**The Role of Suppression in Amblyopia**

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**PURPOSE.** This study had three main goals: to assess the degree of suppression in patients with strabismic, anisometropic, and mixed amblyopia; to establish the relationship between suppression and the degree of amblyopia; and to compare the degree of suppression across the clinical subgroups within the sample.

**METHODS.** Using both standard measures of suppression (Bagolini lenses and neutral density [ND] filters, Worth 4-Dot test) and a new approach involving the measurement of dichoptic motion thresholds under conditions of variable interocular contrast, the degree of suppression in 43 amblyopic patients with strabismus, anisometropia, or a combination of both was quantified.

**RESULTS.** There was good agreement between the quantitative measures of suppression made with the new dichoptic motion threshold technique and measurements made with standard clinical techniques (Bagolini lenses and ND filters, Worth 4-Dot test). The degree of suppression was found to correlate directly with the degree of amblyopia within our clinical sample, whereby stronger suppression was associated with a greater difference in interocular acuity and poorer stereocuity. Suppression was not related to the type or angle of strabismus when this was present or the previous treatment history.

**CONCLUSIONS.** These results suggest that suppression may have a primary role in the amblyopia syndrome and therefore have implications for the treatment of amblyopia. (Invest Ophthalmol Vis Sci. 2011;52:4169–4176) DOI:10.1167/iovs.11-7233
have applied it to quantifying the strength of suppression in both strabismic and anisometropic amblyopes\textsuperscript{12,13} using a global motion stimulus in which signal elements moving in a coherent direction are seen by one eye and noise elements moving in random directions are seen by the other eye. This method is an accurate way, within the context of signal/noise analysis, of measuring\textsuperscript{12,13} and treating\textsuperscript{10} suppression within the central field. In this study we used this approach to assess the strength of suppression in a group of anisometropic, mixed, and strabismic amblyopes. The method provides a more quantitative means (better resolution) of measuring the degree of suppression compared with the Worth 4-Dot test or the use of a red filter and neutral density wedge. We first assessed the relationship between this new signal/noise method that can precisely quantify suppression and more traditional, relatively coarse, measures of suppression (Worth 4-Dot test and modified Bagolini test). We then addressed the following two questions: What is the relationship between visual losses in amblyopia (acuity and stereo) and the degree of suppression? How does suppression vary within the amblyopic clinical population? The answers to these questions bear on the issue of whether suppression plays a causal role in the visual loss that characterizes amblyopia.

**Methods**

**Participants**

A total of 43 amblyopic observers (23 females, 20 males), between the ages of 9 and 56 years (mean age, 20.7 ± 11.9), and 10 normal observers (4 females, 6 males), between the ages of 20 to 35 years (mean age, 29.20 ± 5.93), who met the inclusion criteria were enrolled. Clinical details for the amblyopic observers are provided in Table 1.

The normal observers acted as the control group and had equal visual acuity in each eye of at least 20/20; absence of any ocular, ocularomotor, or binocular abnormalities; normal stereocuity (≥20 seconds of arc); and a spherical equivalent refractive error of between −1.00 and −3.00 D, with an unequal spherical equivalent of not more than a 1-D difference between the eyes detected during a standard ocular examination; and a cylindrical correction of less than 1 D. The amblyopic group was defined according to the Preferred Practice Protocol (PPP) of The American Academy of Ophthalmology\textsuperscript{14} and classified under one of the following clinical conditions: strabismic amblyopia (with an angle of strabismus of less than 35°), anisometropic amblyopia with a visual acuity loss in the worse eye of no worse than 20/100, and mixed (those that met the criteria for both types of amblyopia). Subjects with strabismus due to ocular albinism, diplopia, anomalous correspondence, or a medical history of seizures were excluded. All tests were conducted at a constant room luminance, measured with a digital lux meter (TES Electronic Corp., Taipei, Taiwan). This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Zhongshan Ophthalmic Center and The Hong Kong Polytechnic University. Informed consent was obtained from all participants before data collection. On the basis of previous data from both amblyopic observers\textsuperscript{15} and observers with normal binocular vision (Thompson, unpublished data, 2010), we estimated a difference in fellow fixing eye contrast at a balance point of 70% contrast between controls and observers with amblyopia with a maximum SD of 17%. To detect this difference at a significance level of $P < 0.01$ with a power of $0.99$ would require three participants per group. Our smallest subgroup contained 10 participants.

