that take up considerable time and that impinge on relations with family and friends	☐	☐	☐
146. Repeats or gets stuck in seemingly meaningless behaviours or activities	☐	☐	☐
147. Gets very upset by tiny changes in daily routines	☐	☐	☐
148. Eye contact in face to face situations is abnormal or missing	☐	☐	☐

Do problems with social skills interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Emotional problems:

149. Poor self-confidence	☐	☐	☐
150. Seems to be unhappy, sad, depressed	☐	☐	☐
151. Often complains about feelings of loneliness	☐	☐	☐
152. Has tried to inflict bodily damage to him-/herself or talks about that	☐	☐	☐
153. Has a poor appetite	☐	☐	☐
154. Often expresses a feeling of being worthless or inferior to other children	☐	☐	☐
155. Often complains about bellyaches, headaches, breathing difficulties or other bodily symptoms	☐	☐	☐

	Does not apply	Applies sometimes/ to some extent	Applies
156. Appears tense and anxious or complains about being nervous	☐	☐	☐
157. Becomes very anxious or unhappy when leaving home e.g., when setting to school	☐	☐	☐
158. More sleeping problems than most children of similar age	☐	☐	☐
159. Often has nightmares	☐	☐	☐
160. Walks in sleep or has nocturnal attacks when he/she cannot be "reached" or comforted	☐	☐	☐
161. Often loses temper	☐	☐	☐
162. Often argues with adults	☐	☐	☐
163. Often refuses to follow the instructions of adults	☐	☐	☐
164. Often teases others by deliberately doing things that are perceived as provocative	☐	☐	☐
165. Often blames others for own mistakes or bad actions	☐	☐	☐
166. Is easily offended, or disturbed by others	☐	☐	☐
167. Often gets into fights	☐	☐	☐
168. Is cruel to animals	☐	☐	☐
169. Lies and cheats	☐	☐	☐
170. Steals things at home	☐	☐	☐
171. Often destroys the belongings of other family members or other children	☐	☐	☐
172. Has recurrent episodes of a few days with extremely high activity level and flight of ideas	☐	☐	☐
173. Has recurrent periods of obvious irritability	☐	☐	☐

Obsessive actions or thoughts; Actions or thoughts that he/she appears unable to control

174. Compulsively repeats some activities or has habits that are very difficult to change	☐	☐	☐
175. Has obsessive/fixed ideas	☐	☐	☐
176. Has involuntary movements, tics, twitches or facial grimaces	☐	☐	☐
177. Repeats meaningless movements, such as head shaking, body jerking and finger drumming	☐	☐	☐
178. Emits unmotivated sounds such as throat clearing, sneezing, swallowing, barking, shouting etc	☐	☐	☐
179. Difficulty keeping quiet, e.g., whistles, hums, mumbles	☐	☐	☐
180. Repeats words or parts of words in a meaningless way	☐	☐	☐
181. Uses dirty words or language in an exaggerated way	☐	☐	☐

Do emotional problems, obsessive actions or thoughts interfere with your child's daily function?

Not at all ☐ A little ☐ Pretty much ☐ Very much ☐

Does not apply	Applies sometimes/ to some extent	Applies

Describe the problems of your child that you are most worried about:

Describe the strengths of your child:

Manual

5-15R
(Five-To-Fifteen-Revised)

Nordic questionnaire for evaluation of development and behavior
in children and adolescents

Background and history

This is the manual for the upgraded and re-standardized version of the 5-15 parent and teacher questionnaires - that is 5-15R.

Below is a brief description of the construction and standardization of the original 5-15 parent questionnaire from 2004, followed by a description of the upgrade and re-standardization of the revised version from 2016.

The parent questionnaire, 5-15, was developed in response to a growing need for a research-based (benchmarked and standardized) instrument for examining children and adolescents with developmental and behavioral problems. The questionnaire aimed at helping clinicians identify and measure cognitive, language, and motor impairment as well as social, emotional, and behavioral problems. The target group was children and adolescents between the ages of 5 and 15 with various types of developmental and behavioral problems – in particular children with ADHD, autism spectrum disorders, as well as language and communicative disorders.

The 5-15 parent questionnaire was developed in order to give professionals access to how parents perceive daily life functioning in their children – that is, information about the child's strengths and weaknesses as well as developmental level relative to that of other children of similar age and gender.

The FTF questionnaire is one of the few instruments developed in the Nordic countries and the result of a prolonged work effort in a cross-disciplinary Nordic research group primarily consisting of psychologists, child- and adolescent psychiatrists, and pediatricians. In 2004, the research group presented the instrument, its psychometric properties, and clinical relevance in a special edition of European Child and Adolescent Psychiatry. See references below:

European Child and Adolescent Psychiatry, Volume 13, issue 3, 2004

Kadesjö, B., Janols, L-O, Korkman, M., Michelsson, K., Strand, G., Trillingsgaard, A., & Gillberg, C. (2004). FTF (Five to Fifteen): The development of a parent questionnaire for the assessment of AD/HD and comorbid conditions. European Child and Adolescent Psychiatry, *13,* Supplement 3, 3—13.

Korkman, M., Jaakkola, M., Ahlroth, A., Pesonen, A-E., Turunen, M-M. (2004). Screening of Developmental Disorders in Five-Year-Olds Using the Five to Fifteen Questionnaire: A Validation Study. European Child and Adolescent Psychiatry, *13*, Supplement 3, 31—38.

Trillingsgaard, A., Damm, D., Sommer, S., Jepsen, J.R.M., Østergaard, O., Frydenberg, M., & Thomsen, P.H. (2004). Developmental Profiles on basis of the Five To Fifteen parent

questionnaire. Clinical validity and utility of the FTF in a child psychiatric sample. European Child and Adolescent Psychiatry, *13,* Supplement 3, 39—49.

Airaksinen, E., Michelsson, K., & Jokela, V. (2004). The occurrence of inattention, hyperactivity, impulsivity and coexisting symptoms in a population study of 471 6-8-year old children based on the Five to Fifteen parent questionnaire. European Child and Adolescent Psychiatry, *13,* Supplement 3, 23—30

Bohlin, G., & Janols, L-O. (2004). Behavioural problems and psychiatric symptoms in 5 - 13 year-old Swedish children - a comparison of parent ratings on the FTF (Five To Fifteen) with the ratings on CBCL (Child Behavior Checklist). European Child and Adolescent Psychiatry, *13,* Supplement 3, 14—22.

The original questionnaire was developed by Björn Kadesjö, Lars-Olof Janols and Christopher Gillberg (Sweden); Marit Korkman and Katarina Mickelsson (Finland); Gerd Strand (Norway) and Anegen Trillingsgaard (Denmark).

On the basis of a Swedish population study by Kadesjö et al. (2004) norms were developed and published. The research group made the questionnaire, the manual, and the 2004 norms available for professionals free-of-charge.

In 2007 the web portal www.5-15.org was established and professionals with basic statistical knowledge and a clinical background were able to apply to become a 5-15.org user. At 5-15.org professionals could download questionnaires, input parent responses, and convert data to norm-based tables and graphs – with percentiles and profiles across the 5-15 domains. It was also possible to download and print a results sheets showing statistical and graphical representation of scores in relation to the norm sample.

The 5-15 questionnaire has been extensively used in the Nordic countries and, in addition to being available in the Nordic languages and English, is now also available in Estonian, Spanish, and Russian.

Five-To-Fifteen Revised (5-15R)

The Nordic research group has just finished upgrading the parent questionnaire. Today the 5-15 research group consists of several of the original developers of the 5-15 from 2004 plus a number of new experts within the field.

The present upgrade includes:

1. Inclusion of a teacher questionnaire. The 5-15 items pertain to aspects of child and adolescent functioning that should also be evident outside the family context (e.g., in school), and therefore teachers are considered valuable informants in the assessment of the areas covered by the 5-15. In addition, multi-informant ratings are generally recommended in the clinical assessment and are assumed to contribute to a higher level of reliability.

2. Upward extension of the age range: In recognition of the fact child developmental issues more often than not continue beyond childhood and need continued monitoring, several items from the 5-15 questionnaire have been revised to match an extended age range (5-17 years).

3. Inclusion of impact questions: Impact questions have been added after each domain as problems or symptom count are not always consistent with the parents' experience of impairment.

Presentation of the 5-15R questionnaires

The 5-15R questionnaires (i.e., the parent and the teacher versions) include 181 statements that can be endorsed as "Does not apply"; "Applies sometimes or to some extent" or "Definitely applies".

The 181 statements in the teacher questionnaire are basically identical to those in the parent version, but 'child' has been substituted by 'pupil' where relevant. A number of statements concerning reading and math skills are only rated in children/pupils above a certain grade level.

The 181 statements are arranged into eight general domains covering motor skills, executive functions (including attention), perception, memory, language and communication, learning competencies, social skills, and emotional/behavioral problems. The eight domains are further divided into a number of subdomains.

The following constitutes an overview of the domains and subdomains covered by the instrument:

- MOTOR SKILLS
  - Gross motor skills
  - Fine motor skills
- EXECUTIVE FUNCTIONS
  - Attention and concentration
  - Hyperactivity and impulsivity
  - Passiveness/inactivity
  - Planning/organizing
- PERCEPTION
  - Relation in space
  - Time concepts
  - Body perception
  - Perception of forms and figures
- MEMORY
- LANGUAGE AND COMMUNICATION
  - Comprehension
  - Expressive language skills
  - Verbal communication
- LEARNING SKILLS
  - Reading, spelling, and writing
  - Math
  - Learning new skills and applying knowledge in relation to school
  - The child's ability to solve different types of problems at school and his/her way of encountering a learning situation
- SOCIAL SKILLS
- MENTAL HEALTH PROBLEMS
  - Internalizing
  - Externalizing
  - Obsessive-compulsive actions or thoughts

The impact questions were formulated in general terms such as ''Do problems with X interfere your child's daily function'' (parents) or ''Do problems with X interfere with your pupil's function in school'' (teachers) to be rated as ''Not at all'' (0), ''A little'' (1), ''Quite a lot'' (2) or ''A great deal'' (3).

