Assessing Suppression in Amblyopic Children With a Dichoptic Eye Chart

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Purpose. Suppression has a key role in the etiology of amblyopia, and contrast-balanced binocular treatment can overcome suppression and improve visual acuity. Quantitative assessment of suppression could have a role in managing amblyopia. We describe a novel eye chart to assess suppression in children.

Methods. We enrolled 100 children (7–12 years; 63 amblyopic, 25 nonamblyopic with strabismus or anisometropia, 12 controls) in the primary cohort and 22 children (3–6 years; 13 amblyopic, 9 nonamblyopic) in a secondary cohort. Letters were presented on a dichoptic display (5 letters per line). Children wore polarized glasses so that each eye saw a different letter chart. At each position, the identity of the letter and its contrast on each eye's chart differed. Children read 8 lines of letters for each of 3 letter sizes. The contrast balance ratio was the ratio at which 50% of letters seen by the amblyopic eye were reported.

Results. Amblyopic children had significantly higher contrast balance ratios for all letter sizes compared to nonamblyopic children and controls, requiring 4.6 to 5.6 times more contrast in the amblyopic eye compared to the fellow eye ($P < 0.0001$). Amblyopic eye visual acuity was correlated with contrast balance ratio (r ranged from 0.49–0.57 for the 3 letter sizes). Change in visual acuity with amblyopia treatment was correlated with change in contrast balance ratio (r ranged from 0.43–0.62 for the 3 letter sizes).

Conclusions. Severity of suppression can be monitored as part of a routine clinical exam in the management of amblyopia in children.

Keywords: suppression, amblyopia, bincocular vision

Converging evidence from animal models and clinical research suggests that interocular suppression has a key role in the etiology of amblyopia (see reviews by Birch,[1] Hess and Thompson,[2] and Wong[3]) and that the severity of suppression is correlated with the severity of amblyopia.[4–9] When suppression is alleviated by reducing the contrast of the fellow eye image to rebalance the effective contrast in the two eyes, suppression can be overcome and binocular vision reinstated.[10,11] Treatment regimens designed to alleviate suppression via repeated exposure to contrast-balanced binocular stimuli improve visual acuity in amblyopic adults[12] and amblyopic children.[13–16] Thus, severity of suppression may be a useful baseline and outcome measure in clinical amblyopia research.

Several protocols for determining severity of suppression in amblyopic adults have been described, including dichoptic global motion coherence,[11,17,18] binocular phase,[19–21] and binocular contrast summation.[10,19,20] There have been attempts to apply these tests to amblyopic children, but success has been limited because the protocols rely on equipment that is cumbersome for children (virtual reality goggles, shutter glasses, haploscopic optical systems) coupled with the challenges posed by subtle psychophysical judgments and large numbers of trials.[13]

Our goal was to evaluate the feasibility of a novel, eye chart-based method to assess severity of suppression in children. Eye charts are familiar tests for children as young as 3 years, and have been standardized for electronic display to routinely provide quick and reliable outcome measures for multicenter randomized clinical trials in pediatric ophthalmology.[22–25] The approach of using a dichoptic eye chart to assess severity of suppression, along with pilot data from mildly amblyopic adults, was published recently by Kwon et al.[26] They used stereo shutter glasses to separate the images to each eye. Here, we adapted their method for use in children by presenting on a passive 3-D display that eliminated the need for bulky shutter glasses. Specific aims of the present study were to determine whether amblyopic children exhibited significantly more severe suppression than nonamblyopic children with strabismus and/or anisometropia or controls, whether severity of amblyopic visual acuity deficit was correlated with severity of suppression, and whether changes in visual acuity as a result of treatment or regression were associated with changes in the severity of suppression.

