



Original Article

Seeing the Unseen: The Neurodevelopmental Factors Related to Visual Impairments in Children With Unilateral Cerebral Palsy



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ABSTRACT

Background: In children with unilateral cerebral palsy (uCP), the relation between different factors (brain damage, prematurity, and cerebral palsy side) and visual impairments, which are common but often ‘unseen,’ is not fully understood.

Methods: Visual functions and functional vision were assessed in 41 children with uCP (7–15 years, 21 left-sided, 19 preterm). Brain damage was scored on structural magnetic resonance imaging regarding lesion timing, location, and severity, and corpus callosum (CC) length and splenium thickness. With nonparametric statistics, we investigated the relation between visual outcomes and brain damage (r_s) and differences in visual outcomes and brain damage based on prematurity and uCP side (r). With elastic-net regularized regression models (area under the receiver operating characteristic curve [AUC]; d), we explored if gestational age and brain damage could predict impairments in visual functions.

Results: Damage to the lobes and CC was associated with reduced visual functions and functional vision ($r_s = -0.402$ to -0.611). Compared to children born at term, preterm children mainly showed reduced geniculostriate functions ($r = 0.343$ – 0.443) and damage to the parietal lobe ($r = 0.353$). No differences in brain damage were found between children with left- and right-sided uCP. In regression models, shorter CC length and parietal lobe lesion ($d = -0.526$ to 0.564) were the main predictors for impaired stereoacuity (AUC = 0.77), and occipital lobe lesion ($d = 0.349$) for impaired visuomotor integration (AUC = 0.81). Prediction models of visual perception showed poor predictive performance (AUC < 0.70).

Conclusions: Specific brain damage and prematurity are related to different visual impairments in children with uCP. Our results could guide clinicians in directing their attention to specific visual assessments and subsequent intervention in children with uCP.

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Introduction

Impairments in visual functions are common but often overlooked in children with spastic unilateral cerebral palsy (uCP), a neurodevelopmental disability caused by early brain damage.^{1,2} Spastic cerebral palsy (CP) is the prevailing subtype, defined as unilateral (44%) if sensorimotor impairments are predominantly

present on one side of the body.³ Besides motor areas, brain lesions can affect the visual system of children with uCP, resulting in reduced geniculostriate and visual-perceptual functions.⁴ Although visual impairments are less evident than motor problems, they can severely impact the use of vision in daily activities (i.e., functional vision),⁵ visually-guided movements,^{6–8} and the quality of life of children with uCP. To be able to better predict visual difficulties, several studies attempted to identify a relation between visual impairments and neurodevelopmental factors such as brain damage, prematurity, and the side of CP, reporting no clear relation between visual functions and specific brain structure and mixed results on the relation with prematurity and right or left-sided uCP.^{4,9,10}

The visual system is complex, involving several brain regions, commissures, decussations,^{11,12} and two interacting pathways: the dorsal and ventral streams, responsible for distinct visual functions.^{11,13} Damage to different areas can result in specific visual impairments.¹¹

Qualitative¹⁴ and semiquantitative¹⁵ methods of structural magnetic resonance imaging (sMRI) analysis have been used to classify lesion timing, location, and severity in children with CP.^{4,16} In a recent systematic review, we showed that white matter (WM) lesions, particularly periventricular leukomalacia (PVL), are most frequently associated with visual impairments in children with CP. However, we found limited research on the prevalence of specific visual impairments in relation to particular visual structures in this population.⁴ Additionally, it is well established that the occipital cortex is functionally connected with the thalami and the posterior part of the corpus callosum (CC),^{17,18} structures frequently damaged in children with CP.^{19,20} Although previous findings demonstrated that worse visual functions are related to damage to the thalami in infants with CP and PVL,²¹ and to reduced CC biometry in children with developmental disorders and preterm birth (gestational age <37 weeks),^{22–24} this relation remains underinvestigated in children with uCP.

PVL is also the most frequent lesion type related to preterm birth, responsible for about half of the children diagnosed with CP.^{25–27} Previous studies showed that children born preterm without CP, more frequently present with reduced visual acuity, stereopsis, visual perception, and visuomotor integration compared to children born at term.^{28,29} However, studies on children with bilateral CP do not suggest a correlation between gestational age and visual impairments or brain damage.¹⁰ Lastly, previous research found that children with left-sided uCP perform worse on visual perceptual tests than children with neurotypical development or right-sided uCP.^{9,30} Although the authors explained it by suggesting that the right hemisphere is responsible for visuospatial function, they did not include brain damage data.^{9,30} In our previous work, we found no differences between children with left and right-sided uCP on visual perceptual tests while only children with left-sided uCP presented with worse stereoacuity compared to neurotypical development, supporting the hypothesis that the right parietal posterior cortex is responsible for three-dimensional (3D) depth perception.² Despite the importance of these findings, previous research focused only on a specific factor or type of visual impairment, highlighting the need for studies including a more comprehensive analysis.

Therefore, the present study aims to (1) describe differences in visual outcomes and structural brain damage between children with uCP born preterm and at term and between children with left and right-sided uCP, (2) systematically investigate the relation between visual outcomes and brain damage in children with uCP, and (3) explore to which extent differences in gestational age and brain damage can predict visual impairments in this population.

Materials and Methods

Participants and procedure

Children with spastic uCP, aged between 7 and 15, were recruited via the CP care program of the University Hospitals Leuven (Belgium). The recruitment was performed by two trained child physiotherapists (L.D. and L.K), during which participants were included if they could understand the test instructions and if they were able to actively grasp and stabilize a small block 3 cm × 3 cm × 1 cm and/or a pencil with the nondominant hand (House Functional Classification System ≥4).³¹ Participants were excluded when they received upper limb botulinum neurotoxin-A injections 6 months before testing, or when they underwent upper limb surgery 2 years before assessment. Perinatal variables, ocular and oculomotor data, diagnosis of cerebral visual impairment (CVI)³² according to Ortibus et al.,³³ the side of uCP (i.e., the side of the body mainly impaired), and the level of manual ability, classified according to the Manual Ability Classification System,³⁴ were retrieved from medical records. Visual assessments and magnetic resonance imaging (MRI) were performed by three trained researchers (M.C., L.D., and L.K) in a single day or split into two half days according to the family's preference. All research data were fully anonymized, and each child was assigned a unique study code, distinct from the clinical data code used for the hospital medical records. Consent to participate was provided by parents and children older than 12 years. This study was approved by the UZ/KU Leuven Ethical Committee (S62906).

Measures

Visual assessments

Standardized and age-appropriate tests, performed with both eyes open and best-corrected vision, were used to assess visual functions and functional vision. Visual assessments were independently scored in a double-blind manner by a trained researcher (M.C.) and two pediatric physiotherapy trainees, who were blinded to both clinical and imaging data.

