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Cerebral/Cortical Visual Impairment Classification and Categorization Using Eye Tracking Measures of Oculomotor Function

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Purpose: Cerebral/cortical visual impairment (CVI) is a leading cause of pediatric visual impairment and is frequently associated with abnormal ocular motility. Eye tracking has previously been used to characterize oculomotor function in CVI. The purpose of this study was to evaluate the utility of eye tracking in diagnosis, categorization, and prognostication of CVI.

Design: Prospective longitudinal study.

Participants: Thirty-nine children with CVI and 41 age-matched controls.

Methods: Children with CVI underwent 4 eye tracking sessions over 1 year, and age-matched controls completed 1 eye tracking session. Fixations and saccades were labeled by the eye tracking software and used to compute 9 oculomotor features. In children with CVI, unsupervised data-driven clustering analysis using these 9 features was performed to identify 3 CVI eye tracking oculomotor groups. Clinical and demographic characteristics of eye tracking oculomotor groups were compared.

Main Outcome Measures: (1) Area under the curve (AUC) for eye tracking oculomotor features in classifying patients with CVI and controls; (2) differences between 3 CVI eye tracking oculomotor groups on clinical and demographic characteristics; and (3) change in visual acuity (VA) over 1 year in 3 CVI eye tracking oculomotor groups.

Results: Six oculomotor features (fixation and saccade latency, frequency, and off-screen proportion) had an AUC $\geq$0.90 in classifying children with CVI and controls ($P < 0.0001$). Cerebral/cortical visual impairment eye tracking oculomotor groups had significantly different VA ($P < 0.0001$) and change in VA over 1 year ($P = 0.049$). Patients in group B, who had the greatest improvement in VA, were younger and had higher rates of term hypoxic ischemic encephalopathy.

Conclusions: Eye tracking measures of oculomotor function accurately distinguish between children with CVI and age-matched controls. Clustering analysis revealed 3 CVI eye tracking oculomotor groups with prognostic significance. Eye tracking shows promise as an objective, quantitative measure of oculomotor function in CVI that may in future be useful in both clinical practice (for longitudinal assessment, prognostication, and guiding individualized interventions) and research (as an outcome measure or method to stratify patients in clinical trials).

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Cerebral/cortical visual impairment (CVI) is a leading cause of pediatric visual impairment in the United States and other developed nations and is increasing in prevalence in developing countries.[1,2] It has been defined as "a spectrum of visual impairments caused by an underlying brain abnormality that affects the development of visual processing pathways and is characterized by deficits in visual function and functional vision."[3] Cerebral/cortical visual impairment results from damage to the visual pathways in the brain. The causes of CVI are heterogeneous and include hypoxic ischemic encephalopathy (HIE), prematurity with periventricular leukomalacia (PVL), hydrocephalus, trauma, seizures, and genetic disorders, among others.[1,2,4–7] The visual characteristics of CVI are also heterogeneous and may include decreased visual acuity (VA), higher-order visual perceptual deficits, and oculomotor abnormalities.[8] Although several investigators have described challenges with VA[9,10] and difficulties with visual processing (such as visual search and face and object recognition),[11–13] there are fewer studies characterizing oculomotor deficits in CVI.[14–20] However, Salati et al[14] noted that abnormalities of saccades and pursuits were observed in >90% of patients with CVI following perinatal hypoxia. This suggests that oculomotor features of CVI may be more consistently present than other features of CVI (e.g., difficulties with object and face recognition), which can be highly variable. Thus, oculomotor parameters may be useful for classification or diagnosis of CVI. Indeed, such oculomotor findings have

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already been included in the European multidisciplinary guidelines for diagnosis of CVI.[21]

Furthermore, oculomotor abnormalities vary in severity in individuals with CVI and may progress in stages.[14] This suggests that oculomotor parameters may be useful for categorizing patients with CVI. To date, several methods of subtyping individuals with CVI have been proposed, but none has been universally adopted.[22–24]

The purpose of this project was to assess the utility of eye tracking oculomotor parameters for (1) classification and (2) categorization of children with CVI.

Methods

This study was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki and the United States Health Insurance Portability and Accountability Act of 1996. Informed consent was obtained from the parent or legal guardian of all participants.

Inclusion and Exclusion Criteria

We prospectively recruited children with a diagnosis of CVI from our pediatric neuro-ophthalmology clinic. We diagnosed CVI in children with reduced VA with a normal eye examination or VA worse than expected based on the degree of ocular pathology. (The only intraocular pathology permitted for study inclusion was mild optic atrophy.) Additionally, children were required to have a known neurologic risk factor for CVI (e.g., prematurity with PVL or HIE). We did not include patients with visual perceptual deficits who had normal VA for age.

Inclusion criteria for the CVI group were diagnosis of CVI (as defined in the previous paragraph), age between 12 months and 12 years, and VA sufficient to fixate large objects on a computer monitor (required to participate in eye tracking). Quantitatively, the minimum VA needed to perform preferential looking in our eye tracking protocol was 0.25 cycles per degree (cpd), which corresponds approximately to the highest grating acuity assessed by Teller Acuity Cards (0.23 cpd). We excluded patients with photosensitive epilepsy and those with any intraocular abnormality except mild optic atrophy, which was allowed because of the high proportion of optic atrophy among our patients with CVI. We also excluded patients with oculomotor abnormalities that would preclude accurate assessment of visual function based on visual behavior, such as oculomotor apraxia, as well as those with nystagmus. Patients with nystagmus were excluded because the proprietary eye tracking software (EyeLink DataViewer 4.3, SR Research) used in this study employs an automated algorithm for parsing eye tracking data into fixations and saccades, which may be inaccurate in patients with nystagmus. However, patients with increased saccade latency and strabismus without limitation of ocular ductions were included in this study.