METHODS

Participants

We enrolled 100 children (7–12 years old) in the primary cohort: 63 amblyopic children with strabismus ($n = 10$),
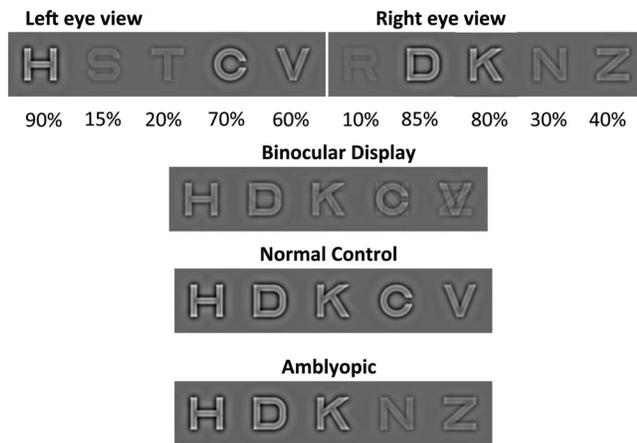
FIGURE 1. Schematic diagram of the dichoptic eye chart. Letters were band-pass filtered Sloan letters chosen from the e-ETDRS letter set. Five letters were presented in a line with varying letter contrast on a gray background. A different letter chart was presented to each eye using an LG passive 3D video display. At each letter position, the identity and interocular contrast-ratio of the letter on each chart differed while the spatial-frequency content of the letter remained the same. Children were instructed to read the 5 letters left to right and completed 8 lines (40 letter/contrast combinations) for each letter size. Contrast balance ratio was defined as the contrast ratio (amblyopic eye contrast/fellow eye contrast) at which 50% of letters seen by the amblyopic eye were reported. For nonamblyopic children with a history of treated amblyopia, the contrast ratio was calculated as previously amblyopic eye contrast/fellow eye contrast. For nonamblyopic children who were never amblyopic and for normal controls, the contrast balance ratio was calculated as right eye contrast/left eye contrast. Three letter sizes were tested, 1.25 (20/480), 2.5 (20/240), and 5 c/deg (20/120), for a total of 120 trials.

anisometropia ($n = 26$), or both ($n = 27$); 25 nonamblyopic with strabismus ($n = 13$), anisometropia ($n = 8$), or both ($n = 4$); and 12 normal control children. In addition, 22 younger children (3–6 years old) with strabismus and/or anisometropia were enrolled in a secondary pilot study: 13 amblyopic and 8 nonamblyopic children.

For this study, amblyopia was defined as a best-corrected visual acuity of ≥ 0.2 logMAR and an interocular difference of ≥ 0.2 logMAR associated with the presence or history of strabismus, and/or anisometropia in an otherwise healthy child who had been wearing spectacle correction for a minimum of 3 months. Strabismic amblyopia was defined as amblyopia in the presence of a heterotropia at distance and/or near fixation, a history of strabismus surgery, or resolution of misalignment following hyperopic spectacle correction, with a spherical equivalent interocular difference of ≤ 1.00 diopter (D) and ≤ 1.50 D interocular difference in astigmatism in any meridian. Anisometropic amblyopia was defined as amblyopia in the presence of a spherical equivalent interocular difference of ≥ 1.00 D or ≥ 1.50 D interocular difference in astigmatism in any meridian with no measureable heterotropia at distance or near fixation. Combined mechanism amblyopia was defined as amblyopia in the presence of the strabismus and anisometropic amblyogenic factors.

Written informed consent was obtained from a parent after explanation of the nature and possible consequences of the study. In addition, written informed assent was obtained from children age 10 to 12 years. All procedures and the protocol were approved by the Institutional Review Board of UT Southwestern Medical Center and followed the tenets of the Declaration of Helsinki.

Enrolled patients had a comprehensive ophthalmic examination performed by their referring pediatric ophthalmologist.

The medical record from this examination provided diagnosis, refractive error as determined by cycloplegic retinoscopy, ocular motility, and measurements of heterotropia or heterophoria by simultaneous prism-and-cover test at near and distance fixation. Strabismic children were only eligible to participate if misalignment of the visual axes due to infantile esotropia, accommodative esotropia, or acquired nonaccommodative esotropia had been treated successfully with glasses and/or surgery (<5 pd residual strabismus). Exclusion criteria were congenital malformation or infection, concurrent treatment with atropine penalization, prematurity ≥ 8 weeks, developmental delay, and coexisting ocular or systemic disease.

