Sweep Visual Evoked Potential Grating Acuity Thresholds Paradoxically Improve in Low-Luminance Conditions in Children with Cortical Visual Impairment

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Purpose. Children with cortical or cerebral visual impairment (CVI) often experience photophobia. In a study conducted to test whether this clinical phenomenon affects visual function, the sweep visual evoked potential (VEP) was used to evaluate cortical responses to grating stimuli in two luminance conditions: low and normal.

Methods. Twenty children (age range, 7 months to 4 years 10 months) with CVI and 17 age-matched control subjects were examined. Testing conditions consisted of a swept grating stimulus shown against a normal background luminance (109 cd/m^2) and against a low-luminance background (20 cd/m^2). Thresholds in these two luminance conditions were compared. Response amplitudes across the spatial frequency domain were also compared.

Results. Children with CVI paradoxically have improved grating acuity thresholds when the stimulus is shown using a low-luminance background ($P = 0.006$). Response amplitudes are also increased in low luminance. In control children, luminance had no significant effect on response amplitudes or thresholds.

Conclusions. Increased luminance causes a worsening of acuity thresholds in children with CVI. Response amplitudes are also diminished in normal luminance. This finding has implications for optimal viewing and learning conditions for children with CVI. (*Invest Ophthalmol Vis Sci.* 2006;47:3220–3224) DOI: 10.1167/iovs.05-1252

The leading cause of vision impairment in children in the Western world is cortical or cerebral visual impairment (CVI), caused by damage to the visual cortex or optic radiations.[1,2] CVI is frequently caused by perinatal hypoxia and ischemia, with premature birth an important etiological event in many cases. With nearly 12% of children in the United States born prematurely, it is easy to understand how CVI is emerging as an important and common cause of bilateral vision impairment in children.[3,4]

Affected children show poor visual acuity but have normal pupil responses and normal findings in eye examinations. Most children with CVI are either preverbal or nonverbal, making the quantitative diagnosis of reduced acuity, at times, a difficult task. Furthermore, children with CVI are rarely completely blinded and retain residual vision in various forms (e.g., reduced acuity or preservation of some visual field or of some color perception).[5]

Children with CVI also often exhibit behavior that is so consistently associated with the condition as to suggest that the behavior itself represents an adaptation to the vision deficit, enabling the afflicted child to gain advantage from some residual visual function. One such behavior, or symptom, is an attraction to light, or light-gazing.[1,6] The child with CVI stares at lights in a room with normal ambient lighting or at the window during daylight. Paradoxically, the same child may be intensely photophobic to brighter lights outdoors, in lighting conditions that would not bother normally sighted individuals. It is as though light coming into the brain cannot be modulated appropriately.

We explored the clinical observation of light sensitivity in children with CVI to learn whether luminance, or intensity of light, affects visual *acuity* in children with CVI. To test whether background luminance affects the vision of children with CVI, we performed an experiment in which grating acuity was measured electrophysiologically using two different background luminance conditions.[7] Previously, we found that moderate reductions in luminance background to 50 cd/m^2 sometimes resulted in improved VEP grating thresholds and sometimes did not.[7] In the present study, a background luminance that would normally reduce acuity thresholds was chosen for one condition (low luminance), and a normal luminance condition was chosen for the other (normal luminance). The goal was to learn optimized viewing conditions for children with CVI.

Materials and Methods

Subjects

VEPs were recorded in 20 patients with CVI (age range, 6 months to 5 years; Table 1) and in 17 age-matched normal infants and young children. Children had the CVI diagnosed clinically on the basis of reduced visual acuity with preserved pupillary reactions and normal results in eye examinations. One child with CVI had been born prematurely (32 weeks of gestational age). The others were at least 36 weeks of gestational age at birth. Control subjects had normal visual acuity or normal visual responses and no history of any vision abnormality. Children with CVI were recruited from the practice of one of the authors (WVG). Control infants and young children were recruited from parent education classes in the San Francisco Bay area and from the nursery at California Pacific Medical Center in San Francisco. The protocol was approved by the Institutional Review Board of the California Pacific Medical Center and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents of the patients with CVI and normal infants and young children, after the recording procedure was explained.