We also recruited age-matched typically developing controls through a web-based recruitment service (BuildClinical, LLC). All controls underwent a screening eye examination confirming normal VA for age and normal ocular motility. Visual acuity was tested using Snellen, HOTV, or Lea charts for typically developing children who were able to verbalize or match pictures or letters. Teller Acuity Cards were used in younger participants. Controls were required to have no ophthalmologic condition (other than corrected refractive error) and no neurologic or neurodevelopmental diagnoses.

Overview of Study Visits

Participants with CVI underwent study visits with eye tracking at baseline, 1 month, 6 months, and 12 months. Controls completed 1 eye tracking visit, during which the screening eye examination was performed. In patients with CVI, standard-of-care dilated or undilated ophthalmology examinations were performed at baseline, 6 months, and 12 months; these eye examinations were coordinated with eye tracking visits at the respective time points.

Ophthalmology Examination

Complete pediatric ophthalmologic examination was performed in children with CVI, including assessment of VA (using a 6-level scale of visual behavior for nonverbal children with CVI[25]), fixation preference, pupillary examination, ocular motility, and anterior segment examination. At baseline and 1 year, dilated fundus examination with cycloplegic refraction was performed. Ocular alignment was assessed with alternate cover testing with prisms if possible, but most patients required measurement using the Krimsky test due to poor fixation and cooperation. Strabismus was diagnosed in patients with any manifest ocular deviation. In patients with strabismus, fixation preference was noted to facilitate eye tracking recording of the fixating eye. Amblyopia was diagnosed in patients with asymmetric visual behavior (or $\geq$0.2 logarithm of the minimum angle of resolution [logMAR] interocular acuity difference if optotype testing could be performed), in the setting of an amblyopia risk factor (strabismus or anisometropia). Refractive errors were considered significant if the American Academy of Ophthalmology Preferred Practice Pattern criteria for spectacle correction were met.[26] Optic atrophy was diagnosed based on optic nerve pallor, as assessed clinically by a pediatric neuro-ophthalmologist. OCT was not possible in any of our participants because of poor vision and cooperation.

Eye Tracking Data Acquisition

We collected eye tracking data using a previously published protocol.[25,27] Briefly, children with CVI wearing their habitual spectacles were seated 60 cm from a computer monitor with an attached SR Research EyeLink 1000 eye tracker to monitor the direction of eye gaze. Recording was performed binocularly in patients without strabismus; in patients with strabismus, the fixating eye was recorded. The recording session began with 3-point calibration, followed by participants viewing still images and videos on the computer monitor for 10 minutes with no specific task instructions (free viewing). The experimental protocol included a series of high-contrast black-and-white vertical square-wave gratings presented randomly to the right or left side of the screen on a luminance-matched gray background. The grating frequency ranged from 0.25 to 20 cpd. These stimuli were used to assess grating acuity by preferential looking, as previously described.[25,27] The remainder of the eye tracking protocol included stimuli to assess other psychophysical measures by preferential looking, as well as realistic and cartoon images and videos to assess visual attention. (The results of these experiments will be reported elsewhere.) Throughout the 10-minute eye tracking session (divided into 163 trials), the X and Y coordinates of each eye were recorded at 500 Hz. This enabled calculation of oculomotor parameters described below.

Eye Tracking Measures of Ocular Motility

The SR Research EyeLink system parsed the eye tracking data into fixations and saccades. Fixations were defined as events when the eyes moved less than 0.1° over a duration of at least 100 ms.

Events were labeled as saccades when eye velocity exceeded 30°/second, acceleration was greater than 8000°/second^2, and amplitude was above 0.1°.

A list of fixations and saccades for each recording session was exported from the EyeLink data analysis software (DataViewer 4.3, SR Research). The following fixation parameters were included: start time, end time, X and Y coordinates, and duration. The following saccade parameters were exported: start time, end time, start and end X and Y coordinates, peak velocity, and amplitude.

Data cleaning was performed to eliminate nonphysiologic fixations and saccades. Fixations with duration or start time <100 ms and saccades with amplitude <0°, velocity <30°/second, or start time prior to trial onset were removed. We also excluded fixations and saccades that were off the screen from the analyses below because the eye tracking camera only reliably records the X and Y coordinates of the eyes within the trackable area (on the screen). However, we used the off-screen data to calculate the proportion of fixations and saccades off the screen.

We then calculated the following oculomotor parameters for each participant:

1. Average fixation latency. Fixation latency was measured as the time (in ms) to the first fixation per trial.
2. Average fixation duration (ms).
3. Fixation frequency, calculated as the total number of fixations per recording session divided by total recording time (600 seconds).
4. Proportion of fixations off screen.
5. Average saccade latency. Saccade latency was measured as the time (in ms) to first saccade at the beginning of each trial.
6. Saccade peak velocity (degrees/second).
7. Average saccade amplitude (degrees).
8. Saccade frequency, calculated as the total number of saccades per recording session divided by total recording time (600 seconds).
9. Proportion of saccades off screen.

Statistical Analysis

Classification (CVI vs. Controls). Using first-visit eye tracking recordings, we compared patients with CVI to age-matched controls on the 9 oculomotor parameters using Mann−Whitney tests. We also calculated the area under the curve (AUC) for each oculomotor parameter. Next, we determined the optimal threshold for classifying CVI for each oculomotor parameter based on the value that maximized the likelihood ratio while maintaining sensitivity greater than 90%. Finally, using these thresholds, we assessed the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the parameters that had an AUC ≥0.90 for classifying CVI and control participants.

