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ORIGINAL ARTICLE

Colour perception develops throughout childhood with increased risk of deficiencies in children born prematurely

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Abstract

Aim: To quantify the impact of prematurity on chromatic discrimination throughout childhood, from 2 to 15 years of age.

Methods: We recruited two cohorts of children, as part of the TrackAI Project, an international project with seven different study sites: a control group of full-term children with normal visual development and a group of children born prematurely. All children underwent a complete ophthalmological exam and an assessment of colour discrimination along the three colour axes: deutan, protan and trytan using a DIVE device with eye tracking technology.

Results: We enrolled a total of 1872 children (928 females and 944 males) with a mean age of 6.64 years. Out of them, 374 were children born prematurely and 1498 were full-term controls. Using data from all the children born at term, reference normative curves were plotted for colour discrimination in every colour axis. Pre-term children presented worse colour discrimination than full-term in the three colour axes ($p < 0.001$). Even after removing from the comparison, all pre-term children with any visual disorder colour discrimination outcomes remained significantly worse than those from full-term children.

Conclusion: While colour perception develops throughout the first years of life, children born pre-term face an increased risk for colour vision deficiencies.

KEYWORDS
childhood, colour vision, development, eye tracking, prematurity

Abbreviation: ROP, retinopathy of prematurity

1 | INTRODUCTION

Unlike other sensory systems, human vision seems to be very immature at birth and visual abilities develop largely during the first months and years of life.[1] Visual development is widely affected by early visual experiences and coexistent perinatal disorders, from exposure to toxic substances to maternal diseases during pregnancy or neonatal pathologies.[2,3]

Pre-term birth has long-term consequences on neurological, cognitive, sensory and behavioural development.[4] Prematurity may interfere with the development of the retina and the visual pathway at different levels, but it also leads to an atypical visual experience by exposing the neonates to early visual stimuli. Therefore, prematurity and all coexisting adverse events related to preterm births are widely known risk factors for many visual disorders rather than retinopathy of prematurity (ROP). Children born pre-term face higher rates of strabismus, refractive errors and reduced visual acuity than term-born peers, even in the absence of ROP.[5,6]

Colour vision deficits, especially tritan subtypes, have been reported in children born prematurely.[7] Exposure to constant high-intensity lighting in neonatal intensive care units was initially proposed as a potential cause.[8] It was subsequently linked to many aetiologies, such as treatments for ROP or retinopathy itself, photoreceptor damage due to prematurity, optic nerve atrophy or even congenital glaucoma.[9]

Colour vision deficiency disadvantages children in performing certain tasks, which may interfere with educational and daily life activities.[10] Colour is used as a resource in schools in most subjects, such as science, art or even phonetics.[11] Awareness of this limitation is crucial for children and teachers to avoid unknown individual barriers to certain learning points. However, colour vision is not routinely assessed, either as part of the healthy child exams throughout childhood or in schools. Therefore, colour vision deficiencies remain mostly undetected in children.

This study aimed to describe the normal development of colour vision throughout childhood and to quantify the impact of prematurity on it. For this purpose, we used an automatic digital colour test assisted by eye-tracking technology, which can be accurately performed by children from 2 years of age.

Key Notes

- There is still little knowledge about the development of colour perception throughout childhood and the impact of prematurity on it.
- Pre-term children face an increased risk for colour vision deficiencies, even in the absence of other coexisting visual disorders.
- Colour vision deficiencies in pre-term children are not fully explained by a higher rate of visual disorders.

2 | MATERIALS AND METHODS

2.1 | Participants

This study regarding colour perception in children was part of the TrackAI Project, whose protocol has already been described in detail.[12] This international project was performed between April 2019 and July 2022 in seven study sites located in Spain, China, Vietnam, Russia and Mexico, with a Coordinating Unit overseeing the process. Its main goal was to develop and validate a screening system to identify children with visual disorders. As secondary goals, we aimed to assess the development of several visual functions throughout childhood and to evaluate the impact of certain perinatal events on visual development. As part of the study, visual parameters were collected from a large population of children, both with full ophthalmological exams and with an automated screening device, DIVE AI Vision Screening (DIVE Medical SL, Spain). Colour perception was among the visual functions assessed in all children, as were oculomotor control, visual acuity and contrast sensitivity.