Stimuli and Apparatus

Stimulus generation and signal analysis were performed by the Power Diva (Digital Instrumentation for Visual Assessment; Smith Kettlewell Eye Research Institute) system on separate computers (Power Macin-

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TABLE 1. Diagnoses of Children with Cortical Visual Impairment

Subject	Age (y)	Etiology of CVI
1	2.7	Metabolic defect
2	2.0	Hypoxic ischemia
3	1.0	Meningitis
4	4.8	Perinatal hypoxia, ischemia
5	1.1	Perinatal hypoxia, ischemia
6	0.6	Hydrocephalus
7	4.0	Cerebrovascular accident in utero
8	1.1	Hypoxic ischemia
9	2.4	Cerebrovascular accident in utero
10	1.5	Choroid plexus papilloma
11	0.9	Cerebrovascular accident in utero
12	0.6	Perinatal hypoxia, ischemia
13	2.0	Perinatal hypoxia, ischemia
14	2.4	Perinatal hypoxia, ischemia
15	1.2	Lissencephaly
16	0.9	Encephalitis at 4 months
17	1.6	Perinatal hypoxia, ischemia
18	1.8	Perinatal hypoxia, ischemia
19	0.8	Perinatal hypoxia, ischemia
20	1.0	Perinatal hypoxia, ischemia

tosh G31; Apple Computer, Cupertino, CA). Stimuli were presented on a multisynch video monitor (1600 × 1200 pixels; vertical refresh, 60-Hz; video bandwith, 150 MHz; model MRHB2000; Richardson Electronics, Inc). For all stimuli, the stimulus field size was 23 cm (height) × 31 cm (width). Viewing distance was 70 cm for CVI subjects and 110 to 150 cm for normal subjects depending on the observer's age.

The grating acuity stimulus was a cosine-wave vertical grating presented at 80% contrast in an on/off configuration at a rate of 3.76 Hz (3.76 cycle of on or off screen per second). Grating acuity thresholds were measured under two different luminance conditions: normal luminance (109 cd/m^2) and low luminance (20 cd/m^2). These values were chosen on the basis of pilot data presented elsewhere that showed that moderate reductions in luminance background sometimes resulted in improved grating acuities and sometimes did not.[7] Schematic examples of the grating acuity VEP stimuli are shown in Figure 1. The swept spatial frequency range was set from 1 to 12 cyc/deg for subjects with CVI, 2 to 24 cyc/deg for the normal subjects who were younger than 12 months, and 2 to 28 cyc/deg for those who were above 12 months (Fig. 1).

VEP Recording and Procedure

Gold-cup surface electrodes (model E-6H; Grass-Telefactor, Quincy, MA) were used to collect EEG data. The EEGs were amplified at a gain of 20,000, with amplitude band-pass filter settings of 0.3 to 100 Hz (model 12 A5; Grass-Telefactor). Three active electrodes were placed over the occipital pole at O_1, O_Z, and O_2, and the reference and ground electrodes were placed at C_Z and P_Z, according to the International 10-20 system. Differential voltages were measured between the reference and each of the electrodes placed O_1, O_Z, and O_2.

During an experimental session, the subject was seated in a parent's lap or, in some cases, was seated in a wheelchair in front of the monitor. VEP responses were measured under binocular viewing conditions in all observers. The experimenter attracted the subject's attention to the stimulus with small toys centered on the monitor's display. Recordings were interrupted when the subject was judged not to be attending to the stimulus and resumed when the subject looked back at the screen. When interruptions occurred, the program interrupted the sweep but not the stimulus appearance or modulation. When the trial resumed after an interruption, data collection re-commenced with the stimulus set to its value at 0.5 seconds before the interruption. No child in either the CVI or control category showed an aversion to the light emanating from the computer screen.