Categorization (CVI Eye Tracking Oculomotor Groups). We performed unsupervised data-driven clustering analysis of oculomotor data from CVI eye tracking recordings. Data from the 9 oculomotor parameters were normalized, and then, principal component analysis was performed to reduce dimensionality. The first 3 principal components, which accounted for >90% of variance, were selected for inclusion in the clustering model. The contributions of the 9 oculomotor parameters to these 3 principal components are shown in Table S1 (available at www.ophthalmologyscience.org).

Next, we performed k-means clustering using these 3 principal components. An elbow plot was generated to determine the optimal number of clusters, which was 3. We ran a k-means algorithm using 3 clusters, resulting in a group assignment for each recording (Fig S1, available at www.ophthalmologyscience.org). These clusters constituted the 3 CVI eye tracking oculomotor groups.

Clinical and Demographic Characterization of CVI Oculomotor Groups

First, we assessed the relationship between group assignment and each of the 9 oculomotor parameters to confirm that our clustering algorithm successfully identified distinct oculomotor groups. Groups were compared using Kruskal−Wallis tests.

Next, we compared oculomotor groups on the basis of age, sex, race/ethnicity, primary language, neurologic comorbidities, and ophthalmologic comorbidities using Kruskal−Wallis tests for continuous variables and Fisher exact tests for categorical variables. The oculomotor group assignment at the baseline visit was used for this analysis. Visual acuity, as measured by preferential looking during the eye tracking session, was also compared among groups using the Kruskal−Wallis test.

Finally, we evaluated whether demographic and clinical factors and oculomotor group assignment at baseline were associated with change in VA over 1 year. We used VA measured by eye tracking preferential looking, since we previously found that this method had higher reliability and validity than Teller Acuity Cards in children with CVI.[27] Change in VA (in logMAR) was calculated as (VA at the 1-year visit) − (VA at the baseline visit). For univariable analysis, simple logistic regression was used for continuous variables (age and baseline VA), Mann−Whitney tests for dichotomous variables (sex and the presence of ophthalmic and neurologic comorbidities including amblyopia, strabismus, optic atrophy, prematurity with PVL, seizures, hydrocephalus, HIE, head trauma, meningoencephalitis, metabolic or genetic disorders, structural brain malformations, and cerebral palsy), and the Kruskal−Wallis test was used for oculomotor group assignment because this variable included 3 categories. Factors significant at $P \leq 0.10$ were included in a multivariate logistic regression model to determine variables associated with change in VA over 1 year.

Principal component analysis and k-means clustering were performed using the scikit-learn Python module.[28] All other analyses were conducted in Prism (version 10.1.1; GraphPad Software). P values <0.05 were considered significant.

Results

We prospectively recruited 39 children with CVI (mean age 4.7 ± 2.9 years) and 41 (5.6 ± 3.4 years) age-matched controls (Table 1). The CVI participants completed a total

Table 1. Demographic Characteristics of Children with Cerebral/Cortical Visual Impairment (CVI) and Age-Matched Typically Developing Controls Included in This Study

	CVI (n = 39)	Controls (n = 41)	P Value
Age (mean ± SD, yrs)	4.7 ± 2.9	5.6 ± 3.4	0.21
Sex (M)	20 (51%)	15 (37%)	0.19
Race/ethnicity			<0.0001*
Non-Hispanic White	13 (33%)	7 (17%)	
Hispanic	19 (49%)	5 (12%)	
Black	2 (5%)	0 (0%)	
Asian	2 (5%)	11 (27%)	
Other or unknown	3 (8%)	18 (44%)	

M = male; SD = standard deviation.
*$P < 0.05$.