Child candidates were all the patients with a clinical appointment during the time of recruitment in the Paediatric Ophthalmology Departments of any of the participating tertiary hospitals.

Among all the participants recruited for the TrackAI Project, two groups of children were included in the study presented here. In order to first define the reference colour perception thresholds throughout childhood, we selected a control group of full-term children aged between 2 and 15 years of age, born at term with at least 37 weeks of gestational age, with no known ocular disease except low ametropia, and no neurological or systemic disorder. All participants with anisometropia, defined by a difference of at least one diopter of spherical equivalent between both eyes, or moderate or severe refractive errors based on cycloplegic refraction were excluded from the study: myopia higher than 3.5 diopters for children younger than 30 months, 3.0 diopters between 31 and 48 months and 2.0 diopters over 48 months; hyperopia higher than 4.5 diopters for children younger than 30 months, 4.0 diopters between 31 and 48 months and 3.5 diopters over 48 months and astigmatism higher than 2.0 diopters for children younger than 48 months and 1.5 diopters over 48 months.

A second study group included children aged between 2 and 15 years who had been born prematurely, <37 weeks of gestational age at birth. Pre-term children were divided into two groups depending on their gestational age: late pre-term, when the gestational age was at least 32 weeks, and early pre-term, when the gestational age was lower than 32 weeks.

Children with known or unknown congenital colour vision deficiency were not excluded from the study to ensure the external validity of our outcomes in both groups.

The study protocol was approved by the local ethics committees of every centre, and written informed consent was obtained from the parents or guardians of each child. Children older than 12 years

provided verbal assent. All procedures adhered to the tenets of the Declaration of Helsinki.

2.2 | Examination

All children underwent an ophthalmological assessment including best-corrected visual acuity, ocular alignment and motility, refraction under cycloplegia and funduscopy exam. Monocular and binocular visual acuity was assessed in cooperative participants using optotypes adapted to each participant's age, based on symbols or letters. Grating acuity was obtained using the preferential looking test, LEA paddles, for infants not cooperating with optotypes assessments.

We assessed colour perception tests using a DIVE device assisted with eye-tracking technology to determine the detection of the target. It was made up of a Huawei Matebook E tablet (Huawei Co., China), with a 12-inch tactile screen corresponding from 65 cm to a visual angle of 22.04 deg horizontally and 14.82 deg vertically, when viewed from 65 cm, with a resolution of 2160 × 1440 pixels, as well as an integrated X3-120 Tobii eye tracker sampling at 120 Hz. The manufacturer specifications for binocular accuracy and precision of the eye tracker were around 0.6° and 0.25°, respectively, and 0.8° and 0.34° for the monocular case. The screen was regularly calibrated with a Datacolor SpyderX calibrator (Datacolor Co., Switzerland) with gamma 2.20, white dot 6500 K and 120 cd/m^2. A 9-point calibration procedure of the eye tracker was always performed prior to the visual assessment. Each individual point was repeated if necessary, until the eye tracker reported a reliable calibration. Moreover, a subsequent validation test showing nine stimuli uniformly distributed across the screen allowed us to quantify the eye tracker's calibration quality for each subject. All the visual assessments with the DIVE Medical device were performed by technicians, who had been previously instructed by one of the technicians from the coordinating centre following the user manual designed for the study. Clinical protocol, patient selection and equipment setup were standardised across all the study sites.

Colour perception was assessed binocularly in all the cases, as part of the vision screening test.

The digital colour test presented visual stimuli composed of an isochromatic background and a figure—triangle, square, circle or star—that appeared in one of the four quadrants of the screen (Figure 1), both decomposed in many circles with different sizes and luminance following the Stilling and Chibret principles.[13,14] The test quantified colour perception thresholds along the three axes using an adaptive method based on the patient responses. The eye tracking system in the device detected if the patient identified the figure following the preferential-looking paradigm. Between each stimulus, central fixation was encouraged by displaying a grey background with a rotating star so that potential post-image effects were avoided. During the examination, random control stimuli were displayed to ensure patients' good collaboration. The colour perception threshold for each confusion line was reported using Delta E units (dE). Delta E units (dE) quantify the perceptual distance between two colour hues, corresponding to the figure and the background. It has been directly related to human colour perception capabilities.