**Stereo Acuity Test**

Stereoacuity was assessed using the Randot stereo graded circle test (Random Dot 2 Acuity Test, Vision Assessment Corp., Elk Grove Village, IL). These values are reported in Table 1.

**Suppression Measurement**

**The Worth-4-Dot Test.** The Worth-4-Dot test was performed at near (35 cm) and far (6 m) test distances. The filters were placed, according to convention: red over the right eye and green over the left eye. To ensure the visibility of each filter, the participants’ eyes were covered alternately to ensure that each eye was visibly aware of the red and green filters. When this testing was performed monocularly, all participants reported seeing two red dots when the left eye was occluded (right eye wearing the red filter) and three green dots when the right eye was occluded (left eye wearing the green filter). Participants were asked to report the number and color of the dots they saw under photopic (118 lux) followed by scotopic (<0.1 lux) conditions. A scoring system was assigned to grade the depth and the size of the suppression scotoma. For example, a four-dot response with the white dot at the bottom was given a score of 0 (no suppression), while a two- or three-dot response received a score of 2 (complete suppression). A score of 1 (partial suppression) was assigned to observers who reported that they saw four dots, with the color of the bottom white dot being perceived as either green or red. The sum of near and far scores, which could range from 0 to 4, was used to represent the overall level of suppression as measured by this test, as we found no reliable difference between the near and far measurements (sign test, $P = 1.0$).

**The Neutral-Density Filter with the Bagolini Striated Lens Test.** The relative depth of suppression in the amblyopic eye was assessed by combining the Bagolini striated lenses test with neutral-density (ND) filters.\textsuperscript{17} Each observer viewed a light source (30 cd/m\textsuperscript{2}) held at 35 cm while wearing Bagolini striated lenses under low ambient room illumination (5 lux). Under normal viewing conditions, participants with normal binocular function perceive an X, representing the combination of the / seen by one eye and the \ seen by the other. However, for participants with suppression, only one line (/ or \) is perceived within the region affected by the suppression scotoma. To measure the strength of this suppression, progressively stronger ND filters can be placed over the fellow eye until the imbalance in luminance between the two eyes is sufficiently strong to overcome the suppression and allow for the percept of the X. To achieve this, ND filters (Wratten; Eastman Kodak Company, Rochester, NY), increasing in 0.3-log-unit increments were mounted on a bar. The filters ranged from 0.3 to 3 log units and had a transmittance ranging from 50% to 0.1%. The ND filter bar was held vertically in front of the fellow fixing (fixating) eye and moved upward to increase the strength of the ND filter. Participants were asked to report when they could perceive an X. The end point of this test was defined as the ND filter strength at which the intensity of the line seen by the amblyopic eye was perceived as the same or slightly stronger than the line seen by the fellow fixing (fixating) eye. To ensure the accuracy of this end point, the ND filter strength was increased by an additional 0.6 log units below this balance point, and the end point was measured again from seeing to nonseeing until a balanced reversal point was achieved.