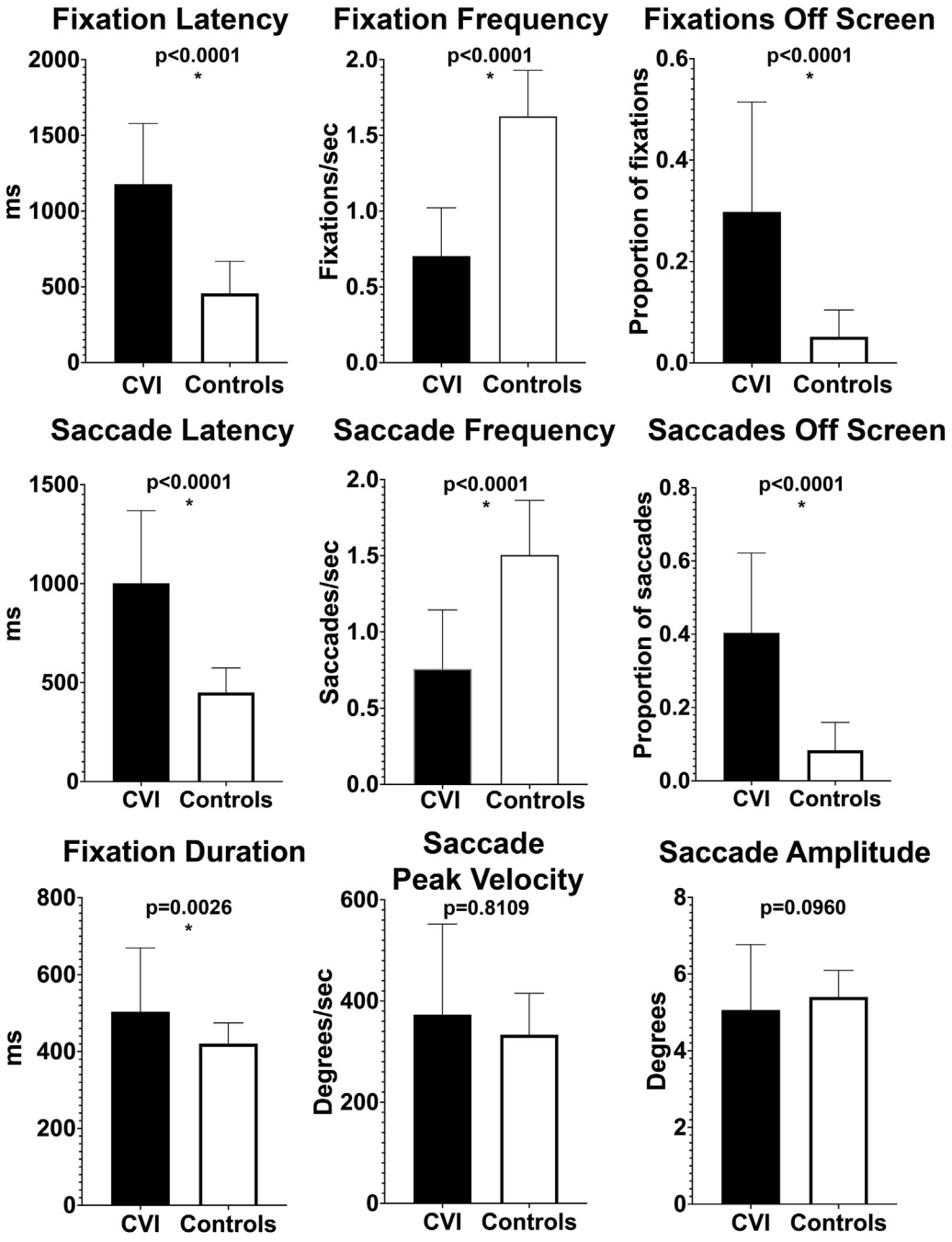

Figure 1. Comparison of 9 eye tracking oculomotor parameters in children with cerebral/cortical visual impairment (CVI) and age-matched typically developing controls.

of 119 eye tracking recording sessions, and controls completed 41 sessions.

Classification

Controls and CVI participants significantly differed on all oculomotor attributes evaluated, except for saccade peak velocity and amplitude (Fig 1, $P \leq 0.0026$). Children with CVI had significantly longer fixation and saccade latency, longer fixation duration, and generated fewer fixations and saccades overall. In children with CVI, a greater proportion of both fixations and saccades were directed off the display monitor.

To determine whether oculomotor features could distinguish CVI recordings from controls, we calculated the AUC for each of the 9 oculomotor characteristics. The receiver operating characteristic curves for the 6 features with an AUC $\geq$0.90 are shown in Figure 2A and B. Fixation and

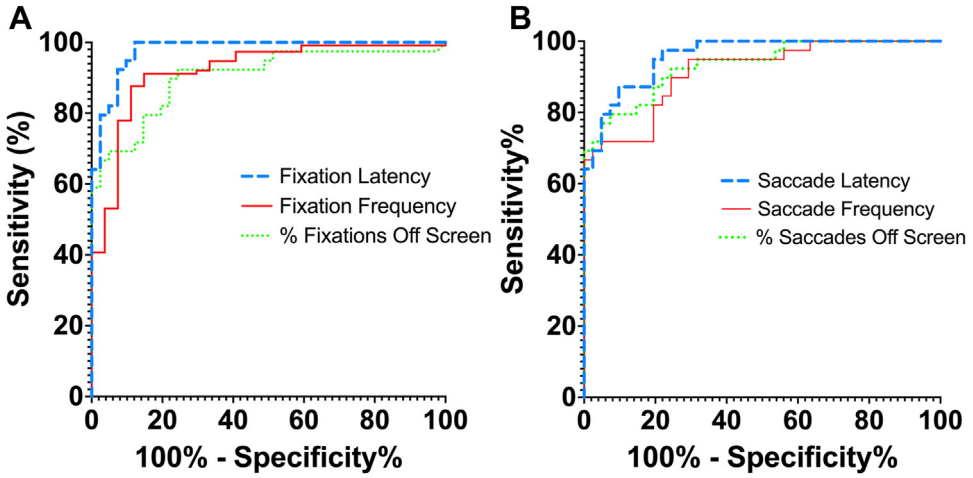

Figure 2. A, Receiver operating characteristic curves for the 3 most discriminative fixation features in classifying children with cerebral/cortical visual impairment and controls. **B,** Receiver operating characteristic curves for the 3 most discriminative saccade features.

saccade latency and frequency, as well as the proportion of fixations and saccades off screen, each achieved an AUC of $\geq$0.90 in classifying eye tracking recordings as representing CVI or control participants. The optimal classification thresholds for each of these parameters are shown in Table 2. Using these thresholds, we calculated that the accuracy of the top 3 fixation metrics in distinguishing between patients with CVI and controls ranged from 83.8% to 92.5%, whereas the accuracy of saccade metrics ranged from 82.5% to 87.5%. Sensitivity, specificity, positive predictive values, and negative predictive values of these metrics are also provided in Table 2.

The AUC values for the 3 remaining oculomotor characteristics not shown in Figure 2 were 0.69 for fixation duration ($P = 0.0029$), 0.52 for saccade peak velocity ($P = 0.81$), and 0.61 for saccade amplitude ($P = 0.095$).

Categorization

Clustering analysis resulted in 3 CVI eye tracking oculomotor groups, which were labeled "A", "B", and "C." As shown in Figure 3, the 3 groups demonstrated increasing differences from control participants on eye tracking oculomotor parameters, with group C displaying the most abnormal oculomotor function. The 3 groups significantly differed from one another on all oculomotor characteristics ($P \leq 0.0001$) except for saccade amplitude.