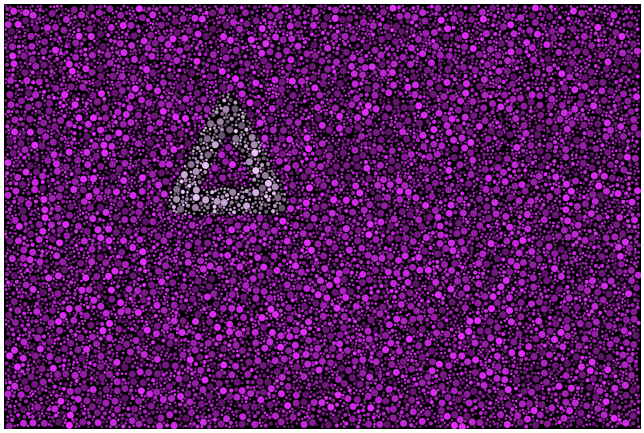

FIGURE 1 Image from the DIVE Colour vision exam.

2.3 | Statistical analysis

All data were analysed using SPSS 25.0 statistical software (SPSS Inc.) and R software (R Core Team). Demographic characteristics and colour vision outcomes were reported by the mean, standard deviation and ranges.

We compared visual outcomes and, more specifically, colour vision parameters between full-term and pre-term children, and between preterm children with and without previous history of ROP, by means of Student's *t* test, after confirming equal variances for all the parameters using the Levene test. Multivariate analyses were performed including gender, age and gestational age at birth as independent variables, and colour discrimination parameters in protan, deutan and tritan axes as dependent variables.

Normative growth curves were created using the Generalised Additive Models for Location, Scale and Shape package in R.[15] The Akaike Information Criteria[16] and *Q* test were used to evaluate goodness of fit. The models for all the variables included parameters that account for skewness and kurtosis in the distribution of the values.

3 | RESULTS

We enrolled a total of 374 children born prematurely and 1498 full-term controls. Gestational age in the preterm group ranged from 24 to 36 weeks, and their birthweights were between 480 g and 4100 g. Out of the 374 preterm children, 28 had presented ROP which required any treatment: 27 received laser photocoagulation of the non-vascularised retina and only one received intravitreal injections of Bevacizumab. All of them were successfully treated with full regression of the retinopathy.

Table 1 presents demographic and visual characteristics of the children from both study groups, born preterm and full-term.

According to the inclusion criteria, no participants in the control group had any visual disorder, while 113 (30.2%) pre-term children showed significant disorders of refraction, 67 (17.9%) strabismus, 27 (7.2%) amblyopia and 25 (6.7%) cerebral visual impairment.

Reference normative curves were plotted as a function of age for colour discrimination in every colour axis, deutan, protan and tritan (Figure 2), using data from the 1498 children born at term with normal visual development.

In a multivariate analysis considering age and gender as independent variables, age was included in all cases as a predictor for colour discrimination in protan, deutan and tritan axes. Gender was only included for the deutan axis (beta coefficient = 2.19, $p = 0.001$), with females presenting higher colour discrimination.

Regarding the impact of prematurity on colour vision, pre-term children presented worse colour discrimination than full-term in the three colour axes, as shown in Table 2.

To avoid the source of bias due to age differences between the two study groups, we performed a multivariate analysis including chromatic discrimination on each axis as dependent variables and gestational age at birth, age and gender as predictors. As a result, gestational age remained related to colour discrimination on the three axes ($p < 0.01$ for gestational age at birth and age at the study).