Geniculostriate visual functions. Binocular far *visual acuity* was investigated using the Freiburg Visual Acuity Test (FrACT) software.³⁵ Eighteen trials of Landolt C rings were displayed on a computer screen at 3 m distance. The FrACT results were scored as a continuous variable in LogMAR (logarithm of the minimum angle of resolution = $-\log_{10}[\text{decimal acuity}]$).³⁶ Visual acuity in LogMAR was categorized as normal (≤ 0.3), mild ($0.3 < \text{LogMAR} < 0.5$), moderately ($0.5 \leq \text{LogMAR} < 1$), or severely (≥ 1) impaired according to the World Health Organization criteria.³⁷ **Binocular stereoacuity** was investigated wearing 3D glasses using the fly and the circle subtests of the Titmus Stereo Fly.³⁸ In the fly subtest, the child must pinch the wings of a fly displayed in a 3D perspective. The circle subtest includes nine trials with a disparity ranging from 800 to 40 arcseconds where the participant has to look at four circles and choose the one that seems to come out closer. Stereoacuity was scored as the last correctly identified circle, with ordinal values ranging between 1 and 9. Information from the fly subtest was retrieved if the child failed to identify the first circle, and scored as 0 if failed and 0.5 if successful.³⁸ Failure to identify the circle number 5 (100 arcseconds) or lower was categorized as impaired stereoacuity.

Visual-perceptual visual functions. *Motor-free visual-perceptual skills* were assessed using five subtests of the Test of Visual Perceptual Skills, Fourth Edition (TVPS-4) in which the participant had to identify a targeted black-and-white image among four or

five options presented in a booklet.³⁹ The visual memory and sequential memory subtests were not administered in our study since we did not aim to assess memory-related impairments. For each subtest, namely visual discrimination, spatial relationships, form constancy, visual figure-ground, and visual closure, the participant's answers were recorded as raw scores (ranging from 0 to 18). According to the manual, TVPS-4 raw scores were translated into the age-equivalent scaled scores (mean = 10, S.D. = 3).³⁹ Motor-dependent visual-perceptual skills were investigated using the visuomotor integration (VMI) subtest of Beery Buktenica Test of Visual-Motor Integration, Sixth Edition,⁴⁰ where the participant is asked to copy increasingly more difficult geometric figures. According to the manual, raw scores of the VMI were calculated as the number of figures copied correctly (ranging between 0 and 30) and translated into the age-equivalent standard scores (mean = 100, S.D. = 15).⁴⁰ The scaled scores of the TVPS-4 subtests and the standard scores of VMI were transformed into standardized z-scores (mean = 0, S.D. = 1), and categorized as normal (> -1), impaired (-2 to ≤ -1), and severely impaired (≤ -2).

Functional vision was assessed using the Flemish Cerebral Visual Impairment Questionnaire (FCVIQ), a 46-item binary-response screening tool filled by the caregivers.⁴¹ Responses were calculated according to the sum of 'yes' items (1: the child presents the characteristic described in the item; 0: characteristic not present) as a total score where a higher score reflects a higher level of functional vision impairment.

Structural MRI

A 3.0 Tesla MRI scanner (Hercules, Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil was used to acquire T1-weighted images (TE/TR/TI 4.2/9.1/760.3 ms, voxel size: 0.9 × 0.9 × 0.9 mm³), T2-weighted images (TE/TR/TI 280/3000/548 ms, voxel size: 1 × 1 × 1 mm³), and T2 fluid attenuation inversion recovery (FLAIR) images (TE/TR/TI 283/4800/1650 ms, voxel size: 1 × 1 × 1 mm³). To familiarize younger children with the MRI scan, a space-themed familiarization protocol was implemented.⁴² Anatomical images were initially scored for lesion timing and severity by a trained researcher (M.C.) and then cross-checked by an expert child neurologist (E.O.), using MRICroGL (version 1.2.2021).⁴³ CC biometry was scored on the MRI viewer of the clinical working station of the University Hospitals of Leuven, by a trained researcher (M.C.), who had previously undergone joint training in CC measurements with an expert pediatric neurologist (M.L.G.), with whom any disagreements were discussed and resolved. The neurologists (E.O. and M.L.G.) involved in the imaging scoring were blinded to the clinical details and results of the visual function testing to ensure unbiased evaluation.

Magnetic resonance imaging classification system for lesion timing. Lesion timing was classified on T1 and T2-weighted images according to the magnetic resonance imaging classification system (MRICS).¹⁴ Results were reported as categorical variables, namely maldevelopments (A), predominant WM injury (B), predominant gray matter injury (C), miscellaneous (D), and normal (E).

Semiquantitative scale for lesion location and severity. Lesion location and severity were assessed on FLAIR anatomical images using a semiquantitative scale validated for children with CP.¹⁵ According to this method of Fiori et al.,¹⁵ brain lesions were graphically represented on a six-axial-slices template (Figure A.1). Raw scores were calculated for the sum of the periventricular, middle, and the cortico/subcortical WM layer of each lobe (occipital, parietal, temporal, and frontal), subcortical structures (lenticular, caudate, posterior limb of the internal capsule, thalamus, and brainstem), CC (posterior, anterior, middle), and cerebellum. Summary scores

were calculated for the occipital, parietal, temporal, and frontal lobar score (sum of the right and left scores for each lobe; [0-6]), subcortical score (sum of the right and left scores of the subcortical structures; [0-10]), and global score (sum of lobar, subcortical, CC, and cerebellum scores, [0-40]) where higher scores represent more severe brain lesions. Since in the present study, we aimed to investigate the specific role of the thalami and CC in relation to visual function outcomes, in addition to the summary scores, the scores of the thalami (sum of left and right thalamus; [0-2]), total CC (sum of the three parts; [0-3]), and posterior CC [0-1] were included in our analysis.

CC biometry. Two linear parameters, namely CC length and splenium thickness, were manually measured according to Gareil et al.⁴⁴ in millimeters (mm), on the midsagittal plane of T1-weighted images. The length of the CC was measured as the distance between the most anterior part and the most posterior part of the CC, while splenium thickness was calculated by tracing a perpendicular line to the curvilinear axis of the CC at the level of the splenium (Figure A.2).⁴⁴ Other CC measurements were not performed since the splenium is the CC part connecting the temporo-parietal-occipital areas known to be involved in visual functions.⁴⁵ CC biometry was not adjusted for overall head size or intracranial volume, since at school-age CC growth is stable until adolescence.⁴⁴ Additionally, results were classified as above or below the median, according to age-normative values reported by Gareil et al.,⁴⁴ which did not include corrections for intracranial volume or overall head size.