Impact questions were placed immediately after domains, with the exception of the executive function domain, where separate impact questions were included after subdomains.

New norms for the 5-15R parent and teacher questionnaire

In 2012, researchers from Aarhus University collected data for the revised 5-15R parent questionnaire and the 5-15R teacher questionnaire. The project was supported by a research grant from the TrygFonden.

Statistics Denmark selected an age- and gender stratified simple random sample (approximately 1%) of the population of children between the ages of 5 and 17 years living in Denmark at the time of the data collection. Subsequently, the children's parents were invited by mail to complete the parent questionnaire and encouraged to forward the teacher questionnaire to their child's primary teacher. A total of 4,258 parent questionnaires (2,116 boys and 2,142 girls) were included in the study. The majority of the children were of Danish descent, and comparisons between responders and the background population indicated small differences only with respect to parental labour force participation and income. For 1,298 (of the 4,258) children a teacher questionnaire was also returned – equivalent to 638 boys and 660 girls. The majority of teachers came from primary and lower secondary schools (77% public, 13% private, 2% special education, and 3% continuation), 3% came from kindergarten-equivalent facilities and 2% from upper secondary schools.

The results from this comprehensive study of the revised 5-15R parent questionnaire indicated that scores on domains, subdomains, and impact questions had acceptable psychometric properties (internal consistency, inter-rater reliability, test-retest reliability and convergent validity). Scores on the 5-15R teacher questionnaire had psychometric properties comparable to those of the parent questionnaire, indicating that the teacher questionnaire is appropriate in the examination of children and adolescents. Extension of the age range to include 16- to 17-year-olds had no influence on the results, which supports that the 5-15R questionnaire is applicable for older age groups. The impact questions yielded information above and beyond that provided by symptom count alone and appeared to increase the ability of the FTF to identify at risk children and adolescents.

In charge of the standardization study was Rikke Lambek and Anegen Trillingsgaard. The research results were published in 2015. See reference below (further details are found in the article).

Lambek, R. & Trillingsgaard (2015) Elaboration, validation and standardization of the five to fifteen (FTF) questionnaire in a Danish population sample. Research in Developmental Disabilities, *38*, 161-170. doi: 10.1016/j.ridd.2014.12.018

Online versions of the 5-15R parent and teacher questionnaires at www.5-15.org

By the end of 2016, the upgraded parent questionnaire and the new teacher questionnaire will be available at the web portal www.5-15.org. The questionnaires can only be administered and scored according to the new norms, which will replace 2004 norms.

As a novel feature, it is now possible to mail a link to parents or teachers and have them open a questionnaire online and answer it electronically – paper versions will still be available at www.5-15.org as will the option to enter scores from the paper version manually and convert to norm-based graphs etc.

Access to the questionnaires and the online resources requires registration as a professional user at www.5-15.org where further details are available. Users who are already registered will be informed about the changes in due time. Guidelines for electronic administration and scoring of 5-15R will be available at www.5-15.org.

Other questionnaires at www.5-15.org

At www.5-15.org, an infant version of the parent questionnaire: '2-5. Nordisk formulär för utredning av barns utvickling och beteende', a version for children between the age of 2 and 5, is also available. This questionnaire is still under construction and norms are not yet available. Presently, the questionnaire should be applied as an interview guide with parents about regarding developmental and behavioral problems in 2- to 5-year-olds. At present only a Swedish version is available. In charge of this questionnaire is Björn Kadesjö, Camela Miniscalco, Bibbi Hagberg and Christopher Gillberg (Sweden), and Anu Haavisto (Finland).

A self-report version for 10- to 16-year-olds is also under construction. In charge of the self-report version is Aud Bredesen and Geir Høstmark (Norway).

5-15.org is a nonprofit organisation

It has been of crucial importance to the developers and the research group, which presently maintain and develop the instrument, that the questionnaires will continue to be available free of charge to clinicians and researchers within the field.

Maintenance and development is supported by:

GNC (Gillberg Neuropsychiatry Center, Sweden), NevSom (Norwegian Resource Center for Neurodevelopmental Disorders and Hypersomnia), and Aarhus University, Denmark.

Appendix

Table 1: 5-15R: Domains and subdomains

Domains	**Statements**	**Subdomains**	**Statements**
Motor skills	1-17	Gross motor skills	1-7
		Fine motor skills	8-17
Executive functions	18-42	Attention and concentration	18-26
		Overactivity and impulsivity	27-35
		Passivity and inactivity	36-39
		Planning and organizing	40-42
Perception	43-60	Perception of space and directions	43-47
		Concepts of time	48-51
		Perception of own body	52-56
		Perception of visual forms and figures	57-60
Memory	61-71	Memory	61-71
Language	72-92	Comprehension of spoken language	72-76
		Expressive language	77-89
		Verbal communication	90-92
Learning	93-121	Reading and writing	93-100
		Arithmetic	101-105
		General learning	106-109
		Coping with learning	112-121
Social skills	122-148	Social skills	122-148
Emotional/behavioral difficulties	149-181	Internalisation	149-160
		Acting out	161-173
		Obsessive actions or thoughts	174-181

Table 2: Cut-off scores in relation to the 90 and 98 percentiles (%)

Boys - answered by parents

Age group	5-7 yo		8-11 yo		12-15 yo		16-17 yo	
%	90 %	98 %	90 %	98 %	90 %	98 %	90 %	98 %
Motor skills	0,47	0,85	0,44	1	0,35	0,91	0,29	0,71
Executive functions	0,76	1,4	0,84	1,4	0,86	1,34	0,76	1,32
Perception	0,49	0,75	0,39	0,86	0,31	0,89	0,19	0,78
Memory	0,64	1,09	0,54	1	0,55	1,18	0,46	1
Language	0,38	1,14	0,33	0,83	0,38	0,86	0,28	0,72
Learning	-	-	0,8	1,48	0,96	1,46	0,81	1,52
Social skills	0,39	1	0,44	1,13	0,44	1,06	0,41	1,11
Emotional/behavioral difficulties	0,3	0,67	0,33	0,71	0,28	0,76	0,33	0,73

Boys - answered by teachers

Age group	5-7 yo		8-11 yo		12-15 yo		16-17 yo	
%	90 %	98 %	90 %	98 %	90 %	98 %	90 %	98 %
Motor skills	0,65	1,13	0,53	1,41	0,46	1,12	0,3	0,71
Executive functions	1,12	1,64	0,95	1,36	1,02	1,52	0,96	1,16
Perception	0,45	1,17	0,33	0,72	0,39	1,12	0,19	1
Memory	0,95	1,64	0,64	1,36	0,73	1,45	0,48	1,27
Language	0,57	1,19	0,48	1,19	0,47	1,3	0,52	0,91
Learning			0,85	1,46	1,07	1,81	1,04	1,47
Social skills	0,59	1,3	0,63	1,22	0,72	1,15	0,37	0,86
Emotional/behavioral difficulties	0,25	0,73	0,28	0,64	0,29	0,7	0,12	0,18

Girls - answered by parents

Age group	5-7 yo		8-11 yo		12-15 yo		16-17 yo	
%	90 %	98 %	90 %	98 %	90 %	98 %	90 %	98 %
Motor skills	0,35	0,68	0,23	0,59	0,23	0,58	0,18	0,71
Executive functions	0,58	1,15	0,53	1,22	0,52	1,06	0,48	1,1
Perception	0,39	0,67	0,28	0,58	0,17	0,53	0,16	0,43
Memory	0,55	1,05	0,37	1,09	0,37	0,91	0,45	0,91
Language	0,33	0,95	0,24	0,79	0,19	0,69	0,2	0,71
Learning			0,5	1,31	0,56	1,22	0,51	1,41
Social skills	0,23	0,67	0,22	0,74	0,22	0,81	0,22	0,67
Emotional/behavioral difficulties	0,24	0,54	0,27	0,62	0,27	0,62	0,27	0,68

Girls - answered by teachers

Age group	5-7 yo		8-11 yo		12-15 yo		16-17 yo	
%	90 %	98 %	90 %	98 %	90 %	98 %	90 %	98 %
Motor skills	0,35	0,93	0,29	0,76	0,18	0,59	0,16	0,56
Executive functions	0,42	0,87	0,5	1,12	0,48	1	0,52	1
Perception	0,27	0,61	0,16	0,94	0,14	0,49	0,07	0,36
Memory	0,55	1,18	0,45	1,32	0,32	1	0,36	0,91
Language	0,33	0,67	0,37	1,26	0,33	0,67	0,17	0,31
Learning			0,67	1,52	0,57	1,33	0,61	1
Social skills	0,26	0,67	0,26	1,31	0,26	0,89	0,37	0,81
Emotional/behavioral difficulties	0,15	0,4	0,17	0,53	0,18	0,46	0,24	0,71

Table 3: Subdomain median, average and standard deviation (SD) for gender and age groups