Data Analysis and VEP Threshold Estimation

Raw scalp potential recordings for each 10-second trial were digitized to 16-bit precision and partitioned into 10 sequential epochs of 1 second's duration (hereafter designated bins). For each bin, a recursive, least-squares algorithm was used to generate a series of complex-valued spectral coefficients representing the amplitude and phase of response components tuned to various harmonics of the stimulus frequency.[8] These spectral coefficients for each bin were averaged together across trials for each subject, channel, harmonic, and stimulus condition. Statistical significance was quantified using probabilities derived from the T^2_{circ} statistic[9] a phase-sensitive, variance-normalized measure of mean amplitude, distributed as $F(2,2n\text{-}2)$, where n is the number of trials (6–12 per condition).

For each swept stimulus condition, response thresholds were estimated by regression of amplitudes from the trial-average bins where the response decreased linearly to the point of stimulus invisibility. The range of bins eligible for regression depended on the statistical significance and phase-consistency of the response according to an algorithm.[10] The regression range was limited to those bins where the following criteria were met: (1) response probability in each bin was at

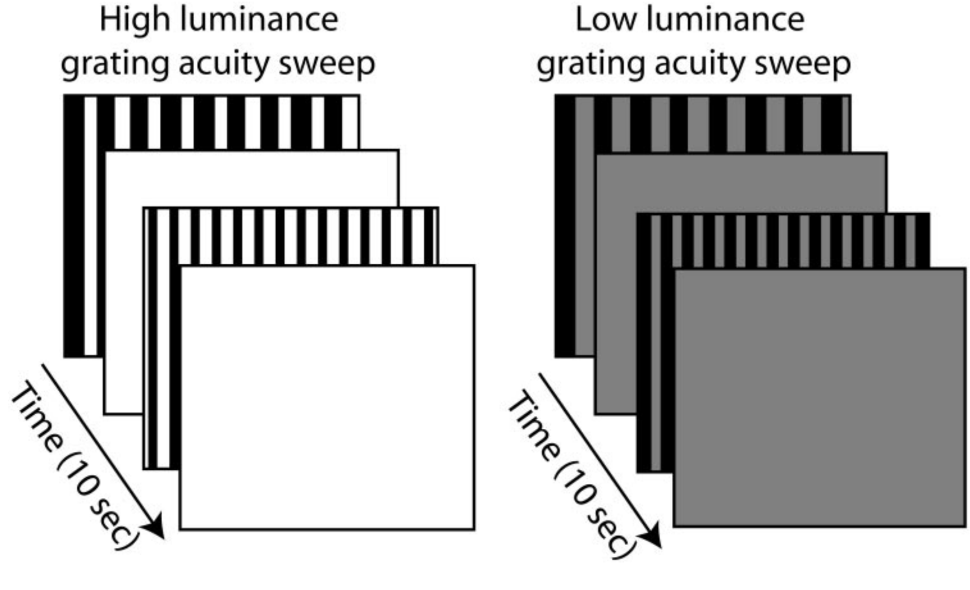

FIGURE 1. Schematic depiction of 109 cd/m^2 mean luminance (*left*) and 20 cd/m^2 mean luminance (*right*) grating onset–offset target used to measure grating acuity. Vertical cosine-wave gratings (shown here as square waves) were alternated with a blank field of equal space–average luminance. Over a period of 10 seconds, the spatial frequency of the grating was systematically increased in a series of 10 equal linear steps.