Stimuli

For the primary cohort of 7- to 12-year-old children, the 11 Sloan font letters used in the electronic visual acuity Early Treatment of Diabetic Retinoscopy Study (EVA e-ETDRS) protocol[22] were used for measuring contrast balance (suppression), with the exception that the letter O was replaced with X (Fig. 1). The O was replaced because, in pilot work, it was found to be much more salient than the other 10 letters. To be able to examine potential spatial frequency dependence of suppression,[26] 3 letter sizes were tested (1.25, 2.5, and 5 c/deg). Letters were spatially band-pass filtered with a cosine log filter (bandwidth = 1 octave; radially symmetric) with peak object spatial frequency of 3 cycles per letter.[26] The object spatial frequency of 3 cycles per letter was chosen because the optimal spatial frequency for recognizing a letter lies between 1 and 7 cycles per letter, depending on letter size.[27–32]

Letters were presented on a passive 3-dimensionnal (3D) display (LG D2343P-BN; 23 in; 1920 × 1080 pixel), with 5 letters per line. Because odd and even lines had opposite polarization, the passive 3D display allowed for dichoptic stimulation with different lines of letters for each eye when children wore LG Cinema 3D polarized glasses. At each position, the identity of the letter and its contrast varied independently for each eye. Letter choice for each of the 5 positions for each eye was random with the exceptions that the same letter could not be repeated with the line of 5 letters, the same letter could not be presented to both eyes in the same position, and presentation of letters to each eye that might form another letter if perceived simultaneously was not allowed to occur (e.g., H and V, which might be perceived binocularly as M). The sum of the left and right eye contrasts always was 100%; for example, when the contrast of the left eye letter was 30%, the contrast of the right eye letter was 70%. The relative contrast of the letters in each eye was determined by an adaptive algorithm.[26] The proportion correct for each contrast ratio was computed and these data were used to estimate the balance point ratio. The estimate was updated each time the child completed reading a line of 5 letters and the updated balance point ratio was used to guide the range of contrast ratios presented on the subsequent line of letters, gradually converging on the balance point ratio.

For the secondary pilot study of 3- to 6-year-old children, the HOTV letter set in the EVA-Amblyopia Treatment Study (ATS) visual acuity protocol[25] was used, with the exception that the O was replaced with X. Because there were only four available letter choices (HVTX), a randomly chosen letter always occurred in two positions in each line of 5 letters.

Procedure

Children wore optical correction, if needed, prescribed by their pediatric ophthalmologist in accordance with American Association for Pediatric Ophthalmology and Strabismus (AAPOS) guidelines (AAPOS Policy Statement, "Medical Need
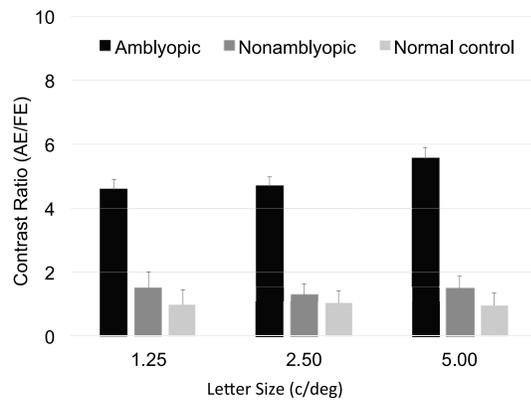
FIGURE 2. Contrast balance ratios (mean ± SEM) of 7- to 12-year-old amblyopic children, nonamblyopic children who had been treated for strabismus and/or anisometropia, and normal control children.

FIGURE 3. Contrast balance ratios (mean ± SEM) of 7- to 12-year-old children with anisometropic amblyopia, strabismic amblyopia, and combined mechanism amblyopia.

for Glasses," available in the public domain at www.aapos.org). Best-corrected visual acuity was obtained for each eye with an opaque occluder patch and either the e-ETDRS (age 7–12 years) or ATS-HOTV (for 3–6 years) method.

For the suppression protocol, children were instructed to read the 5 letters left to right and completed 8 lines (40 letter/contrast combinations) for each of 3 letter sizes (1.25, 2.5, and 5 c/deg). Contrast balance was defined as the contrast ratio (amblyopic eye contrast/fellow eye contrast) at which 50% of amblyopic eye letters and 50% of fellow eye letters were reported. For children who did not have amblyopia, contrast balance was defined as the contrast ratio (right eye contrast/left eye contrast) at which 50% of right eye letters and 50% of left eye letters were reported. If the child was unable to report any letters with 100% contrast for the amblyopic eye, the contrast balance ratio was arbitrarily assigned a value of 10.0.