**Dichoptic Motion Coherence Threshold Measurements**

The method we used for measuring interocular suppression using random-dot kinematograms has been described in detail elsewhere.\textsuperscript{15} Briefly, stimuli were displayed using a video goggle apparatus (Z800 3D Visor; eMagin Corp., Washington, DC) driven by a laptop computer (MacBook Pro; Apple Computer, Cupertino, CA, running MatLab; The MathWorks, Natick, MA) and the Psychophysics Toolbox, version 3.\textsuperscript{12,15,16} This apparatus allowed for separate images to be presented to each eye and for the images in each eye to be aligned by the participants, using routines within the stimulus presentation software. Stimuli were random-dot kinematograms, which consisted of a population of signal dots, all moving in a common direction, and a population of noise dots, that moved randomly. Dots were bright against a mean luminance background (35 cd/m\textsuperscript{2}). The luminance modulation (Michelson contrast) and hence the visibility of the dots could be varied by...
### Table 1. Clinical Details for the Observers with Amblyopia

<table>
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<tr>
<th>Observer</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Type</th>
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<th>LogMAR Visual Acuity (OD)</th>
<th>LogMAR Visual Acuity (OS)</th>
<th>Ocular Dev. (Prism D)</th>
<th>History</th>
<th>Stereopsis (sec arc)</th>
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(continues)
which suppression has been overcome and information is being com-
tic contrast offset as the “balance point,” as it represents the point at
and calculating the intersection of these fits.13 We refer to this dichop-
olds were the same irrespective of which eye saw the signal and which
The fellow fixing eye contrast at which the motion coherence thresh-
were presented to the fellow fixing eye was varied across five contrast levels
further details [their method 1] and illustrative figures of this tech-
increasing the luminance of the dots, with respect to the background,
according to the following equation:
Dot luminance contrast (%) = 100[(L_{signal} - L_{background})/L_{background}]
where $L_{signal}$ and $L_{background}$ are the dot and background luminance,
respectively. Signal dots were presented to one eye, and noise dots
were presented to the other eye. The task was to indicate the motion
direction of the signal dots. A staircase procedure controlled the
relative proportion of signal-to-noise dots in the stimulus to allow for
the measurement of a motion coherence threshold (the number of signal
dots required for 71% correct performance; see Black et al.13 for
further details [their method 1] and illustrative figures of this tech-
nique). To measure suppression, the contrast of the dots presented to
the amblyopic eye was fixed at 100% whereas the contrast of the dots
presented to the fellow fixing eye was varied across five contrast levels
(100%, 80%, 50%, 25%, and 12.5% contrast, equivalent to dot lumi-
nances of 70, 63, 52.5, 43.8, and 39.4 cd/m², respectively), using the
method of constant stimuli. Within a single measurement session, 10
randomly interleaved staircases were presented, five for each contrast
level with the signal dots shown to the amblyopic eye and five for the
signal dot presentation to the fellow fixing eye. Two measurement
sessions were conducted per patient separated by a 30-minute break.
The fellow fixing eye contrast at which the motion coherence thresh-
olds were the same irrespective of which eye saw the signal and which
saw the noise was calculated by fitting linear functions to the average
threshold data for each eye as a function of fellow fixing eye contrast
and calculating the intersection of these fits.13 We refer to this dichop-
tic contrast offset as the “balance point,” as it represents the point at
which suppression has been overcome and information is being combi-
pined between the two eyes in a normal fashion.12,13 Therefore, the
balance point contrast can be considered as a parametric measurement
of suppression.12 For the control group the nondominant eye, as
defined by the hole-in-the-card test, was designated as the amblyopic
eye for these measurements. The alignment of central nonius lines
(one to each eye) was used to ensure accurate alignment of the
stimulus fields seen by the right and left eyes. Subjects were asked to
attend to the central part of the stimulus field. The fact that for this
stimulus corresponding points are not stimulated (i.e., the signal and
noise dots do not overlap in space) allows fusion to occur on a more
global level, and we believe it is this that makes its use as a treatment
so effective. We view the point-wise suppression as more of V1 func-
tion and the global suppression more of extrastriate function.