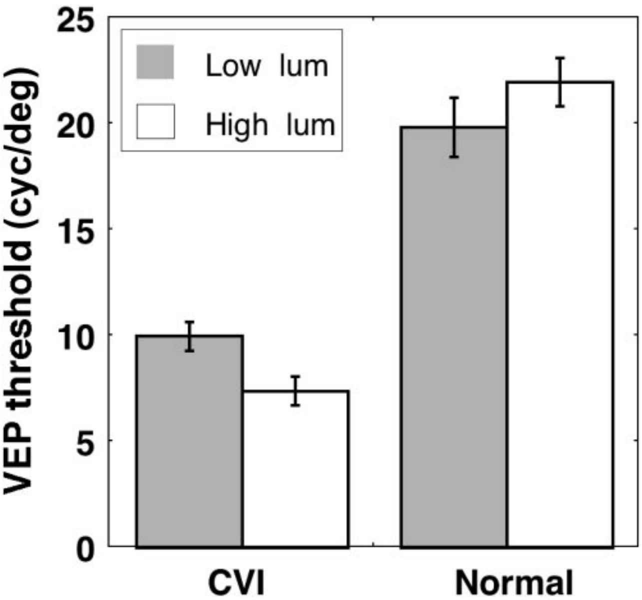

FIGURE 2. Means and SEMs of VEP threshold spatial frequency for patients with CVI and normal subjects in low- and normal-luminance conditions. Thresholds were first averaged across channel for each subject (17 normal subjects, 17 patients with CVI), and then the channel-average thresholds were averaged across subjects for each of the two subject categories and each of the two luminance conditions. Subjects were included in the analysis only if they had a discernable threshold on at least one channel in both luminance conditions. The results indicated better grating acuity thresholds at low luminance in children with CVI.

most 0.16; (2) the difference in response phase for each pair of consecutive bins was between 80° and −100°, where phase increases with response latency; (3) at least one pair of consecutive bins had responses of $P \leq 0.077$ or less; and (4) to exclude spike artifacts, the amplitude of the bin immediately before and the bin immediately after any given bin in the range could not both be <0.3 times the amplitude of that given bin. Once the regression range was established, the threshold stimulus value was determined by extrapolating the regression line to zero response amplitude. When applied to spectral data from background EEG, these criteria yield a 5% false-alarm rate (data not shown).

RESULTS

Figure 2 shows average thresholds across all patients with CVI and normal subjects. Three of the children with CVI did not show measurable thresholds at the normal-luminance stimulus, but did demonstrate thresholds at the low-luminance stimulus. These three children are not included in Figure 2 or the statistical analysis. Even when these three subjects excluded, the patients with CVI showed better grating acuity at low luminance than at normal luminance (range: 5.7–14.2 cyc/deg, low luminance; 4.2–13.2 cyc/deg, normal luminance). Normal subjects showed no difference (range, 13.6–34.9 cyc/deg low luminance and 13.0 to 30.8 cyc/deg normal luminance). Overall, grating acuity of patients with CVI was substantially worse than that of normal subjects, as expected.

Data from Figure 2 were evaluated by repeated-measures ANOVA with subject category and luminance as factors. There was a main effect of subject category, due to higher thresholds for normal subjects, $F_{(1,26)} = 96.249$ ($P < 0.001$). There was also an interaction between subject category and luminance, with patients with CVI and normal subjects showing opposite effects of luminance, $F_{(1,26)} = 9.604$ ($P = 0.005$). In children with CVI, acuity thresholds were significantly improved in low-luminance conditions (paired *t*-test, $P = 0.006$).

Figure 3 shows VEP amplitude as a function of spatial frequency for one CVI patient and one normal subject at O_Z. Response amplitudes are clearly higher under the low-luminance condition, and the VEP threshold in the low-luminance condition increased approximately 1 cyc/deg. In the normal subject, the amplitude and threshold responses did not show much difference between low- and normal-luminance conditions. Figure 4 shows VEP amplitude as a function of spatial frequency for all 20 patients with CVI and 17 normal subjects averaged from three electrode sites (O_1, O_Z, and O_2). Response amplitudes appeared higher under low-luminance conditions, at increasing spatial frequency ranges in CVI. This effect did not occur in normal children. Thresholds were reduced by approximately a factor of three in children with CVI, compared with normal subjects, and signal amplitudes also showed an overall reduction in children with CVI.