Boys - answered by parents

Subdomains	Age	Median	Average	SD	N
Gross motor skills	5-7 yo	0,04	0,13	0,27	499
	8-11 yo	0,03	0,14	0,3	666
	12-15 yo	0,03	0,11	0,26	633
	16-17 yo	0,02	0,1	0,24	318
Fine motor skills	5-7 yo	0,2	0,23	0,27	497
	8-11 yo	0,08	0,17	0,27	666
	12-15 yo	0	0,13	0,25	633
	16-17 yo	0	0,1	0,22	318
Attention and concentration	5-7 yo	0,22	0,34	0,41	494
	8-11 yo	0,23	0,41	0,48	666
	12-15 yo	0,22	0,41	0,5	633
	16-17 yo	0,1	0,33	0,49	318
Overactivity and impulsivity	5-7 yo	0,18	0,32	0,4	499
	8-11 yo	0,1	0,23	0,37	666
	12-15 yo	0,04	0,17	0,31	633
	16-17 yo	0	0,14	0,28	318
Passivity and inactivity	5-7 yo	0,08	0,21	0,34	497
	8-11 yo	0,12	0,29	0,43	666
	12-15 yo	0,21	0,32	0,45	633
	16-17 yo	0,1	0,29	0,44	318
Planning and organizing	5-7 yo	0,19	0,33	0,42	494
	8-11 yo	0,15	0,32	0,45	666
	12-15 yo	0,09	0,26	0,47	633
	16-17 yo	0,06	0,19	0,41	317
Perception of space and directions	5-7 yo	0,07	0,14	0,23	498
	8-11 yo	0,01	0,09	0,21	666
	12-15 yo	0,02	0,06	0,2	633
	16-17 yo	0,02	0,06	0,18	318
Concepts of time	5-7 yo	0,5	0,55	0,48	499
	8-11 yo	0,03	0,25	0,4	666
	12-15 yo	0,04	0,14	0,35	633
	16-17 yo	0,02	0,09	0,27	318
Perception of own body	5-7 yo	0,07	0,15	0,25	498
	8-11 yo	0,05	0,15	0,29	666
	12-15 yo	0,04	0,11	0,26	633
	16-17 yo	0,03	0,09	0,27	318
Perception of visual forms and figures	5-7 yo	0,01	0,1	0,23	499
	8-11 yo	0,03	0,08	0,2	666
	12-15 yo	0,03	0,08	0,24	633
	16-17 yo	0,01	0,05	0,22	318
Memory	5-7 yo	0,18	0,26	0,3	495
	8-11 yo	0,09	0,19	0,26	665
	12-15 yo	0,09	0,19	0,29	632
	16-17 yo	0,01	0,15	0,24	317
Comprehension of spoken language	5-7 yo	0,09	0,21	0,33	499
	8-11 yo	0,01	0,16	0,31	665
	12-15 yo	0,04	0,15	0,33	633
	16-17 yo	0,03	0,13	0,33	317

Expressive language	5-7 yo	0,07	0,14	0,26	498
	8-11 yo	0	0,08	0,2	665
	12-15 yo	0,01	0,09	0,19	633
	16-17 yo	0,01	0,06	0,16	317
Verbal communication	5-7 yo	0,08	0,2	0,37	498
	8-11 yo	0,05	0,16	0,35	666
	12-15 yo	0,05	0,17	0,37	633
	16-17 yo	0,03	0,11	0,3	317
Reading and writing	5-7 yo	-	-	-	0
	8-11 yo	0,12	0,32	0,49	607
	12-15 yo	0,13	0,33	0,49	633
	16-17 yo	0,11	0,28	0,44	318
Arithmetic	5-7 yo	-	-	-	0
	8-11 yo	0,05	0,19	0,41	606
	12-15 yo	0,05	0,27	0,51	633
	16-17 yo	0,02	0,18	0,41	316
General learning	5-7 yo	-	-	-	0
	8-11 yo	0,04	0,15	0,34	607
	12-15 yo	0,01	0,16	0,35	632
	16-17 yo	0,03	0,14	0,35	317
Coping with learning	5-7 yo	-	-	-	0
	8-11 yo	0,11	0,32	0,44	605
	12-15 yo	0,1	0,31	0,44	632
	16-17 yo	0,01	0,25	0,43	317
Social skills	5-7 yo	0,04	0,14	0,24	499
	8-11 yo	0,04	0,14	0,26	666
	12-15 yo	0,04	0,13	0,26	633
	16-17 yo	0	0,13	0,26	318
Internalisation	5-7 yo	0,03	0,08	0,18	499
	8-11 yo	0,03	0,11	0,21	666
	12-15 yo	0,02	0,09	0,21	633
	16-17 yo	0,01	0,09	0,2	318
Acting out	5-7 yo	0,07	0,16	0,26	499
	8-11 yo	0,05	0,16	0,26	666
	12-15 yo	0,01	0,13	0,24	633
	16-17 yo	0,01	0,12	0,26	318
Obsessive actions or thoughts	5-7 yo	0,02	0,07	0,17	499
	8-11 yo	0,02	0,07	0,2	666
	12-15 yo	0,02	0,08	0,21	633
	16-17 yo	0,01	0,06	0,18	318

Boys - answered by teachers

Subdomains	Age	Median	Average	SD	N
Gross motor skills	5-7 yo	0,13	0,23	0,35	120
	8-11 yo	0,01	0,17	0,37	233
	12-15 yo	0,03	0,15	0,31	216
	16-17 yo	0,02	0,09	0,22	49
Fine motor skills	5-7 yo	0,1	0,22	0,32	121
	8-11 yo	0,01	0,19	0,32	235
	12-15 yo	0,01	0,16	0,33	213
	16-17 yo	0,02	0,09	0,19	50
Attention and concentration	5-7 yo	0,22	0,43	0,55	121
	8-11 yo	0,22	0,42	0,5	237
	12-15 yo	0,22	0,47	0,58	219
	16-17 yo	0,02	0,35	0,5	58
Overactivity and impulsivity	5-7 yo	0,05	0,27	0,43	122
	8-11 yo	0,1	0,28	0,44	237
	12-15 yo	0,01	0,17	0,31	220
	16-17 yo	0,01	0,11	0,28	58
Passivity and inactivity	5-7 yo	0,14	0,42	0,58	122
	8-11 yo	0,15	0,35	0,49	237
	12-15 yo	0,17	0,47	0,61	220
	16-17 yo	0,07	0,31	0,52	58
Planning and organizing	5-7 yo	0,11	0,36	0,57	119
	8-11 yo	0,09	0,24	0,43	232
	12-15 yo	0,08	0,27	0,5	216
	16-17 yo	0,05	0,2	0,46	55
Perception of space and directions	5-7 yo	0,02	0,14	0,32	118
	8-11 yo	0,01	0,07	0,17	232
	12-15 yo	0,02	0,09	0,28	213
	16-17 yo	0,01	0,05	0,15	52
Concepts of time	5-7 yo	0,04	0,29	0,43	119
	8-11 yo	0,01	0,14	0,31	235
	12-15 yo	0,03	0,12	0,33	217
	16-17 yo	0,02	0,1	0,31	55
Perception of own body	5-7 yo	0,04	0,14	0,3	117
	8-11 yo	0,01	0,13	0,28	233
	12-15 yo	0,01	0,14	0,31	212
	16-17 yo	0,03	0,09	0,23	51
Perception of visual forms and figures	5-7 yo	0,01	0,12	0,28	119
	8-11 yo	0,01	0,12	0,29	234
	12-15 yo	0,01	0,15	0,36	211
	16-17 yo	0,02	0,08	0,27	53
Memory	5-7 yo	0,09	0,29	0,42	119
	8-11 yo	0,09	0,19	0,32	234
	12-15 yo	0	0,21	0,38	214
	16-17 yo	0,02	0,17	0,31	52
Comprehension of spoken language	5-7 yo	0,02	0,27	0,44	122
	8-11 yo	0,02	0,21	0,38	236
	12-15 yo	0,01	0,19	0,39	219
	16-17 yo	0,01	0,12	0,31	57
Expressive language	5-7 yo	0	0,14	0,28	121
	8-11 yo	0,01	0,11	0,23	236
	12-15 yo	0,02	0,12	0,3	219
	16-17 yo	0	0,1	0,24	58

Verbal communication	5-7 yo	0,08	0,23	0,44	122
	8-11 yo	0,08	0,22	0,43	237
	12-15 yo	0,06	0,2	0,43	220
	16-17 yo	0,04	0,14	0,36	58
Reading and writing	5-7 yo	1,12	-	-	1
	8-11 yo	0,11	0,36	0,5	215
	12-15 yo	0,12	0,37	0,53	220
	16-17 yo	0,02	0,24	0,44	54
Arithmetic	5-7 yo	-	-	-	0
	8-11 yo	0,01	0,17	0,38	207
	12-15 yo	0,01	0,27	0,53	215
	16-17 yo	0,04	0,26	0,54	56
General learning	5-7 yo	0,67	-	-	1
	8-11 yo	0,02	0,24	0,43	216
	12-15 yo	0,07	0,27	0,49	219
	16-17 yo	0,05	0,2	0,44	59
Coping with learning	5-7 yo	1,2	-	-	1
	8-11 yo	0,11	0,3	0,42	215
	12-15 yo	0,11	0,35	0,5	220
	16-17 yo	0,04	0,25	0,42	58
Social skills	5-7 yo	0,06	0,22	0,33	122
	8-11 yo	0,07	0,2	0,32	236
	12-15 yo	0,04	0,2	0,33	219
	16-17 yo	0,01	0,11	0,23	57
Internalisation	5-7 yo	0	0,08	0,14	115
	8-11 yo	0,01	0,07	0,15	223
	12-15 yo	0,01	0,1	0,21	211
	16-17 yo	0	0,04	0,08	54
Acting out	5-7 yo	0	0,13	0,26	120
	8-11 yo	0	0,12	0,25	232
	12-15 yo	0	0,1	0,24	215
	16-17 yo	0,01	0,04	0,12	54
Obsessive actions or thoughts	5-7 yo	0,01	0,07	0,18	122
	8-11 yo	0,01	0,08	0,25	236
	12-15 yo	0	0,06	0,2	220
	16-17 yo	0	0,02	0,06	58