TABLE 1. Clinical Characteristics of Children With Unilateral Cerebral Palsy

General Characteristics	Category	n	(%)
Mean age (S.D.), years: months		11:06 (2:09)	
Sex	Male	22	54
	Female	19	46
Side of cerebral palsy	Right-sided	20	49
	Left-sided	21	51
Magnetic Resonance Imaging Classification	A	2	5
	B	28	68
	C	8	20
System category ¹⁴	D	1	2
	E	2	5
Manual Ability Classification	I	23	56
	II	14	34
System level ^{34,*}	III	4	10
Gestational age ^{*†}	Mean (S.D.), months	36 (3.9)	
	Term	21	51
	Preterm	13	32
	Very preterm	6	15
	Unknown	1	2
Birth weight ^{*‡}	Mean (S.D.), grams	2828,56 (984,77)	
	Normal	28	68
	Low	12	29
	Unknown [§]	1	3

Abbreviations:
 A = Maldevelopments
 B = Predominant white matter injury
 C = Predominant gray matter injury
 CP = Cerebral palsy
 D = Miscellaneous
 E = Normal
 Percentages are calculated out of the total sample of children with unilateral CP (n = 41).
 * Retrieved from medical records.
 † Gestational age refers to completed weeks of pregnancy: term, ≥37 to <42 weeks; preterm, ≥32 to <37 weeks; very preterm, <32 weeks.
 ‡ Birthweight: normal birthweight, ≥2500 g; low birthweight, <2500 g.
 § Unknown reflects no reported data or missing data, which exists because of the retrospective data retrieval.

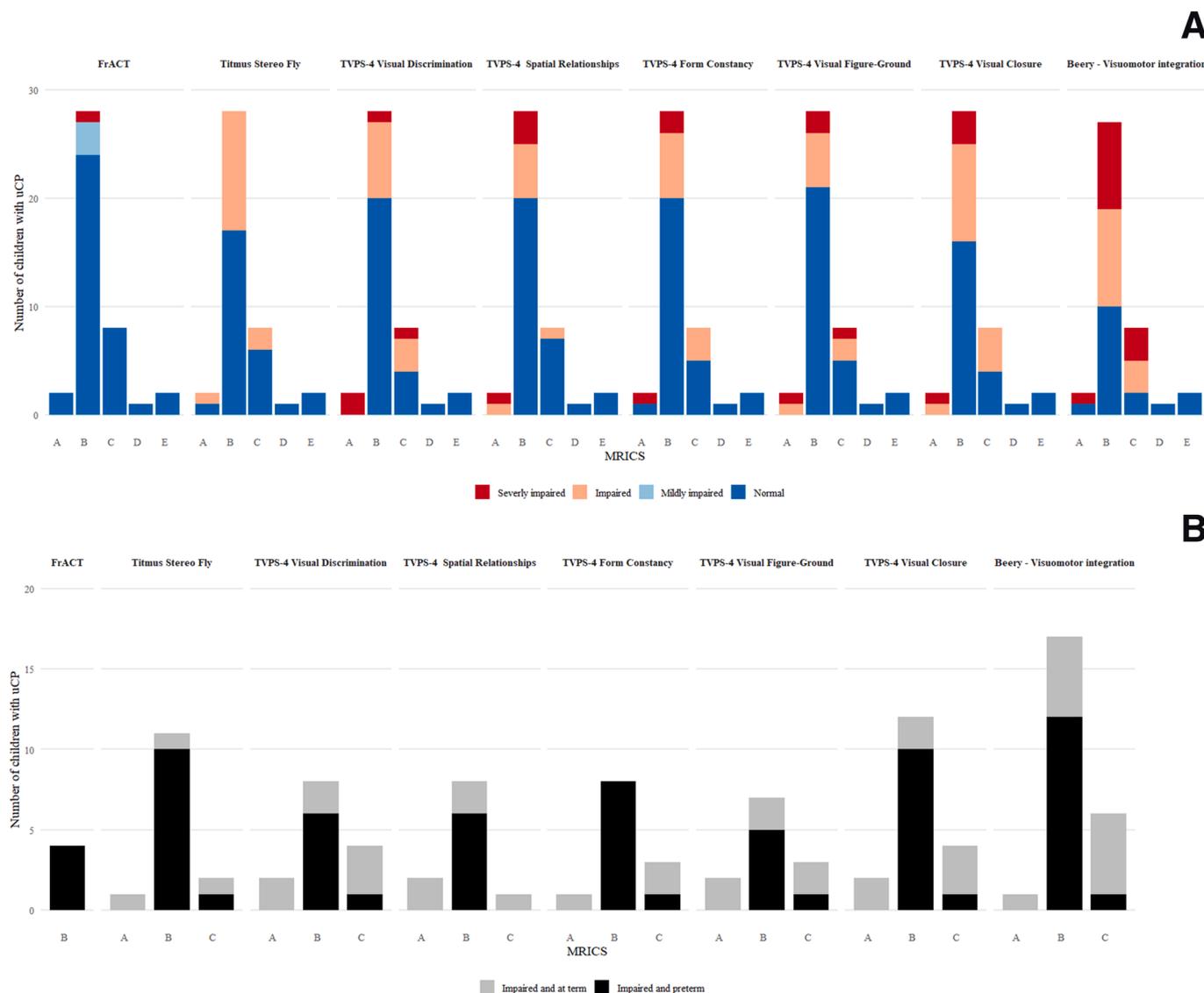


FIGURE 1. Visual outcomes in children with unilateral cerebral palsy with different lesion timing classified on the MRICS (A) and distribution of visual impairments in children born at term and preterm (B). Abbreviations: Beery = Beery-Buktenica Test of Visual-Motor Integration, Sixth Edition; FrACT = Freiburg Visual Acuity Test; MRICS = Magnetic Resonance Imaging Classification System; TVPS-4 = Test of Visual Perceptual Skills, Fourth Edition; uCP = unilateral cerebral palsy. A, maldevelopments; B, predominant white matter injury; C, predominant gray matter injury; D, miscellaneous; E, normal. The color version of this figure is available in the online edition.

Statistical analyses

Frequencies were calculated for descriptive characteristics, visual outcomes, and brain damage. Since our data deviated from a normal distribution, nonparametric statistics were performed, reporting medians and interquartile ranges. For the visual outcomes, only results of the visual assessments performed in this study (i.e., not retrieved from medical records) were included in the statistical analyses described below. Data were analyzed using R (version 4.3.2).

Differences in visual outcomes and brain damage between children with uCP born preterm and at term and between children with left and right-sided uCP

Mann-Whitney *U* tests were performed to investigate differences in visual outcomes and brain damage between children with uCP born preterm and at term and to investigate differences in brain damage between children with left and right-sided uCP.