Statistical Analyses

In analyses conducted with the primary 7- to 12-year-old cohort, amblyopic, nonamblyopic, and normal control contrast balance ratios were compared using 1-way ANOVA and post hoc Bonferroni pairwise comparisons. For amblyopic children in the primary cohort, the main effects of amblyopia and its etiology, and the interaction between these factors were evaluated using 2-way ANOVA and post hoc Bonferroni pairwise comparisons. The association between severity of suppression and severity of amblyopic visual acuity deficit was evaluated using Pearson Product Moment correlation coefficient. The association between changes in the severity of suppression and changes in the severity of amblyopic visual acuity deficit with treatment or amblyopia recurrence was evaluated using the Pearson Product Moment correlation coefficient. For the secondary pilot study of 3- to 6-year-olds, only success rate and descriptive statistics (means and standard errors) were calculated, due to the small sample size.

RESULTS

Amblyopic children had significantly more severe suppression than nonamblyopic children and normal controls ($F_{2,97} = 62.26$, $P < 0.0001$; Fig. 2). Amblyopic children required 4.6 to 5.6 times more contrast in the amblyopic eye than in the fellow eye to overcome suppression and identify the amblyopic eye letters (e.g., 83% amblyopic eye contrast and 17% fellow eye contrast). Nonamblyopic children who had been treated for strabismus and/or anisometropia required only 1.3 to 1.5 times
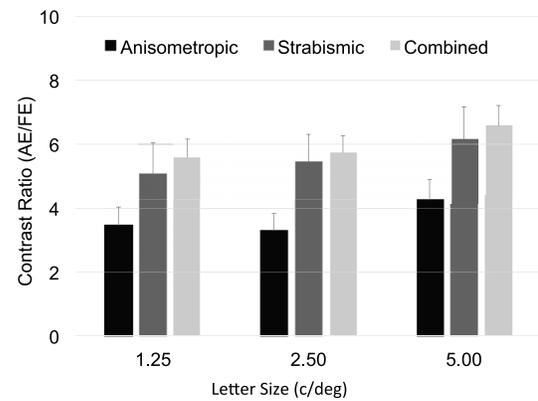
more contrast to overcome suppression; significantly less than for amblyopic children ($P < 0.0001$), but significantly more than the normal controls' mean contrast balance ratio, which was near 1.0 for all three letter sizes ($P < 0.0001$). Neither the main effect of letter size nor the interaction was significant.

With the analysis limited to amblyopic children, there was a significant main effect of etiology (strabismus and/or anisometropia; Fig. 3; $F_{2,60} = 5.32$, $P = 0.007$). Children with anisometropic amblyopia required only 3.3 to 4.2 times more contrast for the amblyopic eye compared to the fellow eye to overcome suppression, significantly less than children with combined mechanism amblyopia ($P < 0.007$). There was no significant difference between strabismic and combined mechanism amblyopia or between strabismic and anisometropic amblyopia. Also, there was a significant main effect of letter size with the analysis limited to amblyopic children ($F_{2,120} = 5.27$, $P = 0.006$), with significantly higher contrast ratios observed for smallest compared to largest letter size (5 vs. 1.25 c/deg; $P = 0.004$) and the medium letter size (2.5 c/deg; $P = 0.011$). The interaction between etiology and letter size was not significant.

In a pilot study of children age 3 to 6.9 years (mean ± SD, 5.3 ± 1.0 years), contrast ratios were evaluated using the HOTX letter set. Of 22 children enrolled, 20 (91%) were able to complete the test, including 8 of 9 nonamblyopic and 12 of 13 amblyopic children. Three of the four 3-year-olds attempted were able to complete the test. Contrast ratios from these two groups of preschool children are shown in Figure 4. Overall, nonamblyopic preschool children who had been treated for strabismus and/or anisometropia had contrast balance ratios near 1.0, similar to older normal controls and older nonamblyopic children. Amblyopic preschool children had mean contrast ratios ranging from 5.8 to 6.6, similar to older amblyopic children.