Girls - answered by parents

Subdomains	Age	Median	Average	SD	N
Gross motor skills	5-7 yo	0,05	0,15	0,28	505
	8-11 yo	0,02	0,1	0,23	670
	12-15 yo	0,03	0,1	0,25	679
	16-17 yo	0,03	0,11	0,26	285
Fine motor skills	5-7 yo	0,08	0,14	0,21	505
	8-11 yo	0,01	0,07	0,18	670
	12-15 yo	0,02	0,05	0,14	680
	16-17 yo	0,01	0,05	0,18	286
Attention and concentration	5-7 yo	0,11	0,24	0,36	505
	8-11 yo	0,08	0,24	0,38	668
	12-15 yo	0,02	0,23	0,38	680
	16-17 yo	0,03	0,2	0,38	286
Overactivity and impulsivity	5-7 yo	0,11	0,24	0,34	505
	8-11 yo	0,01	0,15	0,28	670
	12-15 yo	0,01	0,1	0,22	680
	16-17 yo	0,01	0,08	0,22	286
Passivity and inactivity	5-7 yo	0,06	0,15	0,31	504
	8-11 yo	0,02	0,2	0,36	669
	12-15 yo	0,09	0,23	0,37	680
	16-17 yo	0,02	0,21	0,38	286
Planning and organizing	5-7 yo	0,11	0,24	0,38	502
	8-11 yo	0,07	0,17	0,34	669
	12-15 yo	0,04	0,14	0,34	680
	16-17 yo	0,03	0,1	0,31	286
Perception of space and directions	5-7 yo	0,05	0,1	0,2	506
	8-11 yo	0,03	0,07	0,18	668
	12-15 yo	0,02	0,07	0,18	680
	16-17 yo	0,03	0,08	0,22	286
Concepts of time	5-7 yo	0,48	0,51	0,45	505
	8-11 yo	0,08	0,22	0,37	668
	12-15 yo	0,01	0,08	0,23	680
	16-17 yo	0,02	0,05	0,17	286
Perception of own body	5-7 yo	0,02	0,1	0,23	506
	8-11 yo	0,03	0,08	0,19	669
	12-15 yo	0,02	0,06	0,19	680
	16-17 yo	0,01	0,04	0,14	286
Perception of visual forms and figures	5-7 yo	0,02	0,05	0,18	504
	8-11 yo	0,01	0,03	0,17	668
	12-15 yo	0,01	0,02	0,1	680
	16-17 yo	0,01	0,03	0,16	286
Memory	5-7 yo	0,09	0,21	0,27	503
	8-11 yo	0,09	0,15	0,26	667
	12-15 yo	0	0,13	0,22	680
	16-17 yo	0,01	0,14	0,23	285
Comprehension of spoken language	5-7 yo	0,08	0,18	0,29	506
	8-11 yo	0,03	0,11	0,28	668
	12-15 yo	0,03	0,09	0,25	680
	16-17 yo	0,02	0,09	0,26	285
Expressive language	5-7 yo	0,03	0,11	0,24	505
	8-11 yo	0	0,07	0,19	668
	12-15 yo	0,01	0,06	0,15	680
	16-17 yo	0,01	0,06	0,15	285

Verbal communication	5-7 yo	0,05	0,14	0,31	505
	8-11 yo	0,04	0,11	0,3	668
	12-15 yo	0,02	0,08	0,26	679
	16-17 yo	0,02	0,08	0,29	286
Reading and writing	5-7 yo	-	-	-	0
	8-11 yo	0,01	0,18	0,38	616
	12-15 yo	0,01	0,15	0,32	680
	16-17 yo	0,03	0,15	0,33	286
Arithmetic	5-7 yo				0
	8-11 yo	0,03	0,23	0,43	615
	12-15 yo	0,01	0,26	0,46	678
	16-17 yo	0,06	0,27	0,5	286
General learning	5-7 yo	-	-	-	0
	8-11 yo	0,03	0,11	0,28	616
	12-15 yo	0,04	0,12	0,3	680
	16-17 yo	0,02	0,12	0,34	286
Coping with learning	5-7 yo	-	-	-	0
	8-11 yo	0,01	0,19	0,34	617
	12-15 yo	0,02	0,19	0,34	679
	16-17 yo	0,01	0,16	0,34	286
Social skills	5-7 yo	0,04	0,09	0,19	506
	8-11 yo	0,01	0,08	0,2	668
	12-15 yo	0	0,08	0,21	680
	16-17 yo	0	0,07	0,18	285
Internalisation	5-7 yo	0,03	0,09	0,17	505
	8-11 yo	0,03	0,11	0,21	668
	12-15 yo	0,01	0,11	0,22	680
	16-17 yo	0,03	0,12	0,25	286
Acting out	5-7 yo	0,07	0,13	0,21	505
	8-11 yo	0,01	0,12	0,21	668
	12-15 yo	0	0,1	0,2	680
	16-17 yo	0,02	0,09	0,2	286
Obsessive actions or thoughts	5-7 yo	0,01	0,03	0,13	506
	8-11 yo	0,01	0,05	0,17	668
	12-15 yo	0,01	0,04	0,13	680
	16-17 yo	0,01	0,03	0,13	286

Girls - answered by teachers

Subdomains	Age	Median	Average	SD	N
Gross motor skills	5-7 yo	0,02	0,17	0,3	126
	8-11 yo	0,01	0,14	0,31	252
	12-15 yo	0,02	0,1	0,25	211
	16-17 yo	0,02	0,1	0,28	46
Fine motor skills	5-7 yo	0	0,08	0,16	128
	8-11 yo	0	0,05	0,21	256
	12-15 yo	0,01	0,04	0,15	215
	16-17 yo	0	0,02	0,06	49
Attention and concentration	5-7 yo	0,02	0,17	0,32	129
	8-11 yo	0,04	0,19	0,35	260
	12-15 yo	0	0,2	0,39	220
	16-17 yo	0	0,17	0,34	51
Overactivity and impulsivity	5-7 yo	0	0,09	0,18	129
	8-11 yo	0	0,09	0,23	260
	12-15 yo	0	0,07	0,2	220
	16-17 yo	0,02	0,08	0,2	51
Passivity and inactivity	5-7 yo	0,07	0,24	0,43	129
	8-11 yo	0,06	0,21	0,41	260
	12-15 yo	0,06	0,22	0,39	220
	16-17 yo	0,04	0,2	0,39	51
Planning and organizing	5-7 yo	0,03	0,09	0,22	126
	8-11 yo	0,03	0,1	0,33	260
	12-15 yo	0,03	0,11	0,29	220
	16-17 yo	0,02	0,08	0,26	48
Perception of space and directions	5-7 yo	0,04	0,09	0,19	126
	8-11 yo	0	0,07	0,24	248
	12-15 yo	0,01	0,05	0,17	218
	16-17 yo	0	0,02	0,09	48
Concepts of time	5-7 yo	0,03	0,2	0,33	128
	8-11 yo	0,02	0,09	0,26	255
	12-15 yo	0,02	0,06	0,19	219
	16-17 yo	0,01	0,05	0,2	49
Perception of own body	5-7 yo	0,01	0,04	0,11	128
	8-11 yo	0,02	0,06	0,23	257
	12-15 yo	0,01	0,03	0,14	220
	16-17 yo	0,01	0,03	0,08	48
Perception of visual forms and figures	5-7 yo	0,01	0,05	0,18	127
	8-11 yo	0	0,05	0,22	255
	12-15 yo	0,01	0,03	0,16	216
	16-17 yo	0	0,01	0,04	48
Memory	5-7 yo	0,01	0,18	0,3	126
	8-11 yo	0	0,13	0,31	257
	12-15 yo	0	0,11	0,24	219
	16-17 yo	0	0,09	0,21	49
Comprehension of spoken language	5-7 yo	0,05	0,14	0,27	129
	8-11 yo	0,01	0,17	0,39	260
	12-15 yo	0,03	0,14	0,31	219
	16-17 yo	0,02	0,06	0,15	51
Expressive language	5-7 yo	0	0,09	0,2	129
	8-11 yo	0	0,1	0,25	260
	12-15 yo	0,01	0,06	0,14	220
	16-17 yo	0	0,04	0,09	51

Verbal communication	5-7 yo	0,03	0,1	0,28	129
	8-11 yo	0,03	0,13	0,39	257
	12-15 yo	0,03	0,1	0,3	220
	16-17 yo	0,01	0,03	0,11	50
Reading and writing	5-7 yo				0
	8-11 yo	0,01	0,19	0,41	238
	12-15 yo	0,03	0,14	0,33	220
	16-17 yo	0,01	0,09	0,26	51
Arithmetic	5-7 yo				0
	8-11 yo	0,04	0,23	0,46	234
	12-15 yo	0,03	0,19	0,41	215
	16-17 yo	0,03	0,15	0,38	48
General learning	5-7 yo				0
	8-11 yo	0,02	0,22	0,43	239
	12-15 yo	0,04	0,18	0,38	220
	16-17 yo	0,01	0,13	0,27	51
Coping with learning	5-7 yo				0
	8-11 yo	0,01	0,18	0,34	239
	12-15 yo	0,03	0,18	0,35	220
	16-17 yo	0	0,11	0,25	51
Social skills	5-7 yo	0,03	0,09	0,17	129
	8-11 yo	0,04	0,11	0,27	260
	12-15 yo	0	0,09	0,2	220
	16-17 yo	0	0,1	0,2	50
Internalisation	5-7 yo	0,01	0,08	0,15	121
	8-11 yo	0,01	0,08	0,19	250
	12-15 yo	0,01	0,11	0,22	210
	16-17 yo	0,01	0,12	0,27	47
Acting out	5-7 yo	0	0,05	0,15	128
	8-11 yo	0	0,07	0,2	258
	12-15 yo	0	0,05	0,12	219
	16-17 yo	0,01	0,08	0,17	48
Obsessive actions or thoughts	5-7 yo	0,01	0,01	0,05	129
	8-11 yo	0,01	0,03	0,18	259
	12-15 yo	0	0,02	0,1	219
	16-17 yo	0,01	0,03	0,08	51

Supplemental 3: Task description included in Memoro

Reaction time was tested by participants tapping as fast as possible upon seeing a blue box appearing in the center of the screen. The scores are the mean of 30 trials. In the task that tested executive functions, participants were instructed to tap as fast as possible when a box changed from the color white to blue but refrain when another color was shown. Scores were calculated as the total number of erroneous responses. There are a total of 40 trials (32 GO, 8 NOGO). In the digit span forward and backward tasks, digits between one and nine are presented to the participant on the screen.[1] The task starts with two digits and becomes progressively more difficult by adding more digits. In the forward condition, the participant types in the numbers presented in the order of their prestation. In the backward condition, they type the numbers in the reverse order. The test discontinued if more than 3 consecutive errors are made. The participants are unaware of this criterion. The score is the longest span achieved in both conditions. Processing speed was measured with the symbol coding test in which the participants pair a number to a symbol using a key.[2] Scores were obtained by calculating the number of correct responses and subtracting the erroneous responses. The visual memory task is an object-location memory task where participants are asked to remember ten objects presented in a blank square on the screen for 60 seconds (encoding period) inspired by the Silverman and Eals´ test.[3] After encoding, all objects are presented outside the square and the participant is instructed to place each object back in its original location within the square (immediate recall).[4] The score used in this study was the sum of distances from the correct positions. In the pattern separation test, the participants were presented with 175 successive images and had to indicate if the currently presented image was novel, i.e., presented for the first time, identical, or similar to a previously presented image.[5] Scores were obtained by calculating the ratio of correctly identified similar items minus the ratio of similar responses given to the items not previously seen.