Effect sizes were calculated using correlation coefficients (*r*) and interpreted as small (<0.3), medium (0.3-0.5), or large (≥0.5).⁴⁶

The relation between visual outcomes and brain damage

To study the univariate associations between visual functions, functional vision, and brain damage, pairwise partial Spearman's Rank correlations, corrected for gestational age, were performed using a false discovery rate (adjusted *P* value ≤0.05) for multiple testing correction.⁴⁷ Correlation coefficients (*r_s*) were interpreted as no or negligible (<0.30), low (0.30-0.49), moderate (0.50-0.69), high (0.70-0.89), or very high (≥0.90).⁴⁶

Predicting visual impairments with gestational age and sMRI

To explore if differences in gestational age and brain damage can predict visual impairments in children with uCP, elastic-net regularized regression prediction models, with a nested cross-validation approach, were used. The full procedure has been described in a previous publication.⁴⁸ Only children with

complete data were included ($n = 38$). The results from the semiquantitative scale (i.e., frontal total, temporal total, parietal total, occipital total, global score, CC posterior, CC total) and the CC biometry (i.e., CC length, splenium thickness) that showed significant partial Spearman's Rank correlations as well as the gestational age of the participants were standardized and used as predictors. Results of the visual assessments performed in this study and scored as normal or impaired were included as binary outcomes of the models. Due to the nested cross-validation, each visual outcome was required to have enough participants ($n > 4$) in each group (impaired/normal) to be included in the analysis. Therefore, no prediction model was performed on the results of the FrACT test since only four children had impaired visual acuity. Additionally, no prediction model was performed on the results of functional vision since there is no cutoff available in the literature for the FCVIQ. Therefore, the outcomes included in the prediction models were the results of the Titmus Stereo Fly test, the TVPS-4 subtests, and the VMI. More specifically, for the TVPS-4 subtests and the VMI, we grouped children with scores in the "impaired" range ($-2 < z \leq -1$) and the "severely impaired" range ($z \leq -2$) together under a single category labeled "impaired", while the remaining children with scores in the normal range ($z > -1$) were categorized as "normal". The predictions were compared with the actual visual assessment results to calculate the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. The predictive power of each model was evaluated using the AUC as no (≤ 0.49), poor (0.50-0.69), acceptable (0.70-0.79), good (0.8-0.89), or outstanding (≥ 0.9) discrimination.⁴⁹ The effect size of each predictor was interpreted according to Cohen's d as tiny (< 0.10), very small (0.10-0.19), small (0.20-0.49), moderate (0.50-0.79), large (0.80-1.19), very large (1.20-1.99), and huge (≥ 2.00).⁵⁰

Results

Participants

Forty-one children with uCP (mean age 11y6mo, S.D. 2y19 mo, 22 males, 21 left-sided uCP, 19 preterm) were included in this study. Descriptive characteristics and the prevalence of visual impairments and brain damage in our sample are presented in Table 1 and Table S1, respectively. A detailed overview of missing data is presented in Figure A.3.

Descriptive results of visual assessments and brain damage in children with uCP

The majority of children in our sample (68%) had WM lesions (Table 1). All children with impaired visual acuity ($n = 4$) had predominantly WM lesions. In children with impaired stereoacuity ($n = 14$), 7% presented with maldevelopments (A), 79% with predominantly WM lesions (B), and 14% with predominantly gray matter lesions (C). Depending on the different TVPS-4 subtests, in children with impaired visual perception ($n = 11-18$), 8% to 18% of the children presented with maldevelopments, 57% to 73% with predominantly WM lesions, and 9% to 29% with predominantly gray matter lesions. In children with impaired VMI ($n = 24$), 4% presented with maldevelopments, 71% with predominantly WM lesions, and 25% with predominantly gray matter lesions. No visual impairments were found in children with miscellaneous lesions (D) and normal MRI (E) (Fig. 1A).

The majority of children with uCP born preterm ($n = 19$) presented with WM lesions ($n = 16$; 84%), followed by gray

TABLE 2. Prevalence of Children With Impairment in Visual Function and Brain Damage Quantified on the Semiquantitative Scale and CC Biometry Below the Normative Range

Brain Damage	Visual Acuity (n = 4)		Stereoacuity (n = 14)		TVPS-4 Visual Discrimination (n = 14)		TVPS-4 Spatial Relationships (n = 11)		TVPS-4 Form Constancy (n = 12)		TVPS-4 Visual Figure-Ground (n = 12)		TVPS-4 Visual Closure (n = 18)		Beery-Visuomotor Integration (n = 24)	
	x	%	x	%	x	%	x	%	x	%	x	%	x	%	x	%
Frontal lobe	4	100	14	100	14	100	11	100	12	100	12	100	18	100	23	96
Temporal lobe	4	100	14	100	14	100	11	100	12	100	12	100	18	100	24	100
Parietal lobe	4	100	14	100	14	100	11	100	12	100	12	100	18	100	23	96
Occipital lobe	4	100	14	100	12	86	9	82	12	100	10	83	17	94	24	100
Thalami	2	50	7	50	6	43	2	18	5	42	4	33	6	33	10	42
Total CC	3	75	13	93	12	86	9	82	9	75	9	75	15	83	22	92
Posterior CC	3	75	13	93	11	79	9	82	8	67	9	75	14	78	21	88
Subcortical	3	75	11	79	13	93	10	91	8	67	11	92	15	83	20	83
Fiori global	4	100	14	100	14	100	11	100	12	100	12	100	18	100	24	100
CC total length	3	75	12	86	13	93	10	91	10	83	10	83	13	72	19	79
Splenium	3	75	11	79	11	79	9	82	10	83	9	75	15	83	20	83

Abbreviations:

% = Percentage calculated on the total number of children with impaired visual function (% = x/n)

Beery = Beery-Buktenica Test of Visual-Motor Integration, Sixth Edition

CC = Corpus callosum

FCVIQ = Felmish cerebral visual impairment questionnaire

n = Total number of children with impaired visual function

TVPS-4 = Test of Visual Perceptual Skills, Fourth Edition

x = Total number of children with impaired visual function and lesions or biometry below the median