The clinical characteristics of the 3 CVI eye tracking oculomotor groups are shown in Table 3. Patients in group B were younger at study enrollment (2.9 $\pm$ 2.0 vs. 7.1 $\pm$ 2.1 and 5.5 $\pm$ 2.9 years, $P = 0.0022$). Children in group B were also more likely to have experienced term HIE than those in other groups (50% vs. 25% and 8%, $P = 0.04$). Although prematurity with PVL is generally considered to be hypoxic ischemic in origin, we considered this a separate condition from perinatal or early-onset acquired HIE in term infants, since the manifestations frequently differ.[29] There were no significant differences among groups in rates of PVL.

Figure 4 demonstrates the relationship between eye tracking oculomotor group assignment and VA. There was a significant difference among the groups, with the best (lowest logMAR) VA in group A and the worst VA in group C ($P < 0.0001$).

Finally, among the 25 patients who completed 1 year follow-up, we assessed the association between change in VA over 1 year (in logMAR) and (1) demographic factors, (2) clinical factors, and (3) oculomotor group assignment at baseline. Significant factors (at $P \leq 0.10$) on univariate analysis included baseline VA ($P = 0.01$), presence of a structural brain malformation ($P = 0.02$), and oculomotor group assignment ($P = 0.10$). Specifically, VA improved more in group B compared to groups A and C (Fig 5). On multivariate regression, better (lower logMAR) baseline VA ($P = 0.0099$), structural brain malformation ($P = 0.033$), and oculomotor group B assignment ($P = 0.049$) remained significantly associated with improvement in VA over 1 year.

Discussion

In this prospective study, we found that oculomotor features assessed by eye tracking could distinguish between children with CVI and age-matched typically developing controls with high accuracy. Furthermore, clustering analysis resulted in 3 CVI eye tracking oculomotor groups, which differed significantly in both efferent and afferent function. CVI eye tracking oculomotor group assignment at baseline was predictive of change in VA over 1 year.

In our classification analysis, we found that the oculomotor features that most accurately discriminated between children with CVI and controls were fixation frequency and fixation latency. Decreased fixation and saccade frequency in individuals with CVI are suggestive of less visual exploration during eye tracking sessions. Salati et al[14] noted abnormal scanning of the environment in 78% of children with CVI following HIE, using video recordings to assess ocular motility, which was consistent with our findings. In

Table 2. Area Under the Curve (AUC), Accuracy, Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of the 6 Oculomotor Features with AUC ≥0.90 for Classifying Eye Tracking Recordings from Patients with cerebral/cortical visual impairment (CVI) and Age-Matched Controls

	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV
Fixation latency (>728.9 ms)	0.98 (0.95–1.00) $P < 0.0001$	92.5% (84.6%–96.5%)	92.3% (79.7%–97.3%)	92.7% (80.6%–97.5%)	92.3% (79.7%–97.3%)	92.7% (80.6%–97.5%)
Fixation frequency (<1.183 sec^{-1})	0.98 (0.96–1.00) $P < 0.0001$	92.5% (84.6%–96.5%)	92.3% (79.7%–97.3%)	92.7% (80.6%–97.5%)	92.3% (79.7%–97.3%)	92.7% (80.6%–97.5%)
Fixations off screen (>0.08004)	0.90 (0.83–0.97) $P < 0.0001$	83.8% (74.2%–90.3%)	92.3% (79.7%–97.3%)	75.6% (60.7%–86.2%)	78.3% (64.4%–87.7%)	91.2% (77.0%–97.0%)
Saccade latency (>543.5 ms)	0.96 (0.92–0.99) $P < 0.0001$	87.5% (78.5%–93.1%)	94.9% (83.1%–98.6%)	80.5% (66.0%–89.8%)	82.2% (68.7%–90.7%)	94.3% (81.4%–98.4%)
Saccade frequency (<1.288 sec^{-1})	0.91 (0.85–0.97) $P < 0.0001$	82.5% (72.7%–89.3%)	94.9% (83.1%–98.6%)	70.7% (55.5%–82.4%)	75.5% (61.9%–85.4%)	93.5% (79.3%–98.2%)
Saccades off screen (>0.1290)	0.93 (0.88–0.98) $P < 0.0001$	83.8% (74.2%–90.3%)	92.3% (79.7%–97.3%)	75.6% (60.7%–86.2%)	78.3% (64.4%–87.7%)	91.2% (77.0%–97.0%)

1987, Jan et al[5] published a case series of 50 children with CVI, all of whom were found to exhibit decreased visual attention and lack of visual curiosity. Using eye tracking, we can now precisely quantify this deficit and establish a threshold suggestive of CVI (fixation frequency <1.183 fixations/second).

It is important to note that in our experiments, children were advised to look at the computer monitor but were not provided any specific instructions for exploring the images or performing a task. In previous studies of individuals with CVI who performed visual search tasks while undergoing eye tracking, visual search area was larger than controls, indicating greater exploration of the environment.[11] Thus, the degree of visual exploration in individuals with CVI may be modified by whether specific visual tasks are attempted.

Both fixation and saccade latency were highly discriminative of CVI, which is consistent with prior reports. "Visual latency" is one of the 10 characteristics of CVI in the widely used CVI Range functional vision assessment.[30,31] Fixation latency is also called reaction time to fixation, and this eye tracking parameter has been shown to be significantly elevated in children with CVI compared to controls in multiple studies.[15,16,19,20,32,33] Reaction time to fixation is one of the visual orienting functions suggested by the European multidisciplinary guidelines for diagnosis of CVI.[21] Furthermore, increased saccade latency has been demonstrated by eye tracking in children after brain injury.[17]

We also found that children with CVI made significantly more fixations and saccades "off screen," away from the computer monitor displaying the experimental stimuli. This suggests a deficit in visual attention in our patients with CVI.[34] We reduced visual distractors in our eye tracking laboratory by turning the lights off and using blackout curtains. However, participants looked away from the screen for various reasons during the recording sessions; most commonly, they appeared to be searching for their parents.