### RESULTS

A one-way ANOVA conducted on the balance point data re-
vealed a significant main effect of group (control versus stra-
bismic versus anisometropic versus mixed; $F_{(3,40)} = 12.18, P <
0.0001$. Post hoc Bonferroni tests (corrected for multiple com-
parison) revealed that the control group balance points were
significantly higher than those of each of the three amblyopic
groups (strabismic $P < 0.03$; anisometropic $P < 0.001$; mixed
$P < 0.001$). The amblyopic groups did not differ significantly
from one another ($P > 0.05$). The mean contrast presented to
the fellow fixing (or dominant) eye at the balance point and the
corresponding 95% confidence interval (CI) can be seen in
Figure 1. It is evident that amblyopic participants had a signific-
antly larger imbalance between the eyes than the control
participants (i.e., lower fellow eye contrasts at balance point)
consistent with the presence of interocular suppression. The
fact that control participants did have a small contrast offset
reflects the sensitivity of this test to eye dominance.11,17 The mean coherence thresholds (i.e., the number of signal dots) at the balance point (95% CI) were as follows: controls, 16 (14–19); anisometropic, 10 (9–12); mixed, 11 (8–13); and strabismic, 13 (11–15). These results demonstrate that once balanced, the amblyopic participants performed no worse, in fact a little better, than the control observers; however, thresholds across the groups were generally comparable. The thresholds of amblyopic participants were very similar to those in previous reports using related techniques in a group of observers with amblyopia13 and a group of observers with normal binocular vision who were shown stimuli of equal contrast to both eyes.17 The relatively elevated thresholds we found for the control participants may reflect the fact that this technique is designed to measure suppression, and the use of a large range of contrasts may slightly bias motion coherence estimates when suppression is not present.

As our group of observers with amblyopia included both adult and juvenile (≤17 years of age) patients, we conducted a separate analysis to investigate the effect of age on the balance point data and on motion coherence thresholds. We found no difference between adults and juveniles for either the balance point data (t_{49} = 0.7, P = 0.52; juvenile mean, 56.4 [SD 21.5]; adult mean, 52.7 [SD 15.3]) or the motion coherence threshold data (t_{49} = 0.53, P = 0.60; juvenile mean, 11.5 [SD 3.8]; adult mean, 11.0 [SD 3.1]). We also found no correlation between age and either the balance point data (Spearman’s r = −0.2, P = 0.22) or the motion coherence data (Spearman’s r = 0.07, P = 0.65). These analyses indicate that the patient’s age did not systematically influence these variables. As such, the observers with amblyopia were treated as a single group in subsequent analyses.

To compare the balance point test with clinical tests of suppression, we correlated the results of the Worth 4-Dot test and the modified Bagolini striated lenses test with the balance point contrast. The near and far results for the Worth 4-Dot test were combined to give a score from 0 (no suppression for either test) to 4 (full suppression on both tests). For both suppression measures, there was a significant negative correlation with the fellow fixing eye’s contrast at the balance point (rank; Worth 4-Dot, r = −0.57, P < 0.0001; modified Bagolini, r = −0.74, P < 0.0001; Fig. 2). This finding demonstrates that the larger the difference in contrast between the two eyes that is necessary for normal binocular combination of motion signals (i.e., the lower the contrast in the fellow eye; recall that the contrast to the ambylopic eye remains fixed at 100%), the larger the amount of suppression measured using standard and modified clinical tests.