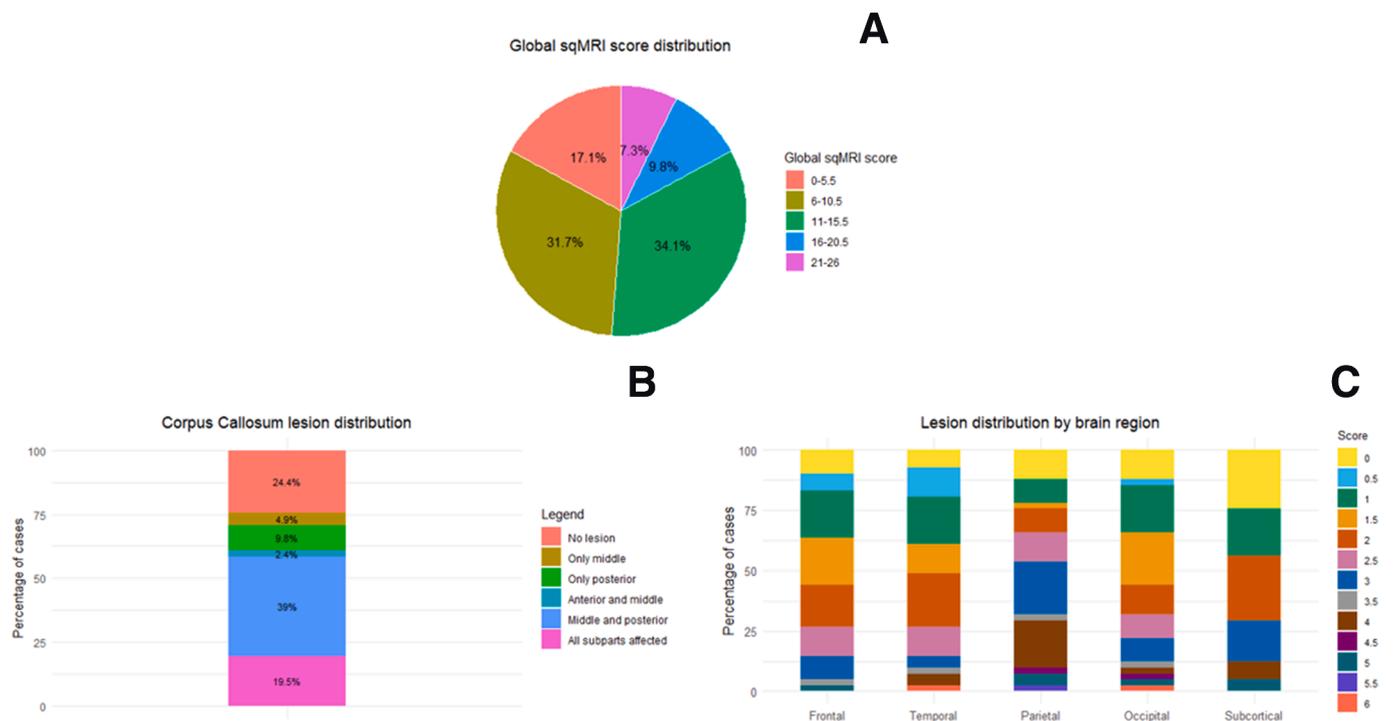


FIGURE 2. Percentage of cases presenting different lesion severity according to the semiquantitative MRI scale (sqMRI) scores: (A) global score (maximum score of 40); (B) corpus callosum lesion distribution; (C) lobar and subcortical score (including right and left side) ranging from 0 to 6. The color version of this figure is available in the online edition.

matter lesions ($n = 2$; 11%), and miscellaneous lesions ($n = 1$; 5%). Overall, most children with visual impairments were preterm with predominantly WM lesions (Fig. 1B). Damage to the WM, particularly in the temporal area (93%), was most frequently reported compared to other structural damage (Table 2). A detailed graphical overview of the results of the semiquantitative scale is presented in Figure 2.

Differences in visual outcomes and brain damage on sMRI based on prematurity and uCP side

Compared to children with uCP born at term, preterm children showed worse visual acuity ($P = 0.005$; $r = 0.443$), stereoacuity ($P = 0.03$; $r = 0.343$), and visual perception on the TVPS-4 subtest form constancy ($P = 0.048$; $r = 0.312$), and more severe brain damage in the WM of parietal ($P = 0.025$; $r = 0.353$) and occipital lobes ($P = 0.048$; $r = 0.312$) (Table 3). No significant differences were found for brain damage outcomes between children with left and right-sided uCP.

The relation between visual outcomes and brain damage in children with uCP

Figure 3 shows the significant Spearman's rank correlations corrected for gestational age between visual outcomes and brain damage in children with uCP after applying false discovery rate correction. A full overview of the partial Spearman's rank correlations is presented in Table S2. Low to moderate correlations were found between increased damage either to the frontal, occipital, parietal, temporal WM ($r_s = -0.402-0.529$, $P = 0.049-0.011$), global scores ($r_s = 0.486$ to -0.555 , $P = 0.018-0.011$), and more impaired visual acuity, stereoacuity, VMI, and the FCVIQ. Total CC ($r_s = 0.411$ to -0.611 , $P = 0.042-0.004$) and posterior CC scores ($r_s = -0.449$ to -0.458 , $P = 0.023-0.019$) of the semiquantitative scale mainly correlated, with low to moderate correlation coefficients, with

stereoacuity and VMI. Reduced CC length ($r_s = -0.463$ to -0.542 , $P = 0.019-0.011$) was correlated with lower scores on visual acuity, stereoacuity, motor-free visual perceptual functions, and FCVIQ, while reduced splenium thickness ($r_s = 0.428$ to -0.456 , $P = 0.031-0.021$) correlated with the TVPS-4 subtest form constancy and the FCVIQ. No correlations were found between visual outcomes and thalamic and subcortical scores.

Predicting visual impairments with gestational age and sMRI

A detailed overview of the AUC, sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for each model of the elastic-net regularized regression analysis is presented in Table 4, and the estimates of the individual predictors are reported in Table 5. In the sections below, we present only the main predictors, showing small to moderate effect sizes, for the models with at least an acceptable discrimination ($AUC > 0.70$) (Fig. 4).

For impairments in *stereoacuity*, the model had acceptable discrimination ($AUC = 0.77$), with damage to the parietal lobe WM ($d = 0.564$) and reduced CC length ($d = -0.526$) showing moderate effect sizes, and gestational age ($d = -0.448$) and damage to the total CC ($d = 0.300$) small effect sizes. For impairments in *visual perception*, the models predicting the TVPS-4 subtests results had poor discrimination ($AUC = 0.53-0.67$). Remarkably, with the available data, we were not able to fit an adequate model for the results of the TVPS-4 subtest visual closure. For impairments in *visuomotor integration*, the model had good discrimination ($AUC = 0.81$), with damage to the temporal and occipital WM lobe, and the global score showing small effect sizes ($d = 0.202-0.349$).

Discussion

In this study, we investigated the relation between visual outcomes and different neurodevelopmental factors showing that

TABLE 3.
Differences in Visual Outcomes and Brain Damage Between Children With uCP Born Preterm and at Term