Prior investigators have reported that fixation duration is decreased in children with CVI,[16,19] whereas we found that fixation duration was borderline increased in our patients. The reason for this discrepancy is unclear but could relate to differences in the eye tracking protocol. In our study, participants viewed naturalistic or cartoon scenes encompassing the entire trackable area of the screen. In contrast, the previously cited studies displayed a cartoon or other simple image spanning 6° in the corner of the screen. It is possible that our experiment encouraged typically developing controls to explore the scenes with multiple shorter fixations, whereas the images in the corner of the screen stimulated longer, sustained fixations. This would lead to deficits in the opposite directions in children with CVI, as observed.

The 2 oculomotor parameters in our study that were not significantly different in children with CVI were saccade peak velocity and amplitude. This is consistent with prior reports that the main sequence is unaltered in CVI.[18]

In this study, we propose a CVI categorization scheme based on clustering analysis of eye tracking oculomotor

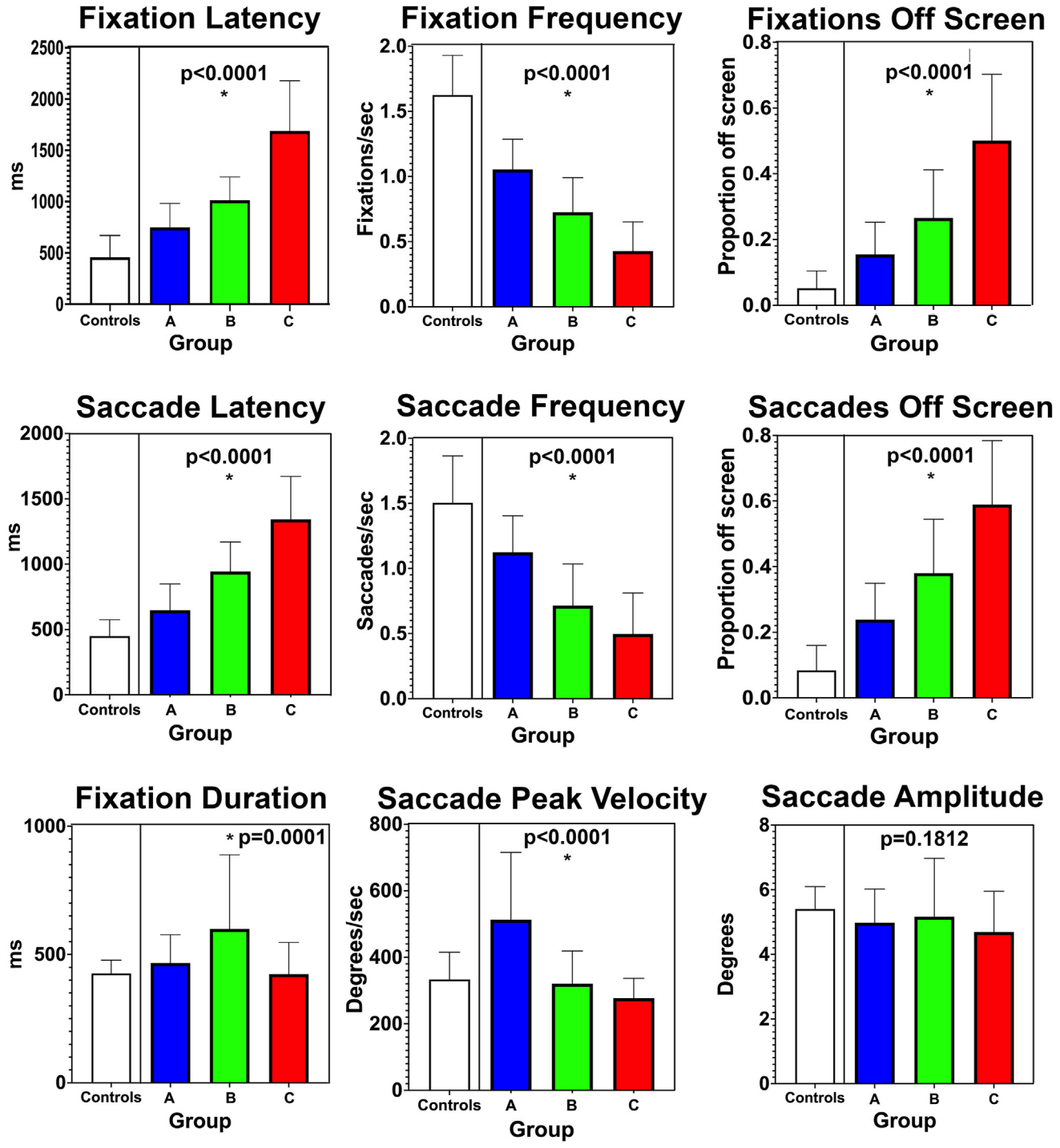

Figure 3. Comparison of oculomotor parameters in the 3 cerebral/cortical visual impairment (CVI) eye tracking oculomotor groups (A, B, and C) and age-matched typically developing controls.

features, which resulted in 3 CVI eye tracking oculomotor groups. Currently, there is no consensus on the appropriate method to categorize individuals with CVI, who are quite diverse with regards to age, underlying neurologic disorders, VA, and visual processing ability. Philip and Dutton proposed 3 groups of patients with CVI based on the level of functioning: (1) those with profound visual impairment, (2) those with impaired but functionally useful vision, as well as cognitive and often motor challenges, and (3) those who have impaired but functionally useful vision and who work at or near the expected academic level for their age.[23] Other investigators have proposed that grouping patients with CVI anatomically (based on involvement of the optic radiations or occipital lobe)[35–37] or electrophysiologically (based on