Colour vision impairments could be related to the higher rate of visual disorders in pre-term children. However, even after removing from the comparison, all pre-term children with any visual disorder—accounting for 149 children out of the 374 preterm children- colour discrimination outcomes remained significantly worse than those of full-term children. However, no differences were observed between pre-term children with and without ROP ($p = 0.641$ for protan, $p = 0.908$ for deutan and $p = 0.475$ for tritan axes). Figure 3 depicts the colour vision outcomes in full-term, late pre-term and early pre-term born children. Although the comparisons among the three groups were statistically significant for the three axes ($p < 0.001$), no differences were found between early and late pre-term children.

4 | DISCUSSION

In this study, we report normative outcomes of colour perception throughout childhood in the three colour axes and confirm the impact of prematurity on this visual function.

Colour perception is based on the brain processing the signals coming from photoreceptor cells located in the human retina: rods and cones. Colour vision is mediated by three types of cones with overlapping spectral peak responsiveness: long-wavelength sensitive cones (L, λ_{max} about 560–580 nm), middle-wavelength sensitive cones (M, λ_{max} about 530–540 nm) and short-wavelength sensitive cones (S, λ_{max} around 440 nm). Proper colour vision requires not only the functioning of the three classes of retinal cones giving rise to trichromatic encoding but also postreceptor neural circuitry. At the neural level, anatomical and physiological studies have located the cerebral processing of colour information in the ventral occipital lobe, with three main areas identified as stimulated by colour: V1, V4 and V4α.[17]

Colour vision in neonates and young children may be constrained by immaturities both in optical-photoreceptoral and neural levels. Optical factors include pupil size, lens transmittance and macular cytoarchitecture. The retina is known to be immature at birth. Postnatal development of the retina has been deeply studied both in histologic samples and in vivo using hand-held Optical coherence tomography.[18] Although most of the structural changes take place during the first year of life, subtle development persists beyond 4 years.[19] From

TABLE 1 Comparison of demographic and visual characteristics between the study groups, preterm and full-term children, with the statistical significance of the differences (p_1 corresponds to the comparison between full-term and preterm children while p_2 to the comparisons between preterm children without and with a previous ROP).

		Preterm children			
	Full-term children	Non ROP	ROP		
N	1498	346	28	p_1	p_2
Age at study (years)	6.84 (2.79)	5.78 (3.09)	6.64 (3.69)	<0.001	0.242
Gender (males: females)	741:757	189:157	14:14	0.046	0.224
Gestational age at birth (weeks)	39.50 (1.01)	31.44 (3.46)	25.96 (1.90)	<0.001	<0.001
Birthweight (g)	3335.75 (414.55)	1646.52 (684.67)	826.64 (187.43)	<0.001	<0.001
Binocular grating acuity (cpd)	7.48 (3.86)	6.15 (3.94)	5.12 (3.18)	0.216	0.430
Right eye visual acuity (LogMAR)	0.05 (0.11)	0.13 (0.20)	0.31 (0.35)	<0.001	0.037
Left eye visual acuity (LogMAR)	0.05 (0.11)	0.14 (0.22)	0.31 (0.32)	<0.001	0.031
Right eye spherical equivalent defect (diopters)	0.75 (1.02)	1.65 (2.06)	−0.57 (4.25)	<0.001	0.037
Right eye cylindrical defect (diopters)	0.63 (0.38)	1.09 (0.88)	1.52 (1.16)	<0.001	<0.001
Left eye spherical equivalent defect (diopters)	0.78 (1.03)	1.66 (2.36)	−0.01 (3.32)	<0.001	0.022
Left eye cylindrical defect (diopters)	0.63 (0.37)	1.09 (0.87)	1.71 (1.29)	<0.001	0.020

Note: Data are presented as mean (SD), except for gender which reports the rate males: females.