	Children with uCP Born at Term (n = 21) Median [IQR]	Children with uCP Born Preterm (n = 19) Median [IQR]	P Value	r
Visual assessments				
FrACT	−0.204 [−0.277,−0.088]	−0.033 [−0.122,0.202]	0.005	0.443
†Titmus stereo fly †	9 [8,9]	3 [1,9]	0.030	0.343
‡TVPS -visual discrimination †	−0.333 [−1.333,0.333]	−0.333 [−1.667,0.5]	0.817	0.037
‡TVPS -spatial relationships †	0 [−0.333,0.667]	0.33 [−1.167,0.667]	0.691	0.063
‡TVPS -form constancy †	−0.333 [−0.667,1]	−0.667 [−1.333,0.333]	0.048	0.312
‡TVPS -visual figure-ground †	0 [−1,0.333]	−0.333 [−1.167,−0.165]	0.384	0.138
‡TVPS -visual closure †	−0.333 [−1,0.333]	−1 [−1.333,−0.333]	0.075	0.282
§Beery- visuomotor integration †	−1.1 [−2.117,−0.583]	−1.4 [−2.1,−0.833]	0.527	0.101
¶FCVIQ †	4 [1,7]	4.5 [1.25,8.25]	0.955	0.009
Brain damage				
‡Frontal total †	1.5 [1,2]	2 [1.25,2.75]	0.057	0.301
‡Temporal total †	1.5 [1,2]	2 [1.25,2.5]	0.261	0.178
‡Parietal total †	2.5 [1,3]	3 [3,4]	0.025	0.353
‡Occipital total †	1.5 [1,2]	2 [1.5,3]	0.048	0.312
‡Thalamic total †	0 [0,1]	0 [0,1]	0.936	0.013
‡CC posterior †	1 [0,1]	1 [0.5,1]	0.433	0.124
‡CC total †	2 [0,2]	2 [1,2]	0.460	0.117
‡Subcortical †	2 [1,3]	1 [0.2,5]	0.375	0.140
‡Global score †	10 [7,14]	13 [8.75,15.75]	0.143	0.231
¶CC length †	65.4 [62.675,69.9]	66.5 [61.6,69.1]	0.704	0.061
¶Splenium thickness †	10.1 [9.4,11.5]	9.3 [8.1,10.35]	0.096	0.264

Abbreviations:

Beery = Beery-Buktenica Test of Visual-Motor Integration, Sixth Edition

CC = Corpus callosum

FCVIQ = Flemish cerebral visual impairment questionnaire

FrACT = Freiburg Visual Acuity Test

IQT = Interquartile range

n = Number of children

r = Effect size calculated as correlation coefficients and interpreted as small (<0.3), medium (0.3–0.5), or large (≥0.5) 46

TVPS = Test of Visual Perceptual Skills, Fourth Edition

uCP = Unilateral cerebral palsy

Significant results are shown in bold type: *P ≤ 0.05, **P ≤ 0.01.

* Results are reported in LogMAR.

† Results report the last circle identified or the fly test.

‡ Results are reported in z-scores.

§ Results calculated as the sum of the 'yes' items (1: the child presents the characteristic described in the item; 0: characteristic not present).

|| Results of the semiquantitative scale.

¶ Results of CC biometry calculated in mm.

†: higher values indicate a better performance or less severe brain damage.

‡: lower values indicate a better performance or more severe brain damage.

prematurity and WM and CC damage impact visual outcomes, while children with left and right-sided uCP did not show any differences in visual functions and brain damage. For all visual functions, the majority of children with impairments were preterm with predominantly WM lesions. Children born preterm (n = 19, 46%) showed mainly reduced geniculostriate functions (i.e. visual acuity and binocular stereoacuity) and damage to the WM parietal lobe compared to children born at term. Additionally, we found that CC damage and length were related to nearly all visual outcomes while, depending on the location (frontal, occipital, parietal, temporal), damage to the WM was related only to specific visual outcomes. Lastly, the models of impaired stereoacuity and VMI showed acceptable discrimination, with shorter CC length and parietal lobe lesions being the most significant predictors for impaired stereoacuity, and occipital and temporal lobe lesions for impaired VMI.

Different mechanisms underlie the development of specific visual functions, particularly in children with brain damage. Visual acuity and stereoacuity develop with the formation of the connections between the thalami and the occipital cortex, which start emerging in utero. In the case of perinatal hypoxic-ischemic events (on the basis of PVL), occurring between 24 and 34 weeks gestation due to premature birth, normal geniculostriate function development might be impaired.⁵¹ In contrast, the WM tracts

responsible for visual perception and visuomotor functions could be less affected by prematurity, since the myelination process continues after birth and up to 9 years within the extrastriate visual cortex maturation.⁵² Our results are in line with previous investigations showing that preterm children (where no specification on CP diagnosis is reported) often experience impaired visual acuity and binocular deficits.⁵³ Additional findings have shown that preterm children exhibit more impairments in visual perception functions compared to children born at term,^{28,29} particularly when assessed during infancy.⁵⁴ However, previous findings suggest that visual perceptual impairments may normalize by school age, which aligns with our findings.⁵⁴ Specifically, while children in the preterm group performed significantly poorer than the control group at age five on motor-free visual perception test, their performance was similar to that of the controls at age 12.⁵⁴ Furthermore, we found more severe parietal lobe WM lesions in children born preterm, in line with the theory that preterm birth has a more profound effect on the dorsal compared to the ventral visual stream.⁵² The lack of a relation between gestational age and the severity of visual impairments or brain damage in other studies on children with CP^{10,55} might be due to the types of visual functions assessed (e.g., mainly oculomotor and geniculostriate impairments summed up in a visual total score) and the limited scores of brain damage they