To further quantify these observations, we examined, for each subject, the upper boundary of the range of spatial frequencies included in the threshold regression analysis. As described in the Methods section, the upper boundary of the regression range depends on several response-related factors, including statistical significance of the response amplitude, and consistency of response phase at sequential spatial frequencies. In effect, the upper limit of the regression range indicates the highest spatial frequency at which we can detect a reliable response to the stimulus. The spatial frequencies corresponding to the upper limit of the regression range for each subject showed nearly identical behavior in response to the thresholds. As was the case for the thresholds, there was a main effect

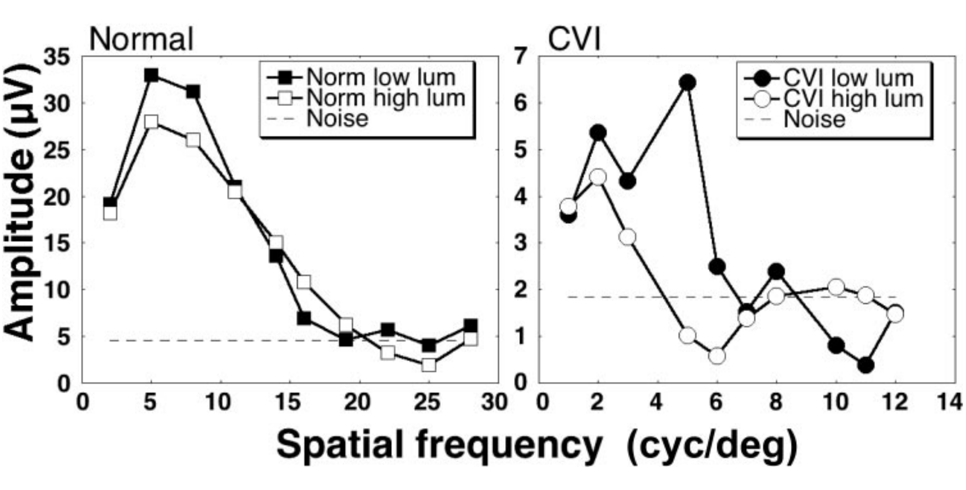

FIGURE 3. VEP amplitude as a function of spatial frequency for a CVI patient and a normal subject recorded at O_Z in low- and normal-luminance conditions. *Dashed line*: average noise level. The response amplitude was clearly higher in the low-luminance condition. The VEP threshold in the low-luminance condition increased approximately 1 cyc/deg in CVI. In the normal subject, the amplitude and threshold did not show much change, comparing low- and normal-luminance conditions.