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Paper II

Retinal structure and visual pathway function at school age in children born extremely preterm: A population-based study

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Abstract

Background: Children born extremely preterm (gestational age < 28 weeks) show reduced visual function even without any cerebral or ophthalmological neonatal diagnosis. In this study, we aimed to assess the retinal structure with optical coherence tomography (OCT) and visual function with pattern-reversal visual evoked potentials (PR-VEPs) in a geographically defined population-based cohort of school-aged children born extremely preterm. Moreover, we aimed to explore the association between measures of retinal structure and visual pathway function in this cohort.

Methods: All children born extremely preterm from 2006-2011 (n= 65) in Central Norway were invited to participate. Thirty-six children (55%) with a median age of 13 years (range= 10-16) were examined with OCT, OCT-angiography (OCT-A), and PR-VEPs. The foveal avascular zone (FAZ) and circularity, central macular vascular density, and flow were measured on OCT-A images. Central retinal thickness, circumpapillary retinal nerve fibre layer (RNFL) and inner plexiform ganglion cell layer (IPGCL) thickness were measured on OCT images. The N70-P100 peak-to-peak amplitude and N70 and P100 latencies were assessed from PR-VEPs.

Results: Participants displayed abnormal retinal structure and P100 latencies (≥2 SD) compared to reference populations. Moreover, there was a negative correlation between P100 latency in large checks and RNFL (r=-.54, *p*=.003) and IPGCL (*r*=-.41, *p*=.003) thickness. The FAZ was smaller (p=.003), macular vascular density (p=.006) and flow were higher (p=.004), and RNFL (p=.006) and IPGCL (p=.014) were thinner in participants with ROP (n=7).

Conclusion: Children born extremely preterm without preterm brain injury sequelae have signs of persistent immaturity of retinal vasculature and neuroretinal layers. Thinner neuroretinal layers are associated with delayed P100 latency, prompting further exploration of the visual pathway development in preterms.

Keywords: optical coherence tomography, visual evoked potentials, extremely preterm, retinopathy of prematurity

Introduction

Children born extremely preterm (gestational age (GA) < 28 weeks) are at increased risk of visual impairments [1] that are not fully explained by sequelae from retinopathy of prematurity (ROP) [2]. The disease is defined by clinically observed pathological neovascularization of the retina during development and retinal detachment in its end stage, resulting in visual impairment [3]. However, neonatal screening identifies individuals needing treatment. Therefore, end-stage ROP is rarely seen in high-income countries [4] and may thus not be the primary contributor to the increased risk of visual impairments observed in children born extremely preterm. Moreover, it has been suggested that ROP is not only a vascular disease but also includes injury to the neurovascular interphase in the retina and/or brain [5]. Indeed, we have suggested that ROP is merely the tip of the iceberg of a more extensive entity coined "Visuopathy of Prematurity" (VOP), which is proposed to encompass neurovascular tissue injury in the retina and the cerebral visual pathways of children born preterm [2].

The fovea is not fully matured until one or two years of age because most inner retinal differentiation occurs before birth, and outer retinal differentiation occurs after birth [6]. During foetal development, the fovea is formed by the centrifugal movement of inner retinal layers to the periphery and migration of the outer photoreceptor layers towards the centre of the foveola [7, 8]. The vascular mesh that covers the retina in early foetal life retracts to leave an avascular zone in the fovea, facilitating light to access foveolar photoreceptors and enabling sharp vision [9]. This process occurs during late gestation, and both the development of the retinal vasculature and the neuroretina may be interrupted by factors associated with preterm birth.

Optical coherence tomography (OCT) angiography provides non-invasive *in vivo* high-resolution imaging of the retinal layers and vasculature and has revealed retinal microstructural abnormalities such as a smaller foveal avascular zone, higher vascular density, and a thicker central macula among children born preterm at age 3-17 years old [10-12]. The retinal abnormalities might also be associated with abnormal functional integrity of the visual pathways. Indeed, altered visual evoked potentials (VEPs) generated in the occipital cortex have been reported in very low birth weight (VLBW; <1500 g birthweight) pre-schoolers [13]. However, the association between OCT and VEP measures has not yet been explored in school-aged children born extremely preterm. Moreover, research findings are inconsistent on whether the pattern of abnormal retinal structure and visual function is more prominent among children born extremely preterm with ROP [14, 15].

Thus, we wanted to assess the structure of the retinal neurovascular development, the visual pathways' function, and possible associations in a population-based cohort of school-aged children born extremely preterm with and without ROP.

Methods and materials

Study design and participants

All children residing in Norway who were born extremely preterm from 2006-2011 in the geographical region of Central Norway were identified via the Norwegian Neonatal Network (NNN), a national medical quality registry that collects data on all new-borns admitted to neonatal intensive care units in Norway. Norway has near-universal health insurance coverage. Information from NNN was cross-checked with medical records, and the children's last names were cross-checked with the Norwegian National Population Register to obtain the addresses of their parents. The study had no exclusion criteria. Sixty-five children were invited via a mailed letter containing information about the study. Parents were contacted by phone for consent; 14 could not be reached. Of the remaining 51, 36 (55%)

consented and were enrolled in the study between March 3 and September 2, 2021. Their median (range) age at visual assessment was 13 years (10-16). Background neonatal data were obtained from NNN and cross-checked in medical records for participants and non-participants (those who declined to participate and could not be reached). There were no significant differences between participants and non-participants in clinical background data [16]. A clinical assessment of brain MRI had been performed as part of an earlier study and confirmed that none of the participants had signs of preterm brain injury [16].

Ophthalmological examination

Best-corrected visual acuity (BCVA) as letter score and the logarithm of the minimum angle of resolution (logMAR) was obtained monocularly and binocularly following subjective refraction at 4 meters distance according to the Early Treatment Diabetic Retinopathy Study (ETDRS) [17]. Subsequent testing was performed with the best correction. Cut-off scores for BCVA were calculated as <85 letter score (equivalent to 20/20 Snellen and a logMAR score of 0.0), which is clinically regarded as normal vision.

Optical coherence tomography

After dilation with one drop of phenylephrine 10% and cyclopentolate 1%, OCT and OCT angiography (OCT-A) were obtained using the Zeiss Cirrus 6000 (Carl Zeiss Meditec, Inc., California, USA). We obtained 512 x 128 mm images from the macula, 200 x 200 mm images from the optic disc, and 3 x 3 mm OCT-A images for both eyes.

Macular vascular density (MVD; mm/mm^2) in the superficial central area, macular vascular flow (MVF; %) in the superficial central area, foveal avascular zone (FAZ) area (mm^2), and FAZ circularity were

obtained from OCT-A images using the AngioPlex Metrix software. In addition, circumpapillary retinal nerve fibre layer (RNFL) thickness (µm) and macular inner plexiform ganglion cell layer (IPGCL) thickness (µm) were automatically quantified and obtained from OCT images (Figure 1).

For eyes in which blood vessels crossed the fovea, the FAZ area was set to zero (Figure 2). Mean central macular thickness (CMT; µm) in the fovea was obtained using the macular cube 512 x 128 protocol, where macular thickness data are presented in nine ETDRS areas. The central subfield (A1) measures 1 mm in diameter and was used to calculate CMT. Central retinal thickness (CRT; µm) was measured manually from the inner limiting membrane to the retinal pigment epithelium (Figure 1).