Table 3. Demographic and Clinical Characteristics of Patients in 3 Cerebral/Cortical Visual Impairment (CVI) Eye Tracking Oculomotor Groups, Based on Baseline Categorization

	A n = 13	B n = 8	C n = 18	*P* Value
Age	7.1 ± 2.1	2.9 ± 2.0	5.5 ± 2.9	0.0022*
Sex (M)	3 (38%)	9 (50%)	8 (62%)	0.59
Race/ethnicity				0.50
Non-Hispanic White	3 (38%)	5 (28%)	5 (39%)	
Hispanic	3 (38%)	9 (50%)	7 (54%)	
Black	1 (13%)	1 (6%)	0	
Asian	1 (13%)	0	1 (8%)	
Other or unknown	0	3 (17%)	0	
Primary language				>0.99
English	7 (88%)	14 (78%)	10 (77%)	
Spanish	1 (13%)	4 (22%)	3 (23%)	
Neurologic comorbidities				
Prematurity with periventricular leukomalacia	1 (13%)	3 (17%)	5 (39%)	0.36
Seizures	6 (75%)	12 (67%)	11 (85%)	0.57
Hydrocephalus	0	1 (5%)	4 (31%)	0.09
Hypoxic ischemic encephalopathy	2 (25%)	9 (50%)	1 (8%)	0.04*
Meningoencephalitis	1 (13%)	1 (6%)	0	0.48
Genetic disorder	2 (25%)	6 (33%)	7 (54%)	0.44
Structural brain malformation	3 (38%)	5 (28%)	4 (31%)	0.91
Cerebral palsy	2 (25%)	5 (28%)	5 (38%)	0.82
Ophthalmologic conditions				
Optic atrophy	3 (38%)	5 (28%)	7 (54%)	0.36
Amblyopia	0	3 (17%)	1 (8%)	0.52
Strabismus	5 (63%)	15 (83%)	10 (77%)	0.48
Significant refractive error†	3 (38%)	7 (39%)	7 (54%)	0.70

M = male.
*$P < 0.05$.
†Refractive errors were considered significant if they met criteria for spectacle correction per the AAO Preferred Practice Pattern.[26]

visual evoked potential responses)[38] may have prognostic implications.

Clustering analysis has been used in 2 prior studies for CVI categorization. Sakki et al[22] performed hierarchical clustering in 43 individuals with CVI based on a battery of assessments, including tests of VA, visual fields, contrast sensitivity, stereoacuity, visual perception, visuomotor integration, cognition, quality of life, and a questionnaire on CVI characteristics (the CVI Inventory). Hierarchical clustering of data resulted in 2 groups (A1 and A2), in addition to a third group of participants who could not complete the battery. Philip et al[24] performed clustering in 51 individuals with CVI using an extended battery (adding eye tracking measures and optic nerve characteristics). The extended battery resulted in 4 groups of patients with CVI: subtle characteristics, higher-level visual function deficits, lower-level visual function deficits, and higher- and lower-level visual function deficits. We identified 3 groups of patients with CVI by eye tracking only. The potential advantage of our technique over those previously described is the efficiency of requiring only 1 assessment (eye tracking) for categorization. Despite including no clinical data in our clustering analysis, our CVI eye tracking oculomotor groups were significantly correlated with VA. Moreover, group assignment was predictive of change in VA over one year, which has not been reported in other categorization schemes.

In reviewing the CVI eye tracking oculomotor groups, we found that the groups significantly differed on oculomotor function, as expected. Additionally, VA was significantly different among groups. This indicates that interrogating the efferent visual system may provide some insight into afferent function in this disorder. Few prior studies have investigated the association between ocular motility and VA in CVI. However, Kooiker et al[16] reported that their eye tracking parameters (reaction time to fixation, fixation duration, and gaze fixation area [a measure of fixation stability]) did not correlate with VA. Possible reasons for the disparity may relate to the specific eye tracking parameters used (in our study, we included saccade as well as fixation metrics), as well as the clustering technique employed in this study. Moreover, in the study by Kooiker et al, 11 of 29 patients had congenital nystagmus, which was considered a form of central visual impairment. However, in our study, we excluded patients with nystagmus because we relied on an automated algorithm to parse eye movements into fixations and saccades, and the oscillations characteristic of nystagmus could result in inaccurate eye movement classification.

Finally, we found that CVI eye tracking oculomotor group assignment at baseline was associated with change in VA over 1 year. Specifically, patients in group B at baseline had significantly greater improvement in VA on multivariate regression analysis. Group B was characterized by patients who were younger with a higher frequency of HIE. Previous

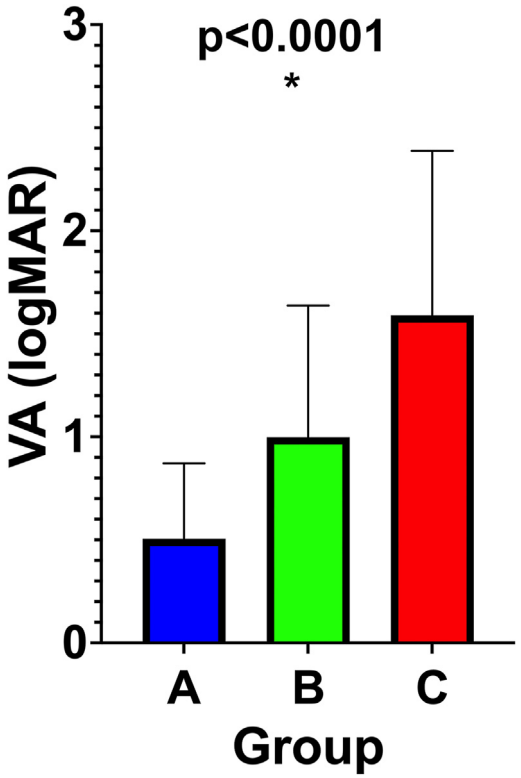

Figure 4. Comparison of visual acuity (VA) in the 3 cerebral/cortical visual impairment eye tracking oculomotor groups. logMAR = logarithm of the minimum angle of resolution.