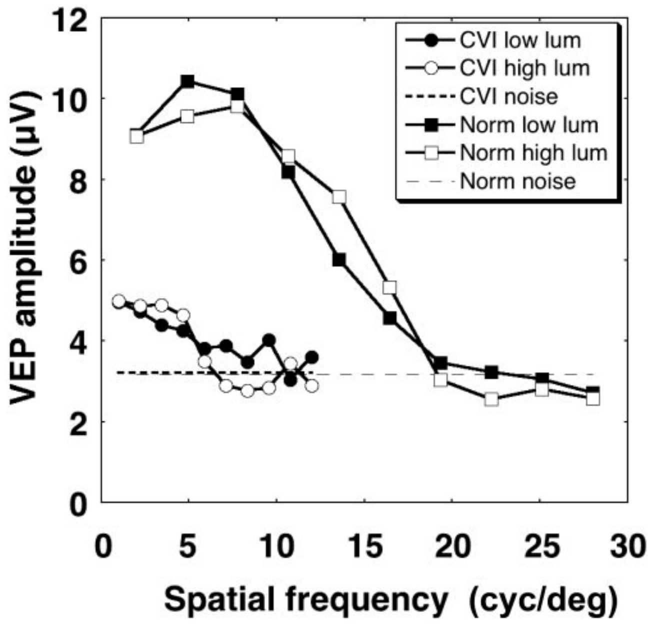

FIGURE 4. VEP amplitude as a function of spatial frequency for all 20 patients with CVI (*circles*) and 17 normal subjects (*squares*) averaged from three electrode sites (O_1, O_Z, and O_2) in the same sweep range. *Dashed line*: average noise level. Response amplitudes appeared higher in low-luminance conditions, at increasing spatial frequency ranges in CVI. This effect does not occur in normal children. Thresholds are reduced by approximately a factor of 3 in children with CVI, compared with normal subjects, and signal amplitudes also show an overall reduction in children with CVI.

of subject category, due to greater responses at higher spatial frequencies for normal subjects ($F_{(1,26)} = 117.451$; $P < 0.001$). As seen with the thresholds, there was an interaction between subject category and luminance, with patients with CVI and normal subjects showing opposite effects of luminance ($F_{(1,26)} = 5.579$; $P = 0.026$). In children with CVI, the responses extended to higher spatial frequencies in the low-luminance condition, but unlike the threshold results, they fell slightly short of statistical significance (paired *t*-test, $P = 0.090$).

In addition to the upper regression limit, the slope of the regression line also helps determine the threshold acuity: The shallower the slope, the higher the threshold. As shown in Figure 4, the response functions for children with CVI appeared to be shallower at the more visible end in the low-luminance compared with the normal-luminance condition. To determine the extent of bias in thresholds generated by this tendency, we analyzed the slopes of the regression lines in our results. Although the slopes (not shown) predicted the thresholds according to the relationship just described, the effects observed in the threshold and regression limit data were greatly diminished for the slope data. The effect of subject category was still present, but much less significant, $F_{(1,26)} = 5.277$ ($P < 0.030$), the interaction between subject category and luminance was not significant ($F_{(1,26)} = 2.312$, $P = 0.140$), nor was the effect of luminance for the children with CVI ($P = 0.144$). In conclusion, the effects on threshold were predominantly driven by the magnitude of the response at the upper end of the spatial frequency range and were only slightly influenced by spurious effects of slope at the lower end of the spatial-frequency range.

Amplitude as a function of spatial frequency is shown in larger detail for patients with CVI in Figure 5. The difference in response amplitudes between low- and normal-luminance conditions is particularly pronounced at the higher spatial frequencies. Under low-luminance conditions, the average amplitude response remains above 3 μV, but dips below this line, when grating acuity is measured under normal-luminance conditions.

DISCUSSION

Unlike normally sighted children whose VEP grating acuity was similar under the two luminance conditions, the visual acuity of children with CVI was better under low-luminance viewing conditions than under normal-luminance conditions. Although children with CVI showed reduced grating acuity thresholds and reduced amplitudes across the entire frequency spectrum that was tested, low luminance had the most pronounced beneficial effect on the evoked potential at higher spatial frequencies. The expected finding was that low-luminance conditions used in this study would *reduce* or have no effect on acuity in CVI. The improved acuity in low luminance is a surprising finding with potential ramifications for rehabilitation of children with CVI.

Several possible explanations can be invoked to attempt to explain improved acuity under low-luminance testing conditions. Traditional views hold that the retina modulates luminance. However, luminance-sensitive cells are found in cerebral cortex.[11,12] It is possible that damage to these cells as would occur in the diffuse central nervous system (CNS) injury of CVI could affect the child's ability to cope with increased luminance conditions, resulting in an effect on acuity per se in certain viewing conditions.