Visual Acuity and Suppression

Among amblyopic children, visual acuity was correlated with severity of suppression (Fig. 5). Correlation coefficients ranged from 0.49 to 0.57 ($P = 0.008$, 0.025, and 0.016 for the large, medium, and small letter sizes, respectively). For 30 of the amblyopic participants, contrast balance ratio was measured on two visits so that the relationship between visual acuity change and contrast balance ratio change could be examined. Contrast balance ratio changes were correlated with changes in visual acuity due to regression or improvement with treatment (Fig. 6). Correlation coefficients ranged from 0.43 to 0.62 ($P =$
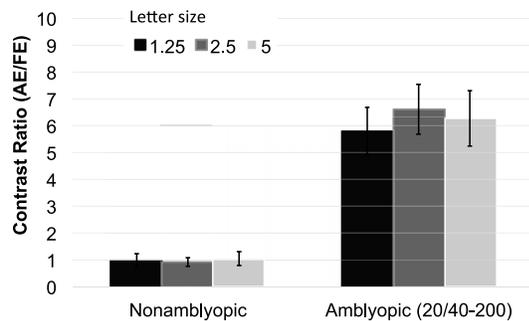
FIGURE 4. Contrast balance ratios (mean ± SEM) of 3- to 6-year-old amblyopic children and nonamblyopic children who had been treated for strabismus and/or anisometropia.

0.021, <0.0001, and 0.013 for the large, medium, and small letter sizes, respectively).

DISCUSSION

Although the classical view is that interocular suppression arises as a secondary compensatory response to conflicting monocular visual inputs, recent evidence suggests that suppression may instead be the primary progenitor of amblyopia and that treatment aimed at reducing interocular suppression is effective in improving visual acuity in amblyopic children and adults.[1–3,5,6,9,13–16,20,33] With this new emphasis on suppression and the importance of its remediation during treatment, the inadequacy of current clinical suppression tests that provide only binary outcomes is conspicuous. To address the need for quantitative assessment of severity of suppression and response to treatment, we developed a novel dichoptic eye chart, adapted from a protocol originally described by Kwon et al.,[26] that can be used to quantify severity of suppression in amblyopic children as young as 3 years old.

We chose to use a letter chart format because children as young as 3 years are familiar with letter chart tests, making the test easy to administer. Also, previous studies have used similar bandpass filtered letters successfully to measure adult contrast sensitivity in clinical settings.[34–36] A third rationale for the letter chart is that some amblyopic children exhibit greater visual acuity deficits with optotype visual acuity than with grating acuity, perhaps related to abnormal binocular function.[1] Finally, letter charts have a low chance level, and so are likely to provide more accurate and reliable estimates of suppression than two-alternative tests with a limited number of trials, especially for children.

The validity of the dichoptic eye chart as an outcome measure for severity of interocular suppression was supported by three results. First, amblyopic children exhibited signifi-

cantly more severe suppression than nonamblyopic children with strabismus and/or anisometropia or normal controls, and normal controls had a contrast balance ratio near 1.0. The approximate 5:1 contrast ratio found in amblyopic children in the present study is similar to that reported by a number of previous studies of interocular suppression in amblyopic adults that used a variety of dichoptic tasks, including the dichoptic eye chart protocol of Kwon et al.,[26] dichoptic phase discrimination,[21,37] and dichoptic global motion coherence.[38] Two recent studies have reported that the contrast ratio was dependent on spatial frequency;[20,26] for example, Kwon et al.[26] reported a significantly lower contrast ratio for very large letters (0.5 c/deg) than for 2.5 or 5.0 c/deg letters. Very large (0.5 c/deg) letters were not included in the present study due to constraints of the passive 3D display size. Nonetheless, when the analysis was limited to amblyopic children, we did observe significantly higher contrast balance ratios for the smallest letter size compared to the other two letter sizes.

We found no significant difference in contrast balance ratio between nonamblyopic children and controls. Others have reported that strabismus, in the absence of amblyopia, is associated with suppression.[21,39] However, some or all of the adult patients studied were exotropic, many with exotropia ≥ 5 pd. Our nonamblyopic cohort on the other hand, included only strabismic children who had been corrected to <5 pd as well as anisometropic children. Longstanding exotropia ≥ 5 pd may be associated with suppression.