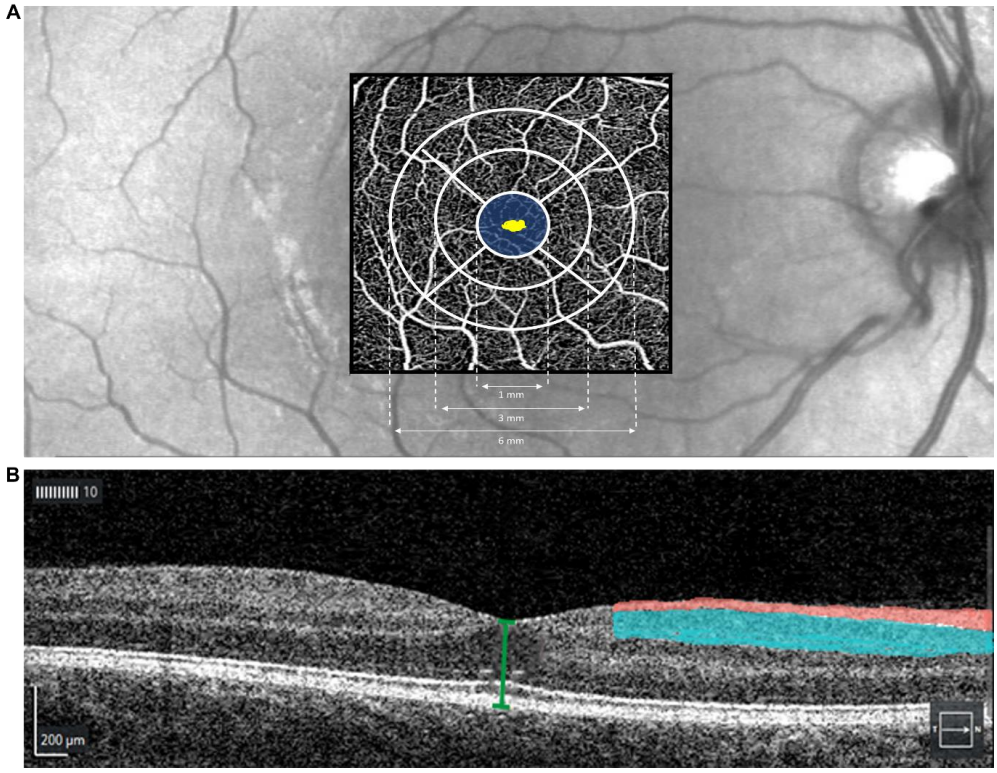

Figure 1. Illustration of the OCT parameters extracted for analysis

A: OCT-angio image with the foveal avascular zone (yellow area) and the central macular thickness measured in 1 diameter (blue area). B: OCT image of the retinal with the central retinal thickness (green line) measured from the inner limiting membrane to the retinal pigment epithelium, the retinal nerve fibre layer thickness (red area), and the inner plexiform ganglion cell layer (blue area).

Cut-off scores defined as the limit for abnormal values for the FAZ area (<0.3 mm/mm^2) and FAZ circularity (<0.7) were calculated based on reference values obtained from a PlexElite 9000 (Carl Zeiss Meditec, Inc., California, USA) OCT machine from a group of 19 children (6-8 years old at examination) born at term [18]. Cut-off scores for RNFL thickness (<83 µm) were based on reference values obtained on a spectral domain Cirrus (version 6.0.2.81, Carl Zeiss Meditec, Inc., California, USA) from a group of

57 children (6-15 years old at examination) born at term [19]. Cut-off scores for IPGCL thickness (<99 µm) were based on reference values obtained on a Cirrus HD-OCT (Carl Zeiss Meditec, Inc., California, USA) from a group of 114 children (mean age 8.1 years old at examination) born at term [20]. Cut-off scores for central macular thickness (>255 µm) were calculated based on reference values measured with spectral-domain Cirrus (version 6.0.2.81, Carl Zeiss Meditec, Inc., California, USA) from a group of 57 children (6-15 years old at examination) born at term [21].

Visual evoked potentials

Pattern-reversal visual evoked potentials (PR-VEPs) from the left and right eye were recorded on a Keypoint computer (Keypoint, Neurolite Software, Natus, Switzerland) using a View Sonic Graphics Series 670 fmb CRT monitor (17 inches). Electrodes were placed according to the 10-20 system on occipital, frontal, and parietal areas (Oz, Fz, and Pz) [22]. PR-VEPs were recorded from the occipital midline (Oz) and referred to the mid-frontal electrode (Fz) according to the ISCEV standards [23]. Impedance was < 5 kΩ, and a 1 Hz-1 kHz filter was used. The rejection level was set to ± 90 µV.

The subjects were seated in a relaxed position in a chair with neck support. One eye was covered with an eyepatch. The PR-VEP task consisted of high-contrast black-and-white checks with a red fixation point in the middle of the checkboard. The PR-VEP recording was performed in a dark room at 1 m from the CTR monitor. PR-VEPs were recorded in one eye at a time with 66' (12x16) (large checks) and 16' (48x64) (small checks) checks with 100 stimulations per run and a stimulations frequency of 1 Hz. A minimum of two runs for each eye and check size were conducted to assess the reproducibility of the responses. Two reproducible responses were required to be reliable for analysis.

An experienced specialist in clinical neurophysiology (AG) blinded for ROP status visually identified and placed cursors on N70, P100, and N145 peaks. The N70 and P100 latency (ms) and peak-to-peak N70-P100 amplitude (μV) were obtained for analysis. Latencies were measured from stimulus onset to the peak of the N70 and P100 waves, and amplitude was measured between the N70 and P100 peaks. Cut-off scores for PR-VEP potentials were calculated as ≥ 113.5 ms (+2 SD) and ≥ 119.3 ms (+3 SD) for the P100 latency of small checks, and ≥ 109.4 ms (+2 SD) and ≥ 114.8 ms (+3 SD) for P100 latency of large checks. The cut-off for the VEP amplitude was calculated as ≤ 3.9 μV (-2 SD) and ≤ 2.5 μV (-3 SD) for the small checks and ≤ 2.7 μV (-2 SD) and ≤ 1.5 (-3 SD) for the large checks. The cut-off scores are based on local reference values collected from an adult population (n= 93 and n= 96 for small and large checks, respectively) at the Department of Clinical Neurophysiology at St. Olavs Hospital, Trondheim, Norway.

Statistical analyses

All statistical analyses were conducted using the SPSS software 27.0 (IBM, New York, USA) and RStudio 4.2 (PBC, Boston, MA). Histograms and Q-Q plots were visually inspected to assess the normality of the data distributions. The FAZ area, FAZ circularity, and N70 latency showed non-normally distributions. However, due to the small sample size, we used parametric tests for all analyses to reduce the likelihood of Type II errors. All analyses were performed using data from the eye with the best corrected visual acuity (better eye). If the BCVA ETDRS letter score were equal in both eyes, the right eye was chosen for analyses.

Independent two-sample t-tests with p-values adjusted for unequal variances were performed to assess differences in scores on OCT parameters and PR-VEP variables between participants with and without ROP. Further, a partial Pearson's correlation analysis controlling for the effect of age was

performed to investigate the relationship between PR-VEP variables and ganglion cell layer thickness and the relationship between gestational age and study variables.

One participant had missing OCT data due to excessive movement during the examination, which caused unclear images. Two participants had missing VEP data points due to 50 Hz noise making it difficult to identify the VEP components. In addition, two participants had missing VEP and OCT data due to nystagmus, and P100 latency for one subject with large checks was excluded because the component could not reliably be identified.

Results

Ophthalmological examination

The standardized medical ocular history has been published earlier[16]. In brief, two participants had nystagmus (6%), five (14%) had been treated for amblyopia, and 15 (42%) used glasses or lenses. Mean intraocular pressure was 17.5 (SD= 3.6) mmHg for the better eye and 17.0 (SD= 3.5) for the worse eye (normal range of IOP 6-21 mmHg).

Twenty-six participants had no history of ROP, while 7 participants (19%) had a history of ROP. Of the children with ROP, two developed type I and were treated. One participant had type II that regressed, and four had mild ROP (stage 2). The mean BCVA ETDRS letter score for the better eye was 74.6 (SD= 18.8) for participants with ROP and 86.0 for participants without ROP (SD= 4.1), and almost half (49%) of the participants had an ETDRS letter score lower than 85 (equivalent to Snellen 20/20 and logMAR 0.0) in their better eye [16].

Retinal structure (OCT)

Most participants displayed an abnormal retinal structure (Table 1). 97% had a smaller FAZ area (mean= 0.05, SD= 0.08), and 93% had a poorer FAZ circularity than the cut-off (mean= 0.30, SD= 0.30). In addition, 77% displayed a thinner RNFL (mean= 91.8, SD= 10.1), and 60% had a thinner IPGCL than the cut-off (mean= 81.8, *SD*= 6.7). The central macular thickness was thicker than the cut-off in all participants (mean= 291.4 µm, SD= 19.3). Central retinal thickness was 274.2 µm (SD= 26), mean macular vascular density was 17.2 mm/mm^2 (SD= 3.0), and mean macular vascular flow was 32% (SD= 4.8).

Table 1. OCT and PR-VEP variables for the better eye in participants presented by gestational age

Gestational age (weeks)				
	≤ 24	**25**	**26**	**27**
	(n= 6)	(n= 5)	(n= 7)	(n= 15)
OCT parameters				
FAZ (mm^2)	.03 ± .04 [a]	.03 ± .04 [a]	.01 ± .02 [a]	.07 ± .11 [a]
<0.3 mm^2 (n (%))	5 (100)	4 (100)	6 (100)	13 (93)
FAZ circularity	.20 ± .30 [a]	.30 ± .30 [a]	.20 ± .30 [a]	.30 ± .30 [a]
<0.7 (n (%))	5 (100)	4 (100)	6 (100)	12 (86)
MVD (mm/mm^2)	18.0 ± 1.9 [a]	18.3 ± 3.3	17.8 ± 1.3 [a]	16.2 ± 3.7 [a]
MVF (%)	33.0 ± 3.4 [a]	31.8 ± 4.0	32.5 ± 1.8 [a]	31.0 ± 6.3 [a]
CMT (µm)	299.2 ± 27.4	285.8 ± 11.0	297.0 ± 7.5	287.6 ± 21.4
>255 µm (n (%))	6 (100)	5 (100)	7 (100)	15 (100)
CRT (µm)	283.3 ± 25.8	274 ± 15.2	288.6 ± 21.2	264 ± 28.2
RNFL thickness (µm)	88.0 ± 10.8 [a]	92.6 ± 10.1	87.2 ± 12.2 [a]	94.9 ± 8.7 [a]
<99 µm (n (%))	4 (80)	4 (80)	5 (83)	10 (71)
IPGCL thickness (µm)	80.4 ± 4.0 [a]	81.8 ± 10.1	75.7 ± 5.7 [a]	84.9 ± 4.7 [a]
<83 µm (n (%))	4 (80)	3 (60)	6 (100)	5 (36)
PR-VEP variables				
(66') N70 latency (ms)	68.0 ± 3.3 [a]	66.0 ± 2.3 [a]	72.3 ± 13.8	65.7 ± 5.6
(66') P100 latency (ms)	107.4 ± 9.3 [a]	103.9 ± 8.6 [a]	110.0 ± 19.3	101.0 ± 5.1 [a]
≥ 109.4 ms (+2 SD) (n (%))	1 (20)	1 (25)	3 (43)	1 (7)
≥ 114.8 ms (+3 SD) (n (%))	1 (20)	1 (25)	2 (29)	0
(66') N70-P100 µV	19.8 ± 8.1 [a]	17.5 ± 9.2 [a]	15.8 ± 7.8	19.5 ± 10.3 [a]
(16') N70 latency (ms)	75.8 ± 2.0 [a]	76.2 ± 3.9 [a]	81.4 ± 10.3	74.3 ± 6.2 [a]
(16') P100 latency (ms)	120.2 ± 13.2 [a]	115.5 ± 6.2 [a]	109.3 ± 13.6	109.8 ± 8.9 [b]