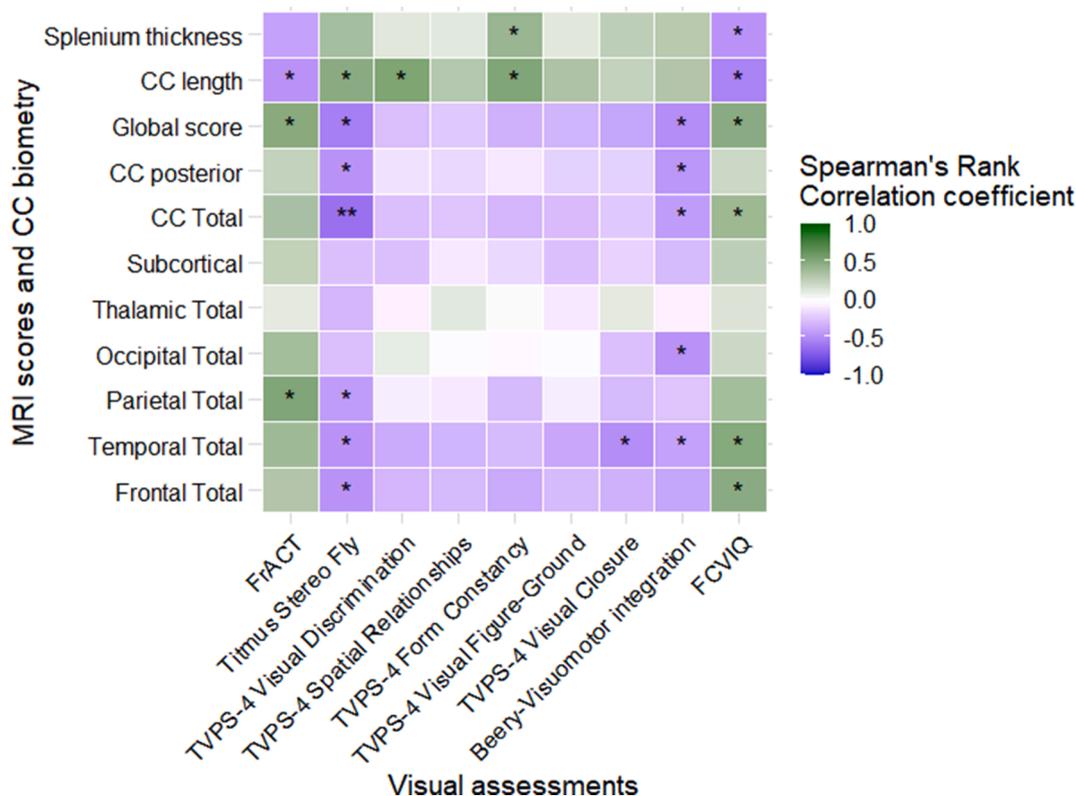


FIGURE 3. Partial Spearman's rank correlation matrix showing the significant correlations between visual outcomes and MRI score and corpus callosum biometry. Significant results are shown as * $P \leq 0.05$, ** $P \leq 0.01$. Abbreviations: Beery = Beery-Buktenica Test of Visual-Motor Integration, Sixth Edition; CC = corpus callosum; FCVIQ = Flemish cerebral visual impairment questionnaire; FrACT = Freiburg Visual Acuity Test; MRI = magnetic resonance imaging; TVPS-4 = Test of Visual Perceptual Skills, Fourth Edition. The color version of this figure is available in the online edition.

included.^{10,55} Lastly, we found no differences in brain damage between children with left and right-sided uCP. This could be attributed to the presence of widespread (bilateral) lesions in our cohort while the classification (i.e., right/left-sided uCP) is based on their clinical motor performance, which does not always accurately reflect the presence of bilateral lesions. Therefore, further studies including participants with more focal and unilateral brain lesions (i.e., children with congenital stroke), are needed to further investigate differences in visual outcomes in children with uCP.

Brain damage was assessed using the MRICS, a semi-quantitative scale, and CC biometry, all easily accessible methods to clinicians. In line with previous findings, we showed that higher

global scores on the semiquantitative scale were associated with reduced geniculostriate functions.¹⁰ Additionally, we found that higher global scores were also related to reduced VMI and functional vision and reduced CC biometry to reduced geniculostriate function, visual perception, and functional vision in children with uCP.

According to the literature, both reduced visual acuity and stereoacuity were associated with WM parietal lobe damage and reduced CC length.⁵⁶⁻⁵⁹ Additionally, reduced *stereoacuity* was also related to frontal, temporal, and CC damage, suggesting that 3D perception might rely on a more complex brain network compared to visual acuity. Results on stereoacuity were supported by the regression analysis, in which damage to the WM parietal lobe was

TABLE 4. Performance of the Models on the Prediction of Visual Impairments in Children With uCP

Visual Assessments	AUC	Sensitivity	Specificity	Accuracy	PPV	NPV
Titmus stereo fly	0.77	0.71	0.83	0.79	0.71	0.83
TVPS -visual discrimination	<i>0.67</i>	0.71	0.67	0.68	0.56	0.80
TVPS -spatial relationships	<i>0.56</i>	0.55	0.67	0.63	0.40	0.78
TVPS -form constancy	<i>0.54</i>	0.50	0.69	0.63	0.43	0.75
TVPS -visual figure-ground	<i>0.53</i>	0.50	0.73	0.66	0.46	0.76
Beery- visuomotor integration	0.81	0.63	0.93	0.74	0.94	0.59

Abbreviations:

AUC = area under the curve used to evaluate the model performance and interpreted with no (≤ 0.49), poor (0.50-0.69) in italics, acceptable (0.70-0.79) in bold italics, good (0.80-0.89) in bold, or outstanding (≥ 0.9) discrimination.⁴⁹

Beery = Beery-Buktenica Test of Visual-Motor Integration, Sixth Edition

NPV = negative predictive value

PPV = positive predictive value

TVPS-4 = Test of Visual Perceptual Skills, Fourth Edition

uCP = unilateral cerebral palsy

TABLE 5. Results of the Elastic-Net Regularized Regression With the Effect Sizes (Cohen's d) of Each Predictor

Visual Assessments	GA	Frontal Total	Temporal Total	Parietal Total	Occipital Total	CC Posterior	CC Total	Global Score	CC Length	Splenium Thickness
Titmus stereo fly	-0.448	-0.026	0.059	0.564	0.027	0.051	0.300	0.008	-0.526	-0.016
TVPS -visual discrimination	0	0.003	0.011	0	0	0	0.011	0	-0.534	0
TVPS -spatial relationships	*0.000	0	0	-0.002	-0.003	0	0	0	-0.390	0
TVPS -form constancy	-0.275	-0.005	-0.028	<i>0.116</i>	0.003	-0.038	*0.000	*0.000	-0.442	-0.062
TVPS -visual figure-ground	0.002	-0.029	0.377	-0.333	-0.433	0	-0.005	0	-0.554	-0.125
Beery- visuomotor integration	-0.186	<i>0.141</i>	0.202	<i>0.193</i>	0.349	<i>0.175</i>	<i>0.196</i>	0.239	-0.079	-0.161

Abbreviations:

Beery = Beery-Buktenica Test of Visual-Motor Integration, Sixth Edition

CC = Corpus callosum

GA = Gestational age

NA = Data not available since we were unable to fit an adequate model for this outcome

TVPS-4 = Test of Visual Perceptual Skills, Fourth Edition

The estimate of each individual predictors was used as effect sizes (Cohen's d) and interpreted as tiny (<0.10), very small (0.10-0.19) in italics, small (0.20-0.49) in bold italics, moderate (0.50-0.79) in bold, large (0.80-1.19), very large (1.20-1.99) and huge (≥ 2.00).⁵⁰

* The average estimate is less than 0.001; 0: The average predictor is not selected as meaningfully contributing to the model's ability to predict visual impairment.

the main predictor of impairments in this function, in line with the hypothesis that the parietal posterior cortex is responsible for 3D perception.⁵⁸ Additional significant predictors were lower gestational age, reduced CC length, and more severe CC damage on the semiquantitative scale, in line with studies on impaired stereoacuity in children at 4 years of age born preterm.²³ Our results further extend these findings to school-aged children with uCP, supporting the role of CC in the binocular integration of 3D stimuli.^{60,61}

Inferences on the relation between *visual perception* outcomes and brain damage are difficult to make since the correlation analysis reported limited associations and the regression models showed no or poor discrimination performances. A possible explanation is that visual perception includes complex functions in which connections between brain areas rather than single lobes are involved, as partially supported by our results showing a positive relation between lower scores on TVPS-4 subtests and shorter CC length. Hence, further studies involving more complex techniques (e.g., diffusion MRI, fMRI) might help to better understand the underlying mechanism of visual perception.