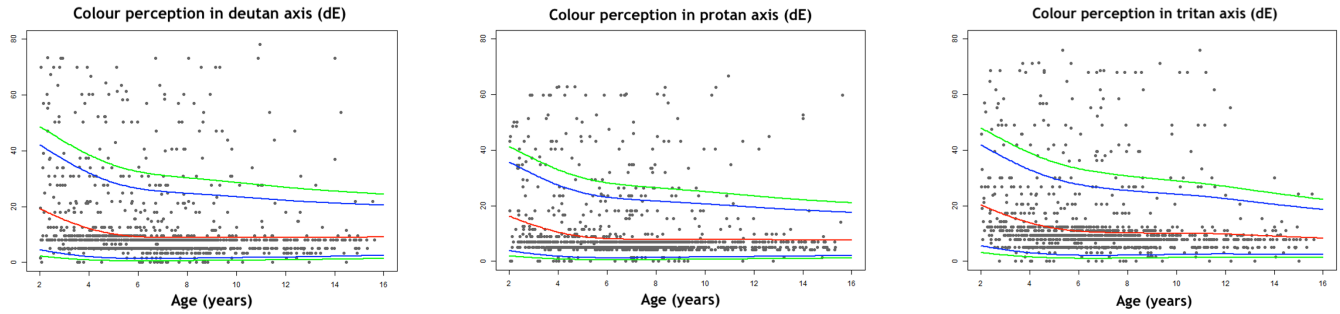

FIGURE 2 Scatterplots of colour perception outcomes versus age for deutan, protan and tritan axes, together with reference normative curves. The grey dots are the observed values, while the curves indicate age-specific fitted centiles: 5th and 95th (green), 10th and 90th (blue), and 50th centile (red).

TABLE 2 Comparison of colour discrimination outcomes in protan, deutan and tritan axes in preterm and born-term children, with the statistical significance of the differences.

	Full-term children	Pre-term children	
n	1498	374	*p*
Colour discrimination in protan axis (dE)	9.58 (11.15)	12.40 (12.87)	0.003
Colour discrimination in deutan axis (dE)	11.12 (12.81)	17.58 (18.38)	<0.001
Colour discrimination in tritan axis (dE)	12.18 (12.24)	17.88 (16.11)	<0.001

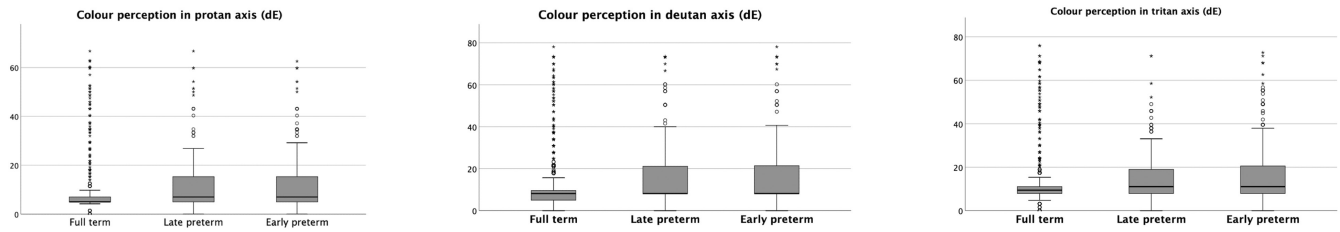

FIGURE 3 Boxplots representing colour perception outcomes in each study group: full-term (born after 37 weeks of gestational age), late preterm (born between 32 and 37 weeks of GA) and early preterm (born before 32 weeks of gestational age).

birth to 15 months, there is a migration of inner retinal layer cells from the fovea towards the periphery, which deepens the foveal pit.[20] Simultaneously, cones migrate centralward and develop their outer segments and basal axonal processes.[19] The inner and outer segments of the cones are shorter in neonates, compared to adult life, while inner segments are much wider. At birth, foveal cones are immature and sparsely populated compared to the adult fovea, with cone density not reaching adult levels until about 45 months.

The first studies focused on the development of chromatic vision were performed in the 1980s and 1990s by Teller et al.[21] They measured luminance and chromatic discrimination, without brightness cues, following a forced preferential looking procedure. Visual stimuli were presented as coloured bars or figures embedded in white screens. In all cases, the colour cards were shown by an examiner who assessed detectability based on the infant's fixation behaviour observed through a peephole in the centre of the screen. With different studies also based on forced-choice preferential looking paradigm, Knoblauch and col. and other authors found a later age of maturation of colour discrimination after 10 years of age or even later.[22,23] In all these studies assessment of correct discrimination was performed manually by an examiner and the duration of each exam varied between 10 and 20 min. Long durations of the studies may interfere with younger children's attention and be a limiting source of bias.