≥ 113.5 ms (+2 SD) (n (%))	3 (60)	3 (75)	2 (29)	5 (36)
≥ 119.3 ms (+3 SD) (n (%))	2 (40)	1 (25)	1 (14)	2 (14)
(16') N70-P100 µV	18.7 ± 11.3 [a]	13.7 ± 9.3 [a]	13.9 ± 7.2	18.2 ± 8.7 [a]

Data are presented as mean ± SD with n (%) of the participants below/above cut-off scores (described in the methods section), presented by gestational age at birth. BCVA= best corrected visual acuity; CMT= central macular thickness; CRT= central retinal thickness; FAZ= foveal avascular zone; IPGCL= inner plexiform layer; mm^2= square millimetre; ms= milliseconds; MVD= macular vascular density; MVF= macular vascular flow; RNFL= retinal nerve fibre layer; µV= amplitude; µm= micrometre; 66'= large checks; 16'= small checks.

[a] Data are missing for one participant, [b] Data are missing for two participants.

Participants without ROP had a thinner central retina than those with ROP (p=.032). In addition, participants with ROP displayed thinner RNFL (p=.006) and IPGCL thickness (p=.014), a higher macular vascular density (p=.006), and macular vascular flow (p=.004) compared to participants without ROP (Table 2). Furthermore, none of the participants with ROP had a measurable FAZ area, while this was the case for 5 of 29 participants (17%) in the no-ROP group (Figure 2).

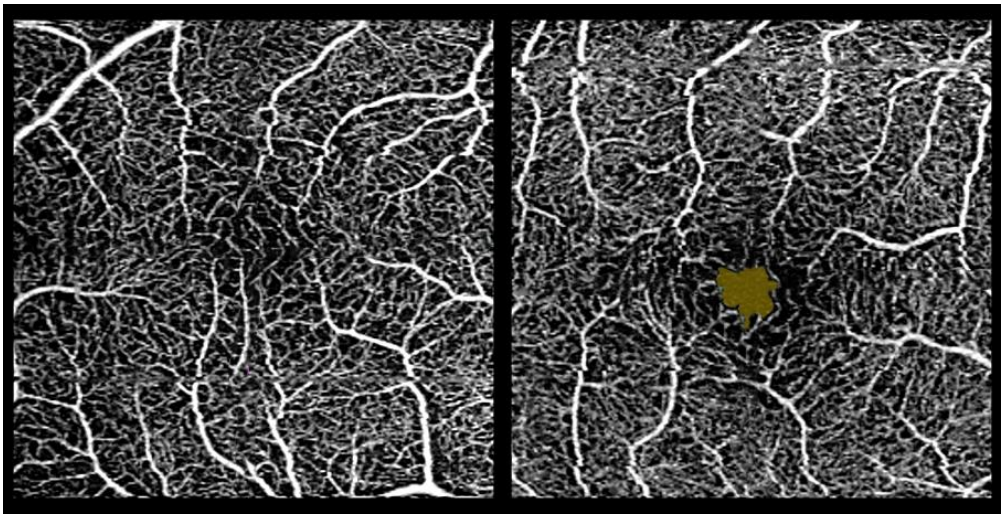

Figure 2. OCT images illustrating the FAZ area (yellow area) of a participant with (right) and without (left) ROP.

FAZ= foveal avascular zone; OCT= optical coherence tomography; ROP= retinopathy of prematurity. The FAZ area is not visible in the participants with ROP due to blood vessels going through the fovea.

Table 2. OCT and PR-VEP variables for the better eye between participants with and without ROP.

	ROP (n= 7)	No-ROP (n= 33)		
	Mean ± SD	**Mean ± SD**	**p-value**	**95% CI**
OCT parameters				
FAZ (mm^2) [1]	.00 ± .00 [6]	.06 ± .09	.003	(.02, .09)
FAZ circularity [1]	.00 ± .00 [6]	.03 ± .03	.000	(.03, .04)
MVD (mm/mm^2) [2]	19.8 ± 1.6	16.7 ± 3.0	.006	(-5.1, -1.1)
MVF (%) [2]	34.6 ± 1.1	31.1 ± 5.0	.004	(-5.7, -1.2)
CMT (µm) [3]	297.0 ± 23.6	290 ± 18.3	.515	(-5.1, 1.1)
CRT (µm) [3]	295.7 ± 23.6	268.5 ± 23.3	.032	(-51.6, -2.9)
RNFL thickness (µm) [2]	80.4 ± 7.0	94.1 ± 9.0	.006	(5.2, 22.2)
IPGCL thickness (µm) [2]	74.6 ± 5.1	83.2 ± 6.0	.014	(2.4, 14.9)
PR-VEP variables				
(66') N70 latency (ms) [4]	75.3 ± 15.6	66.1 ± 4.6	.258	(-28.6, 10.1)
(66') P100 latency (ms) [2]	117.1 ± 19.7	102.0 ± 6.6	.163	(-39.4, 9.2)
(66') N70-P100 µV [4]	16.6 ± 9.7	18.8 ± 9.0	.645	(9.5, 14.0)
(16') N70 latency (ms) [2]	82.7 ± 12.3	75.2 ± 5.0	.248	(-22.7, 7.7)
(16') P100 latency (ms) [5]	123.0 ± 16.6	110.0 ± 8.3	.156	(-33.3, 7.3)
(16') N70-P100 µV [2]	13.5 ± 8.0	17.3 ± 8.9	.377	(-5.9, 13.6)

Mean ± SD and p-value with 95% CI from independent two-sample t-tests corrected for unequal variances for OCT and PR-VEP variables with ROP status as the grouping variable. BCVA= best corrected visual acuity; CMT= central macular thickness; CRT= central retinal thickness; FAZ= foveal avascular zone; IPGCL= inner plexiform layer; mm^2= square millimetre; ms= milliseconds; MVD= macular vascular density; MVF= macular vascular flow; RNFL= retinal nerve fibre layer; uV= amplitude; µm= micrometre; 66'= large checks; 16'= small checks.

* [1] ROP (n= 4), No-ROP (n= 25); [2] ROP (n= 5), No-ROP (n= 25); [3] ROP (n= 7), No-ROP (n= 26); [4] ROP (n= 5), No-ROP (n= 26); [5] ROP (n= 5), No-ROP (n= 24).

[6] The foveal avascular zone was not measurable in participants with ROP.

Visual pathway function (PR-VEPs)

were born before 26 gestational weeks. Sixlarge checks66') the reference values of +2 SD cut-off (Table 2). Also, one participant born at 26 weeks GA displayed a weaker N70-P100 amplitude than the reference population. Mean P100 latencies (small checks/large checks) was 123/117.1 ms for those with ROP compared with 110/102 ms for those without ROP (Table 1).

Associations between ganglion cell layer thickness and PR-VEP variables

Both IPGCL and RNFL showed a significant negative correlation with P100 latency (large checks; 66') (IPGCL: r=-.53, p=.005; RNFL: r=-.64, p<.001). Figure 3 presents the P100 latency (66') data distribution and IPGCL and RNFL thickness.