The contrast at the balance point also correlated significantly with both stereo sensitivity (r = 0.47, P = 0.002; the greater the stereo sensitivity, the less the difference in contrast between the eyes) and the acuity difference in log units between the eyes (r = −0.60, P < 0.001; the greater the acuity difference, the greater the contrast difference). These correlations are shown in Figure 3. To assess whether the relationship between these two variables and the contrast at balance point differed among anisometric, mixed, and strabismic amblyopes, we performed a univariate general linear model analysis on the contrast at balance point data with amblyopia type (anisometric versus mixed versus strabismic), acuity difference between the eyes, and stereo sensitivity as covariates. The model revealed a significant interaction between amblyopia type and acuity difference, F = 10.02, P = 0.003, demonstrating that the effect of visual acuity difference on balance point contrast varied across the different amblyopia subtypes. There was no significant interaction between amblyopia subtype and stereo sensitivity, suggesting that the effect of stereo sensitivity did not vary across the different amblyopia subtypes. To explore the interocular visual acuity difference and amblyopia subtype interaction further, we correlated interocular visual acuity difference with balance point contrast separately for each amblyopia subtype. Both the strabismic and mixed amblyopes showed significant negative correlations (strabismic: r = −0.62, P = 0.018, mixed: r = −0.82, P = 0.023). The anisometropic amblyopes also showed a negative correlation, but it did not quite reach significance (r = −0.42, P = 0.053), suggesting that the presence of strabismus influenced the
strength of the relationship between acuity difference and balance point contrast.

We have shown that dichoptic motion coherence thresholds can be used to assess sensory ocular dominance in observers with normal binocular vision. Since the participants in this previous study did not have any interocular suppression, we did not vary contrast between the eyes but rather presented stimuli at 100% contrast to both eyes and calculated the motion coherence threshold ratio for signal dots presented to the left eye versus signal dots presented to the right eye. To assess the relationship between this measure and the balance point measure for amblyopic observers, for each participant, we calculated the threshold ratio when stimuli were presented at 100% contrast for both eyes and correlated the result with the balance point measure. The threshold ratio was calculated as amblyopic eye threshold/fellow eye threshold, and therefore larger ratios indicate a greater degree of suppression of the amblyopic eye. As shown in Figure 4 these two measures correlated significantly ($r = 0.77$, $P < 0.001$). This relationship did not covary with amblyopia subtype ($F_{1,40} = 0.17$, $P = 0.69$).

Next, we assessed whether the amount of suppression was greater in participants who had never received treatment for their amblyopia. Within our sample, 16 anisometropic and 7 strabismic amblyopes had never received treatment, 6 anisometropic and 1 mixed amblyope had received patching only, 6 strabismic and 2 mixed amblyopes had received surgery only, and 4 strabismic and 1 mixed amblyope had received both patching and surgery. We found that the patients who had received treatment showed no difference in any of our measurements relative to the nontreated group (between-subjects $t$-tests, $P > 0.05$) and none of our outcome measures covaried with treatment and amblyopia subtype (univariate ANOVA with covariates of treatment type and amblyopia subtype). Figure 5 shows the mean contrast for the fellow fixing eye at balance point (Fig. 5A) and the mean interocular acuity difference (Fig. 5B) for each of the treatment groups (no treatment, patching only, surgery only, and both surgery and patching).

Finally, we considered only the participants with strabismic or mixed amblyopia who still had strabismus to assess whether the extent of strabismus was related to the strength of suppression. The relationship between angle of deviation and suppression is shown in Fig. 6 for both the balance point measure (Fig. 6A) and the Bagolini measure (Fig. 6B) of suppression. Exotropes and esotropes are identified in these plots by the use of filled and hollow markers, respectively. There were no reliable relationships between deviation angle and strength of suppres-
sion; however, in the esotropes there was a trend toward increasing suppression with increasing angle of deviation for the balance point measure, which did not reach significance, probably due to the small sample size of this group (n = 5; p = −0.7, P = 0.2). In addition, we found no relationship between angle of deviation and stereo acuity or interocular acuity difference (P > 0.05 for both).

**DISCUSSION**

In this study, we set out to answer the three questions detailed below.

