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ORIGINAL ARTICLE

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]

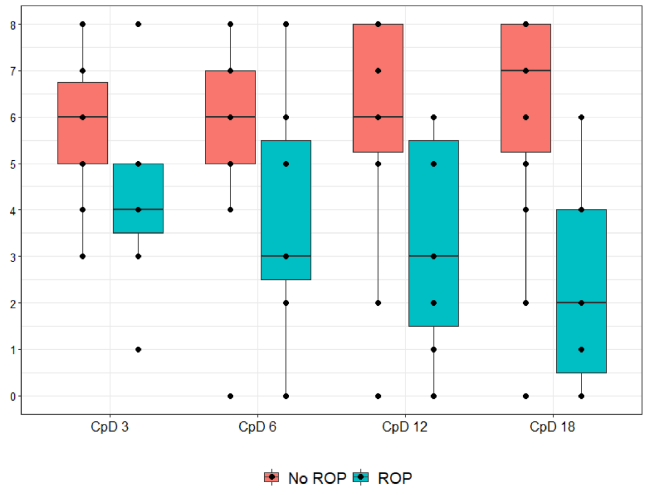

FIGURE 1 Boxplot with median and range of contrast sensitivity thresholds in extremely preterm school-aged children born in Central Norway between 2006 and 2011 with ROP (*n* = 7) and no ROP (*n* = 26) in the neonatal period. CpD, cycles per degree; ROP, retinopathy of prematurity.

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

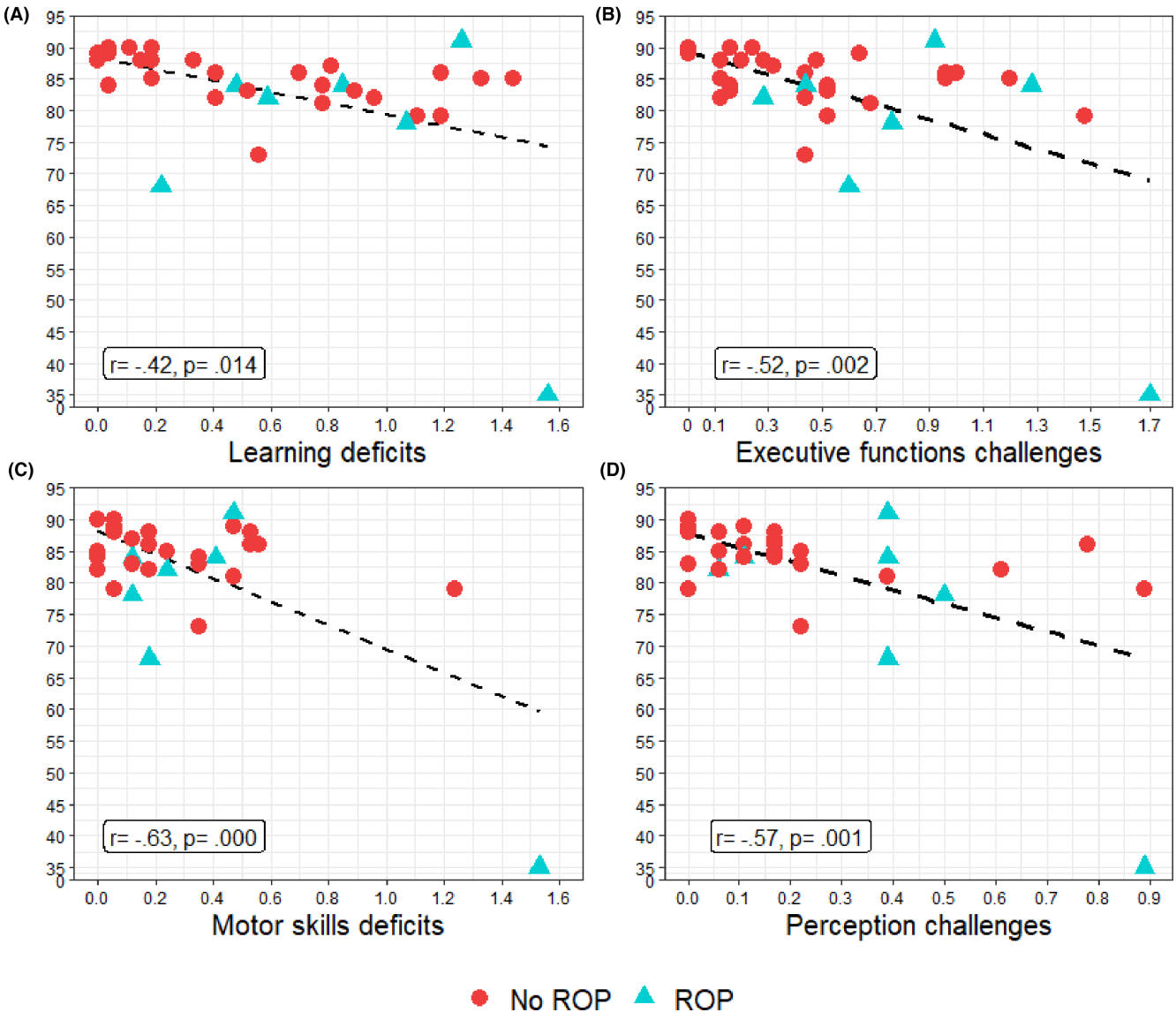

FIGURE 2 Scatterplots of correlations between best-corrected visual acuity (BCVA) and parent-reported challenges in extremely preterm born school-aged children born in Central Norway between 2006 and 2011 with ROP ($n = 7$) and without ROP ($n = 26$) in the neonatal period. r, Pearson's correlation coefficient; 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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