Another possible explanation is that neurologic damage in CVI affects areas of the brain that modulate afferent input (i.e., the thalamus). The syndrome of thalamic dazzle caused by ischemia to the thalamus is known to cause photophobia and dazzle and can make visual activity uncomfortable.[13] This syndrome has been described in adults, although damage to basal ganglia occurs commonly in children with CVI, as well. Photophobia also occurs in another type of neurologic damage: paracentral, small, homonymous visual field defects.[14] Again, patients with this problem who have been described to date have been adults with relatively preserved visual acuity, in contrast to patients in this study who were children with poor

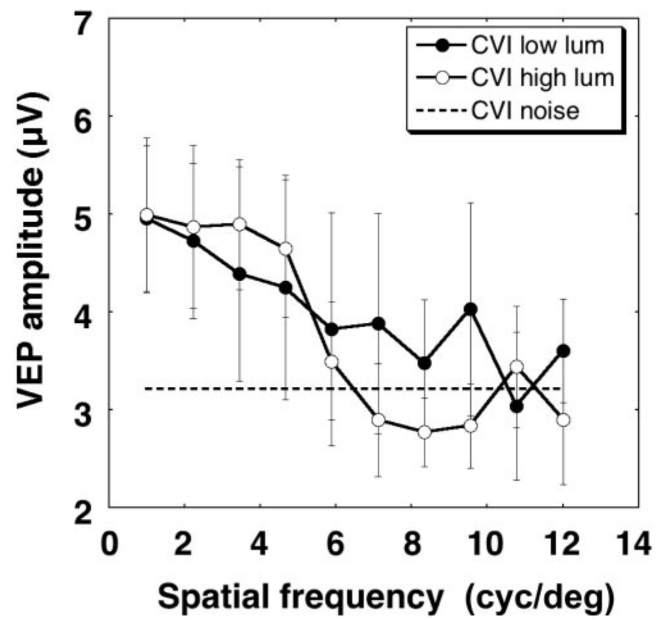

FIGURE 5. VEP amplitudes in response to swept spatial frequency in patients with CVI only. Means and SEMs across observers for low and normal luminance are plotted. *Dashed line*: average noise level.

acuity. However, visual field loss in CVI occurs frequently and could be a partial explanation for this phenomenon.

Several ocular conditions also cause photophobia, including cataract, corneal and other media opacity, and optic nerve damage, but none of these conditions was present in patients in this study. Similarly, unilateral or asymmetric optic nerve injury sometimes causes photophobia, but this was not a finding in children in this study.

There are limitations to the interpretation of the findings in the study, one of which is the possibility that the sweep VEP does not actually measure grating acuity, but measures some other neurologic epiphenomena. This is unlikely, given the results of other experiments, which have shown that VEP grating acuity thresholds are usually similar to behaviorally measured thresholds and to clinical estimations of acuity in children with CVI,[7] although not all children with CVI show comparable behavioral and VEP grating acuities.[15] Another explanation for the finding could be that children with CVI simply turn away from the computer monitor during acuity testing, due to their aversion to light. This is unlikely, because the stimulus sweep can be stopped and restarted when children break eye contact from the monitor, and children were carefully monitored while taking the test. Furthermore, any deficits in accommodation in children with CVI should have caused diminished acuity under *both* low- and normal-luminance viewing conditions.

As there is no medical treatment to prevent or reverse damage to the optic radiations or visual cortex, visually impaired children with CVI can only be managed with rehabilitation efforts. It is currently standard procedure in many settings to show visually impaired children visual targets against a bright background light, such as an x-ray light box, and to use brightly colored visual targets. Such interventions make the assumption that poor acuity can be countered in some measure with increased stimulus intensities. However, this is not an evidence-based approach to rehabilitation of visually impaired children. In this study, we have shown that visual acuity of children with CVI improved under low-luminance viewing conditions, confirming the clinical observation that children with CVI are bothered by bright lighting. This finding offers evidence that efforts to work with visually impaired children who have CVI can be conducted under low or normal lighting conditions and not the very bright lighting that is generally used. This study did not show whether a low-luminance treatment program, per se, could favorably affect the development of visual acuity or other aspects of neurologic functioning of such children. Evidence that visual rehabilitation using low-luminance targets improves acuity and visual function will necessitate further research.

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