Second, severity of amblyopia was correlated with severity of interocular suppression; that is, we found a direct relationship between the strength of suppression and the depth of amblyopia. Similar results have been reported in studies of amblyopic adults using a dichoptic global motion coherence task,[5,6,8,38] dichoptic phase discrimination,[8] and global orientation discrimination[8] to measure the severity of suppression. Support for a direct relationship between severity of suppression and depth of amblyopia also comes from a study that used an adaptation of the global motion task to quantify suppression in amblyopic children[7] and a study of amblyopic children and adolescents that used an interocular phase task quantify suppression.[21] In addition, animal models of amblyopia also argue for a direct relationship between the degree of suppression and the degree of amblyopia in neuronal populations in V1 and V2 areas of visual cortex.[9,40]

Third, changes in contrast ratio balance were correlated with changes in visual acuity. Most of the children in the present study who showed visual acuity improvement with treatment were participants in an ongoing study of a binocular amblyopia treatment based on the protocol originally described by Hess et al.[2,13,15,33,41] Previous reports of amblyopic adults who participated in similar binocular treatment protocols reported correlated improvements in contrast ratio balance and amblyopic eye visual acuity.[2,12,33,38,42–45] However, prior studies of amblyopic children who participated in
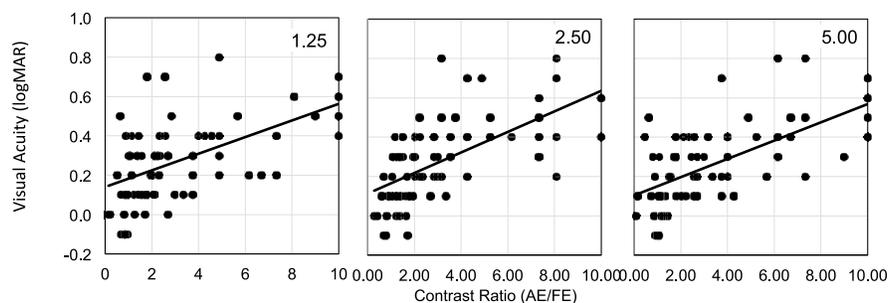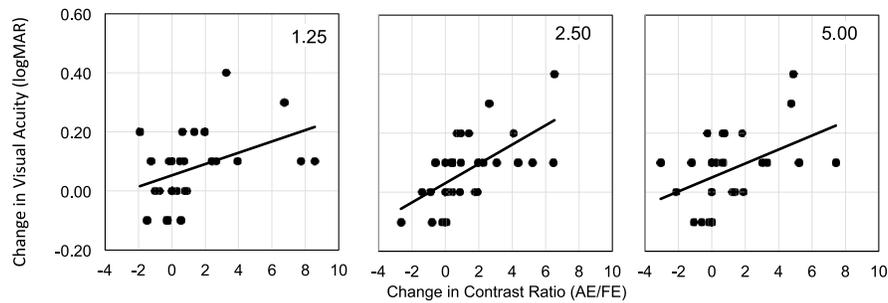

FIGURE 5. Amblyopic eye visual acuity as a function of contrast balance ratio (amblyopic eye/fellow eye).

FIGURE 6. Changes in contrast balance ratio (baseline − outcome ratio) and change in logMAR visual acuity (baseline − outcome) for 30 children tested on two visits. For both changes, positive numbers indicate improvement, while negative numbers indicate regression.

binocular treatment have consistently failed to show improvement in contrast ratio balance despite improvements in visual acuity.[13,14,16,46] These earlier studies in amblyopic children relied on the dichoptic global motion coherence task to quantify severity of suppression. The combination of virtual reality goggles, subtle psychophysical judgments, and large numbers of trials may have been difficult for children, leading to noise in the data and low sensitivity to changes with treatment. The ability of the dichoptic eye chart protocol to detect changes in contrast ratio balance that are correlated with changes in visual acuity during amblyopia treatment supports its validity as an outcome measure for severity of interocular suppression in amblyopic children. This quantitative measure of interocular suppression may provide an important outcome measure for clinical trials of amblyopia treatment.

Acknowledgments

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