More recent attempts to develop a colour vision test for young infants have been designed based on the pseudoisochromatic principle[24,25] Among all of them, only the Colour Vision Testing Made Easy[24] has been used with some success with preschool children and infants. However, the Colour Vision Testing Made Easy test presents some drawbacks that may preclude its results and limit its use in clinical practice. It assesses colour perception with only four chromatic plates, with a common background: two with Munsell hues falling on a red/green confusion line and two on a blue/yellow confusion line. Chromatic targets are presented either to the right or to the left sides, with a high risk of false-positive responses. Finally, detectability is subjectively assessed by an examiner based on the infant's behaviour.

To overcome all the constraints found in previous colour tests, we use a test based on the preferential-looking paradigm, assisted by eye-tracking technology. Visual stimuli are pseudoisochromatic

plates deployed digitally with a fully analytical description for chromaticity and luminance.

In agreement with current knowledge on the anatomical and neural basis of colour vision, we describe a reference curve for development throughout childhood. Greater improvement is observed as expected during the first 4 years of life when the visual system is experiencing major structural and functional changes.

As expected, females performed better in colour perception in the deutan axis. The reasons underlying these differences have a genetic basis since the most common form of congenital colour vision deficiency is an X-linked recessive manner. This means that congenital colour vision deficiency affects around 8% of males and 0.5% of females, with differences between geographically diverse populations.[26] Among all forms of congenital colour vision deficiencies, deuteranomaly is the most frequent with a prevalence of 4.6% in males, followed by deuteranopia in 1.3%. Our results in a large sample of paediatric patients are consistent with these findings.

Prematurely born children exhibit a high prevalence of ophthalmologic and neurodevelopmental disorders. Among all the visual disorders, ROP is the first entity to appear and is related to the poorest visual outcomes. The risk of visual deficiencies is greater in children with a previous ROP requiring treatment. However, prematurity itself is also related to higher rates of several visual disorders compared to full-term children.

Although describing visual disorders was not the main goal of our study, we found significant refractive errors in 24% and strabismus in 15% of our pre-term cohort, which is similar to previous findings. Besides the rate of ROP or cerebral visual impairment, refractive errors and strabismus are also directly related to gestational age at birth, with more frequent defects in children born at earlier GA.[6]

Although there is vast evidence of impaired colour vision in children born preterm, the causes underlying this finding remain unclear. At the cellular level, both rods and cones have shown impaired function in extremely preterm infants born before 27 weeks of gestational age via electroretinographic recordings.[9,27] Between foetal weeks 25 and 40, major retinal developments take place, from full vascularization of the retina to structural changes in the morphology of retinal cells, including photoreceptors.[20] The disruption of foetal environment as the consequence of premature birth may indeed interfere, even more, if certain adverse events occur. The causal relationship between colour deficiencies and gestational age, birthweight or the presence of ROP is still controversial and gives rise to conflicting outcomes. While some authors reported a positive correlation between cones and rod function and gestational age at birth, no relationship is found in other studies, which relate colour impairment in pre-term children to a consequence of ROP or its treatments.[9,28] The lack of agreement among studies may be due to differences in the samples of children, such as gestational age at birth, coexisting disorders or clinical ROP phenotypes.

In our large cohort of 374 pre-term children with ages throughout all developmental stages, gestational age was directly related to colour vision in the three axes, with greater differences between early and late pre-term found in the tritan axis. However, we found no impact of ROP on future colour vision once adjusted for GA. Similar outcomes had already been reported for ROP and for all its treatments, such as cryotherapy or laser photoablation.[29]

Furthermore, constant high-intensity illumination in neonatal intensive care units has been linked to tritan deficiencies, since blue cones seem to be more vulnerable to light-induced damage in animal models.[8] It could also explain the greater differences in tritan axis found in our sample of early pre-term children, who might have been more exposed to high-intensity illumination due to longer hospital admissions.

It is noteworthy that some authors, such as Jackson et al.,[28] found similar colour vision between children born prematurely and at term and related previous findings to unreliable colour tests.