**How does the new balance point method compare with the current clinical standards (Worth 4-Dot test and modified Bagolini test) across a clinical population?** Using a novel approach involving the measurement of dichoptic motion thresholds for stimuli of different interocular contrast, we show that the degree of suppression is significant in strabismus, anisometropia, and mixed amblyopia, but that there was no significant difference across our clinical sample in the different subgroups (i.e., strabisms, anisometropes, and mixed). We also demonstrate that this new quantitative approach to the measurement of suppression correlates strongly with traditional, albeit qualitative, clinical measures. Finally, we show a significant correlation between the balance point measure and a more abbreviated measurement based on the same principle previously used to quantify sensory dominance in the normal population. This conclusion is supported by data on eye dominance within the normal population. In all, these results suggest that this new approach has promise for quantifying suppression in binocular dysfunction and eye dominance in both clinical and normal populations.

**What is the relationship between visual losses in amblyopia (acuity and stereo) and the degree of suppression?** We determined the extent to which the contrast of the stimuli (signal or noise) presented to the fellow fixing eye had to be reduced in order for normal sensory binocular combination to take place (the contrast of stimuli seen by the amblyopic eye was fixed at 100%). As discussed above, this measure of suppression is in close agreement with standard clinical measures. We found that the degree of suppression measured using this technique significantly correlated with the degree of amblyopia and stereo loss. In other words, the greater the suppression, the greater the amblyopia. This result is contrary to accepted wisdom that stronger suppression is associated with weaker amblyopia, but is consistent with previous reports demonstrating stronger suppression with deeper amblyopia. It should be noted that our study differed from that of Holopigian et al. in several ways. Our sample was larger and had a greater range of amblyopia severity than did the sample reported by Holopigian et al., which mainly contained patients with very mild amblyopia (visual acuity of 20/30 or better in the amblyopic eye). Also their sample contained a disproportionate number of patients with alternating strabismus (8 patients in a sample of 10), which may represent a special category. A comparison of our findings with those of Holopigian et al. therefore raises the possibility that the suppression found in patients with amblyopia may differ from that in patients with alternating strabismus without amblyopia or in patients with very mild amblyopia. In addition, our primary measure of suppression differed from that used by Holopigian et al., who used monocular and dichoptic increment threshold measurements for 3.3-cyc/deg sinusoidal gratings presented foveally. Of note, their data show the same, albeit a weaker, relationship between suppression and stereopsis that we report wherein stronger suppression results in reduced stereopsis, as one would expect.

Our results, while being consistent with the idea that amblyopia results from suppression rather than the other way around, do not in themselves prove a causal connection. It is possible that they are positively correlated because both are the result of another factor, as yet unknown. What we can say is that if suppression were simply a mechanism to stop the diplopic vision from an amblyopic eye from reaching perception, then a greater degree of suppression would be necessary for mild compared with severe amblyopia. That is not what we found.

**How does suppression vary among the amblyopic clinical population?** Although it is commonly thought that the greatest degree of suppression occurs in cases of strabismic amblyopia and the least in cases of anisometropia, we did not find any significant differences between the degree of suppression in adults with strabismus, anisometropia, or mixed amblyopia and anisometropia using our balance point measurement. Furthermore, we did not find that the degree of suppression depended on the angle of the strabismus or the type of deviation in agreement with previous studies. However our sample size was necessarily small, and therefore these results are not definitive. A caveat is needed here, because our method averages sensitivity over the central 20° and can only provide a global measure of suppression. Since there is evidence that the size and extent of suppression scotomata depend on the type and angle of squint, a more localized measure is needed to address this issue. We are currently investigating this question.
CONCLUSIONS

If it is indeed the case that suppression plays a causal role in amblyopia, as our current data suggest, then there is an argument to be made for incorporating therapeutic approaches that directly target amblyopic eye suppression into amblyopia treatment regimens. We have recently shown that repeated exposure to dichoptic motion coherence threshold stimuli can improve visual acuity and stereopsis. These findings add further weight to the hypothesis that suppression plays a primary role in the amblyopia syndrome and the importance of considering suppression when treating amblyopia. These visual improvements are sustained and have so far been demonstrated in adults well beyond the critical period of visual development. We are presently developing a handheld, take home device on which the balance point principles are implemented in the form of a video game, suitable for the younger age group.

References