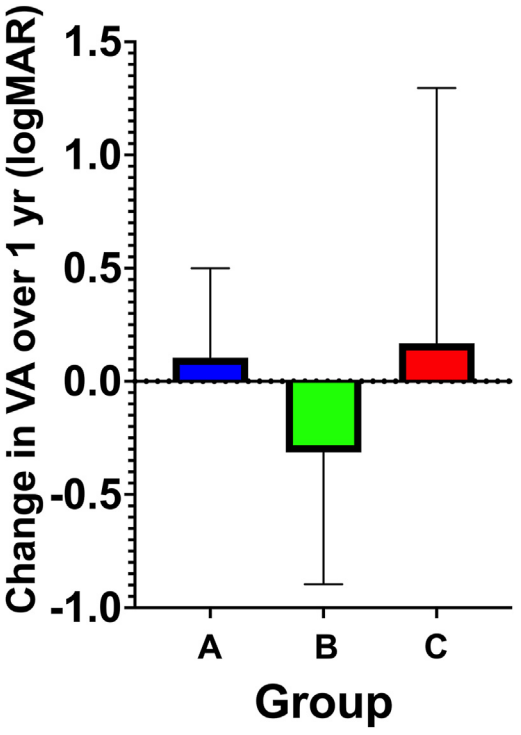

Figure 5. Change in visual acuity (VA) over 1 year in logarithm of the minimum angle of resolution (logMAR) in patients in the 3 cerebral/cortical visual impairment (CVI) eye tracking oculomotor groups, based on initial categorization.

investigators have found that younger age at diagnosis of CVI (<3 years) is associated with better visual prognosis.[6,39,40] This is likely related to the known effect of age on neuroplasticity of visual pathways (as well as other pathways) in the brain.[41] The literature is mixed with respect to the impact of etiology on visual prognosis in CVI.[7,40,42] Handa et al[40] reported that there was no relationship between etiology and visual improvement, whereas Jimenez-Gomez et al[42] found that perinatal HIE and seizures were associated with worse visual outcome. In contrast, Khetpal and Donahue[7] reported that children with CVI due to HIE and hydrocephalus had better visual prognosis than those with other etiologies. Surprisingly, although younger age and HIE were associated with group B assignment, when analyzed independent of the oculomotor group, these factors were not significantly associated with change in VA over 1 year. However, the presence of a structural brain malformation was associated with significantly greater improvement in VA. This has not been previously reported in the literature. We hypothesize that this could be related to the nonprogressive nature of congenital structural brain malformations. However, further research is necessary to clarify the association between neurologic disorders and visual prognosis in CVI.

Other than etiology and age, clinical factors that have been associated with improved vision in children with CVI include good control of underlying neurologic conditions (particularly seizures) and participating in therapies, including early childhood intervention, physical and occupational therapy, and wearing glasses.[40,42] Our study adds oculomotor function to the list of potential prognostic markers in CVI.

The main limitation of this study is the relatively small sample size. Because of this, the analysis must be considered exploratory. Moreover, some patients were lost to follow-up, with 1-year data available for only 25 (64%) patients with CVI. Additionally, we used automated eye tracking software to identify fixations and saccades. This is ideal to promote large-scale adoption of our technique, but the lack of manual inspection of eye movement traces precludes us from determining whether fixations and saccades were accurately classified in all cases. Because we used this automated algorithm, we also elected to exclude patients with nystagmus, which may introduce errors in parsing eye tracking data as saccades and fixations. Approximately 20% of individuals with CVI have nystagmus,[7] so future studies should determine whether the inclusion of patients with nystagmus confounds the results of ocular motility analysis. Eye tracking in patients with strabismus also presents challenges. When evaluating patients with strabismus, we recorded from the fixating eye, and we did not detect any cases where fixation alternated. In other patients with alternating fixation (not included in this study), we have successfully performed eye tracking with 1 eye occluded, to prevent switching fixation. However, there may be differences in monocular

vs. binocular eye movements, especially in patients with latent nystagmus. Finally, because we required patients to have VA sufficient to track images on a computer monitor in order to perform eye tracking, our study does not represent patients with CVI with the lowest levels of visual function.

In summary, eye tracking measures of ocular motility accurately distinguish between children with CVI and age-matched controls. Clustering analysis of eye tracking parameters revealed 3 CVI eye tracking oculomotor groups, which correlated with VA both at the time of recording and over 1 year. Eye tracking to measure oculomotor function in children with CVI shows promise as an objective and quantitative technique that may be useful for prognostication, longitudinal assessment, and inclusion as an outcome measure in future clinical trials.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. This study was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki and the United States Health Insurance Portability and Accountability Act of 1996. Informed consent was obtained from the parent or legal guardian of all participants.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Chang, Borchert

Data collection: Chang, Borchert

Analysis and interpretation: Chang, Borchert

Obtained funding: Chang

Overall responsibility: Chang, Borchert

Abbreviations and Acronyms:
AUC = area under the curve; **CVI** = cerebral/cortical visual impairment; **HIE** = hypoxic ischemic encephalopathy; **logMAR** = logarithm of the minimum angle of resolution; **PVL** = periventricular leukomalacia; **VA** = visual acuity.

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