Colour impairments may also be related to certain visual disorders, such as inherited retinal dystrophies, amblyopia or lens opacity. Colour vision is also among the affected visual functions in children with cerebral palsy, with impairments along the three confusion axes. Tetraplegic patients are the most affected clinical group compared to the diplegic and hemiplegic groups.[30] Chromatic discrimination seems to be related to motor performance (i.e. to GMFCS scores).

Children with cerebral visual impairment or cerebral visual dysfunction may face difficulties performing tests because of different reasons, such as visual field defects related to visual pathway lesions usually caused by periventricular white matter damage. On the other hand, preterm children have an increased risk for visual figure ground deficiencies, which could interfere with the performance of pseudoisochromatic tests, and for oculomotor control disorders, which could affect the performance of a test based on a preferential-looking paradigm. As far as the latter, it should not be a source of bias since the algorithms to define a stimulus as detected or not detected do not require high oculomotor performance and, therefore, the test is feasible and accurate even in children with certain deficits in attention, fixation or saccadic movements. Although pre-term children in our study had a higher rate of most visual and neurological disorders, they did not fully explain impaired colour discrimination, since it was also present in children with normal exams, who performed with no difficulties in other visual tests based on the same paradigms.

Inconclusive results among the published studies may be due to differences in the age of the patients at the time of inclusion in the study, clinical protocol performed or clinical features of the study groups may be some of the reasons behind.

In order to overcome most of previous limitations, we have performed a study with the objective of describing colour vision and assessing the impact of prematurity throughout childhood. We used a digital test able to assess colour perception in the three colour axes, which required very low cooperation from the child and an adaptive strategy. It enabled to obtain accurate and reliable data from children as young as 2 years of age and to use the same clinical test for all the patients up to adult life.

5 | CONCLUSION

In conclusion, colour vision develops throughout the first years of life, as most visual skills do. Children born preterm face an increased risk for colour vision deficiencies among many visual and neurologic disorders. Colour vision tests should be included in routine eye exams in preterm children in order to provide early detection of any deficiency which could interfere with their educational or social activities.

AUTHOR CONTRIBUTIONS

Victoria Pueyo: Conceptualization; funding acquisition; methodology; project administration; resources; supervision; writing – original draft; writing – review and editing. **Mauricio Cedillo Ley:** Methodology; project administration; resources; writing – review and editing. **Álvaro Fanlo-Zarazaga:** Conceptualization; formal analysis; methodology; writing – review and editing. **Liu Hu:** Investigation; project administration; resources; writing – review and editing. **Xian Pan:** Formal analysis; software; visualization; writing – review and editing. **Teresa Perez-Roche:** Conceptualization; formal analysis; methodology; writing – review and editing. **Victoria Balasanyan:** Investigation; resources; writing – review and editing. **David Solanas:** Data curation; software; visualization; writing – review and editing. **Sandra de Fernando:** Investigation; resources; writing – review and editing. **Esther Prieto:** Conceptualization; formal analysis; investigation; methodology; writing – review and editing. **Jason C. S. Yam:** Investigation; project administration; resources; writing – review and editing. **Chau Pham:** Investigation; project administration; resources; writing – review and editing. **Marta Ortin:** Conceptualization; formal analysis; funding acquisition; project administration; software; supervision; writing – review and editing. **Olimpia Castillo:** Conceptualization; investigation; methodology; writing – review and editing. **Diego Gutierrez:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; resources; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Victoria Pueyo, Marta Ortin, Belen Masia and Diego Gutierrez are cofounders of DIVE Medical Startup, while Marta Ortin, Xian Pan, Alvaro Fanlo-Zarazaga and David Solanas work for DIVE Medical start-up. The remaining authors have no conflict of interest to declare.

COMMERCIAL RELATIONSHIPS DISCLOSURE

Victoria Pueyo, Marta Ortin and Diego Gutierrez are cofounders of DIVE Medical Startup, while Marta Ortin, Xian Pan, Adrian Alejandre, Alvaro Fanlo-Zarazaga, Marina Vilella, David Solanas and Marta Lacort work for DIVE Medical start-up.

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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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