Lower scores on the *VMI* were associated with temporal, occipital WM lobe, and CC damage, supporting the involvement of

the ventral stream in object identification and the role of the CC in visuomotor processing. These results were partially supported by the elastic-net regression analysis, showing that more severe temporal, occipital WM lobe damage and higher global score of the semiquantitative scale are potentially useful predictors of impaired VMI. Lastly, higher scores of the *FCVIQ* were associated with damage to the frontal, temporal WM lobes, and CC. These relations might be explained within the framework of the temporal cortex attention network and the involvement of the frontal lobe in cognitive functions.^{62,63} Indeed the *FCVIQ* items reported more frequently by parents were related to visual attention and complex problem-solving. Additionally, both attention and cognitive functions require good inter-hemispheric connections, which could explain the relation between the *FCVIQ* scores and damage to the CC.⁶⁴ However, no prediction model could be performed on impairment in functional vision, since no cutoff is described for the *FCVIQ*. Nevertheless, if a child in our study exhibited a high *FCVIQ* score potentially suggestive of CVI, he/she was referred to the Center for Developmental Disabilities of Leuven for a comprehensive CVI diagnostic procedure, following the recommendations of Ortibus et al.³³ Future studies should consider alternative screening methods tailored to children with

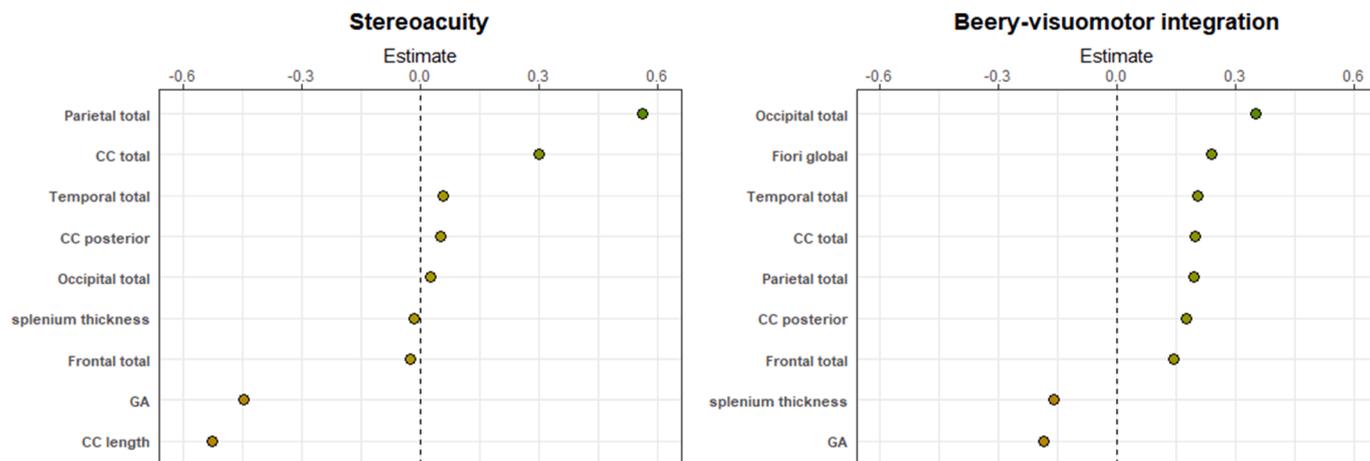


FIGURE 4. The predictors of the elastic-net regularized regression models with at least an acceptable discrimination for impairments on the visual assessments. The average estimate is displayed for only the predictors that were included in at least one fold of the leave-one-out-cross-validation. Abbreviations: Beery = Beery-Buktenica Test of Visual-Motor Integration, Sixth Edition; CC = corpus callosum; GA = gestational age. The color version of this figure is available in the online edition.

CP such as the Visual Function Classification Scale, a five-level system specifically designed for screening functional vision in this population.⁶⁵

Remarkably, although 39% of children presented with lesions to the thalami, in contrast with previous findings, no association was found with visual outcomes.¹⁰ Differences could be explained by the fact that we did not include a visual total score, but we specifically studied different visual functions. Since the role of the thalami in visual development is well recognized,²¹ further studies using automatic brain parcellation⁶⁶ and diffusion MRI might help in elucidating the relation between the thalami and specific visual functions in children with uCP.

Overall, in the regression analysis, we acknowledge that only the models of impaired stereoacuity and visuomotor integration showed at least acceptable discrimination, with tiny to moderate effect sizes. A possible explanation is the relatively small sample size, which could lead to imprecise parameter estimates of the regression models. Nevertheless, we performed elastic-net regularized regression which allowed to handle more predictors compared to the sample size,⁶⁷ compensating for the risk of overfitting. Additionally, to the researcher's knowledge, for the first time, we showed that specific brain damage and differences in gestational age can predict distinct visual impairments in children with uCP. Despite its limitations and the explorative nature of our study, our findings are promising since they can be the starting point to understand, based on standardized methods accessible to clinicians, which visual functions could be more at risk of impairments based on early brain injury in children with uCP. Based on our findings, we would suggest that in children with uCP, presenting with damage to the WM parietal lobe and shorter CC length, particular attention should be given to the assessment of stereoacuity, while in those with damage to the WM occipital and temporal lobes to the assessment of VMI. Additionally, in children with uCP born preterm, we recommend giving specific attention to geniculostriate assessments, with particular consideration to stereoacuity, in children with parietal lobe damage, given its association with deficits in this area.

Conclusions

In conclusion, using sMRI scoring methods, we first showed that in children with uCP prematurity is mainly related to reduced geniculostriate functions and parietal lobe WM lesions. Secondly, we found that CC damage and length are related to nearly all visual outcomes, while the relation between visual functions and WM lobe damage depends on the location. Lastly, our explorative analysis suggests that lesions to the WM lobes and reduced CC length are potentially useful predictors of stereoacuity and VMI impairments in children with uCP. Our results could guide clinicians in directing their attention to specific visual assessments based on early brain injury, to prevent visual function worsening that can severely impact the overall functioning and quality of life of children with uCP.

CRedit authorship contribution statement

Monica Crotti: Writing – original draft, Investigation, Conceptualization, Visualization, Formal analysis, Writing – review & editing, Methodology, Data curation. **Nofar Ben Itzhak:** Writing – review & editing, Methodology, Writing – original draft, Conceptualization, Supervision. **Lisa Maillieux:** Supervision, Writing – review & editing, Methodology, Writing – original draft, Conceptualization. **Lize Kleeren:** Methodology, Conceptualization, Writing – review & editing, Investigation, Writing – original draft, Data curation. **Lisa Decraene:** Writing – review & editing, Data

curation, Methodology, Investigation. **Nicolas Leenaerts:** Writing – review & editing, Methodology, Writing – original draft, Formal analysis, Visualization, Conceptualization. **Manuel Lubián-Gutiérrez:** Writing – original draft, Methodology, Writing – review & editing, Conceptualization. **Hilde Feys:** Supervision, Writing – review & editing, Funding acquisition, Writing – original draft. **Els Ortibus:** Writing – original draft, Supervision, Conceptualization, Writing – review & editing, Methodology, Funding acquisition.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pediatrneurol.2026.01.023>.

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