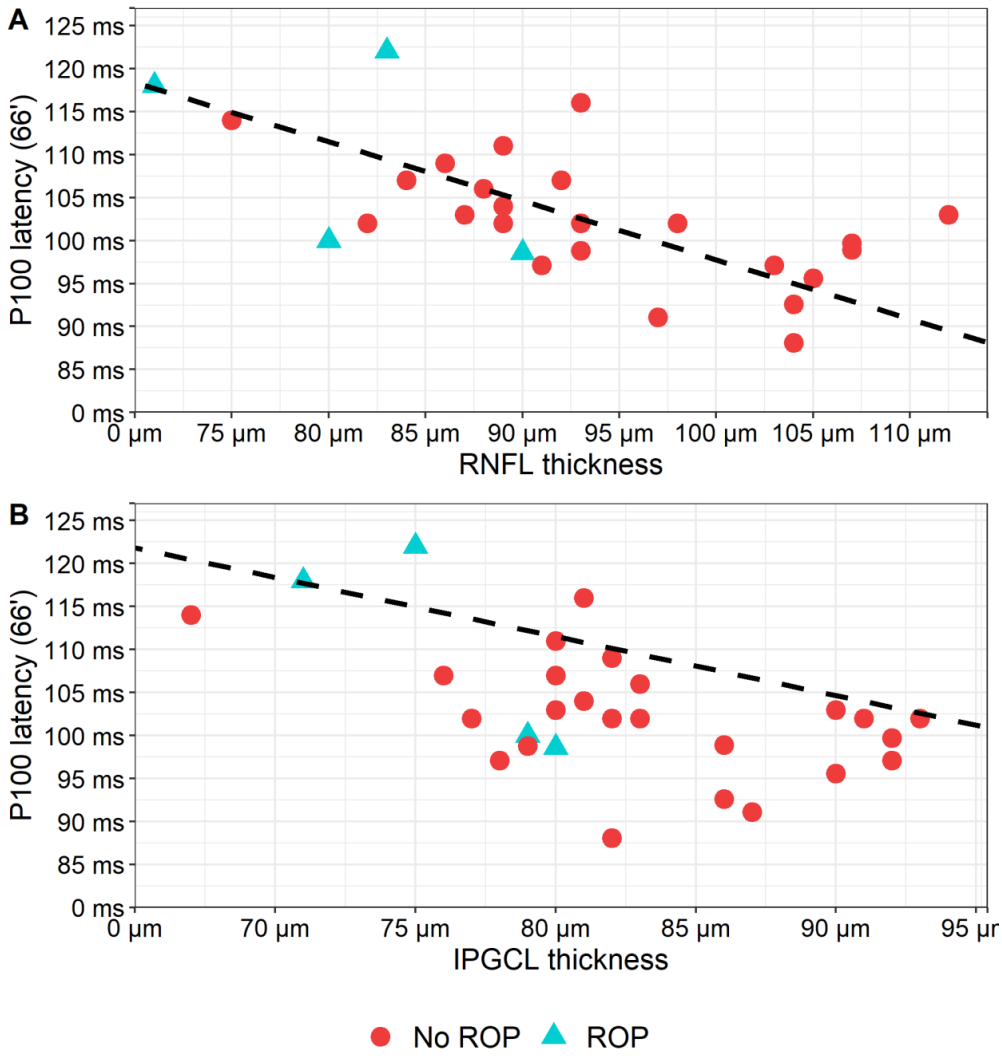

Figure 3. Association between P100 latency and ganglion cell layers thickness in participants with and without ROP

IPGCL= inner plexiform ganglion cell layer; ms= milliseconds; r= Pearson's correlation coefficient; RNFL= retinal nerve fibre layer; ROP= retinopathy of prematurity. The association between RNFL thickness (A), IPGCL thickness (B) (x-axis) and P100 latency (y-axis) with Pearson's correlation coefficient and Deming regression line for two dependent variables measured with error (dashed line). Blue triangles represent participants with ROP (n= 4), while red circles represent participants without ROP (n= 24).

Discussion

In a geographically defined population of school-aged children born extremely preterm, thinner neuroretinal layers were associated with delayed P100 latencies. Also, several participants displayed delayed P100 latencies, and all children born extremely preterm had abnormal central macula thickness compared to reference populations. In addition, individuals with ROP showed signs of immature foveal vasculature and neuroretinal layers.

To the best of our knowledge, the association between neuroretinal layers and P100 latencies in large checks in a cohort of school-aged children born extremely preterm without identifiable cerebral abnormalities has not been reported earlier. However, a similar association has been observed in patients with multiple sclerosis and optic neuritis [24, 25]. The two major parallel visual pathways, the magnocellular and parvocellular pathways, begin in the retina and project to the primary visual cortex via the lateral geniculate nucleus. The parvocellular pathway responds to high spatial resolution (small checks), low luminance contrast sensitivity, and low temporal resolution. In contrast, the magnocellular pathway responds to low spatial resolution (large checks), high luminance contrast sensitivity, and high temporal resolution [26-28]. The association between delayed P100 latencies in large checks with thinner ganglion cell layers in this study may indicate an abnormal development of the magnocellular pathway, activated in low spatial frequency stimulus conditions. Moreover, several participants had abnormal P100 latencies with small checks (16'), indicating a delayed development of the parvocellular pathways in school-aged born extremely preterm.

While 39% of our participants had delayed P100 latencies compared to norms in the small checks, only 18% had delayed P100 latencies in the large checks. A previous study found that children (with a mean age of 5.8 years) born late preterm (GA week 32-37) exhibited no significant differences in P100

latency compared to children born at term [29], while another study found that children (4-6 years of age) born with GA between 28 and 32 weeks had significantly delayed P100 latencies compared to controls [13]. These conflicting results may be due to the difference in gestational age. In this study, the delayed P100 latencies in higher spatial frequencies (smaller checks) are consistent with our earlier findings that approximately 60% of participants from the same study sample had lower than normal contrast sensitivity abilities, especially in higher spatial frequencies [16] which might indicate a delayed development of the parvocellular pathway. The parvocellular pathway's high-resolution capacity in the fovea results from the close synaptic connectivity between cones and projecting bipolar and ganglion cells [30]. Cone photoreceptor anomalies caused by abnormal retinal development could explain the delayed latencies from small checks conveyed by the parvocellular pathway. Indeed, decreased cone-mediated pupillary response to photopic stimuli has been shown in children born preterm with macular developmental arrest characterized by a shallowed pit with significantly reduced outer nuclear layer to inner retinal layer ratio in the fovea [31, 32]. Cone anomalies in the fovea due to an immature retina at birth could cause poor synaptic connections with projecting ganglion cells, leading to slower VEPs reaching the visual cortex for processing.

Our findings of more prominent foveal anomalies in participants with ROP align well with earlier findings of a decreased FAZ area and circularity in 6-13-year-old children born preterm with ROP [11, 14, 18]. The FAZ area mainly comprises elongated photoreceptors, and its lack of vascularity facilitates sharp vision in the foveola. When the development of the retinal vasculature is interrupted by, for instance, preterm birth, it can affect several aspects of vision. A small FAZ area with capillaries and astrocytes close to the fovea may disrupt the inner retinal layers' centrifugal migration during development, leading to abnormal visual development [33]. In our study, approximately half of the participants without ROP had no measurable FAZ area, while this was true for all participants with ROP, suggesting that factors associated with preterm birth are also risk factors for abnormal FAZ

development in general but more prominent in those born preterm with ROP. The increased central macular thickness observed in this study cohort corroborates previous findings of increased central macular thickness in preterm children compared to children born to term with similar ages [7, 14, 34]. In this study, the ROP status did not have a large impact on central macular thickness. However, the small number of participants with ROP means that the results should be interpreted cautiously.

Strengths and limitations

A strength of this study is the geographically defined population-based research design, inviting all children born extremely preterm within a geographically defined area during a specific time period. Moreover, the similarity of neonatal background data from participants and non-participants suggests that our findings are representative of the larger population of children born extremely preterm in Norway. A limitation of this study is its small sample size, especially the low number of participants with ROP. Although some differences between those with and without ROP did not achieve formal statistical significance, probably at least in part due to insufficient statistical power, the observed differences in retinal maturity and PR-VEP latencies were large and could still be of clinical significance. The comparisons between individuals with and without ROP should therefore be investigated in larger populations. We applied cut-offs based on normative data obtained locally as recommended by the International Federation of Clinical Neurophysiology [35] and the International Society for Clinical Neurophysiology of Vision [23]. The reference VEP data were from an adult and not a paediatric population. Although P100 latency attains adult-like values from 5 years of age [36], P100 latency shows some decline from 5 to 19 years of age [37]. This could lead to slightly overestimating the number of abnormal P100 values.

Conclusion

In a geographically defined population of school-aged children born extremely preterm without preterm brain injury, ganglion cell layer thickness and retinal nerve fibre layer thickness were negatively correlated with P100 latencies, indicating a relationship between the neuroretina and visual pathway function among children born extremely preterm. Furthermore, most participants displayed an immature structure of the neuroretina and vasculature. ROP status was associated with differences in OCT(-A) parameters but not visual evoked potentials. Our results suggest that OCT(-A) and PR-VEP findings might be markers for VOP and should be studied in larger populations of children born extremely preterm to determine their clinical usefulness for the identification of visual pathway abnormalities in preterm children.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (2020/100434). Written informed consent was obtained from both parents of the child before enrolment in the study.

Consent for publication (Not applicable)

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

S.H.I contributed with study design, performed data cleaning, statistical analysis, and wrote the main manuscript text. K.M performed the data collection of retinal layers. A.G performed the data collection of visual evoked potentials. P.M.O contributed with the analysis and manuscript text. O.D and D.A contributed with revision of the manuscript. T.S.M contributed with study design, revision, and writing of the manuscript. All authors reviewed and approved the manuscript before it was submitted.

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List of abbreviations

BCVA=	best corrected visual acuity
CMT=	central macular thickness
CRT=	central retinal thickness
ETDRS=	Early Treatment Diabetic Retinopathy Study
FAZ=	foveal avascular zone
GA=	gestational age
IPGCL=	inner plexiform ganglion cell layer
logMar=	logarithm of the minimum angle of resolution
MRI=	magnetic resonance imaging
MVD=	macular vascular density
MVF=	macular vascular flow
NNN=	Norwegian Neonatal Network
OCT=	optical coherence tomography
OCT-A=	optical coherence tomography angiography
PR-VEPs=	pattern-reversed visual evoked potentials
RNFL=	retinal nerve fibre layer
ROP=	retinopathy of prematurity
SD=	standard deviation
VEPs=	visual evoked potentials
VLBW=	very low birth weight
VOP=	Visuopathy of Prematurity

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Paper III

Visual outcomes and their association with grey and white matter microstructure in adults born preterm with very low birth weight

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Abbreviations: AD= axial diffusivity; BCVA= best corrected visual acuity; CC= corpus callosum; cpd= cycles per degree; CS= contrast sensitivity; DTI= diffusion tensor imaging; ETDRS= Early Treatment of Diabetic Retinopathy Study; FA= fractional anisotropy; GM= grey matter; IFOFs= inferior-fronto occipital fasciculus; IVH= intraventricular haemorrhage; LGNs= lateral geniculate nucleus; MD= mean diffusivity; MRI= magnetic resonance imaging; NSI= neurosensory impairments; OCT= optical coherence tomography; ORs= optic radiations; PR-VEPs= pattern-reversed visual evoked potentials; RD= radial diffusivity; RNFL= retinal nerve fibre layer; ROI= region of interest; ROP= retinopathy of prematurity; VLBW= very low birth weight; VOP= visuopathy of prematurity; WM= white matter.

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