Objectives: To examine deficits in monocular and binocular vision in adults with amblyopia and to test the following 2 hypotheses: (1) Regardless of clinical subtype, the degree of impairment in binocular integration predicts the pattern of monocular acuity deficits. (2) Subjects who lack binocular integration exhibit the most severe interocular suppression.

Methods: Seven subjects with anisometropia, 6 subjects with strabismus, and 7 control subjects were tested. Monocular tests included Snellen acuity, grating acuity, Vernier acuity, and contrast sensitivity. Binocular tests included Titmus stereo test, binocular motion integration, and dichoptic contrast masking.

Results: As expected, both groups showed deficits in monocular acuity, with subjects with strabismus showing greater deficits in Vernier acuity. Both amblyopic groups were then characterized according to the degree of residual stereoacuity and binocular motion integration ability, and 67% of subjects with strabismus compared with 29% of subjects with anisometropia were classified as having “nonbinocular” vision according to our criterion. For this nonbinocular group, Vernier acuity is most impaired. In addition, the nonbinocular group showed the most dichoptic contrast masking of the amblyopic eye and the least dichoptic contrast masking of the fellow eye.

Conclusion: The degree of residual binocularity and interocular suppression predicts monocular acuity and may be a significant etiological mechanism of vision loss.

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AMBYLOPIA IS A DEVELOPMENTAL VISUAL DISORDER CHARACTERIZED BY ABNORMAL FORM VISION AND BINOCULAR FUNCTIONS. PAST RESEARCH HAS DIFFERENTIATED THE PERFORMANCE OF SUBJECTS WITH STRABISMIC AND ANISOMETROPIC SUBTYPES OF AMBLYOPIA. OFTEN THE MOTIVATION IS TO BETTER UNDERSTAND THE PATHOGENESIS OF AMBLYOPIA. AN IMPORTANT SOURCE OF EVIDENCE IS MONOCULAR POSITION ACUITY TASKS. FOR EXAMPLE, VERNIER ACUITY LOSS IS MORE SEVERE IN SUBJECTS WITH STRABISMUS COMPARED WITH THOSE IN SUBJECTS WITH ANISOMETROPIA. IN SUBJECTS WITH STRABISMUS, THE DEFICIT IS LARGER THAN THAT PREDICTED BY LINEARLY SCALING THEIR GRATING ACUITY, INDICATING THAT ADDITIONAL DEFICITS ARE INVOLVED. DIFFERENT MODELS AT-
monocular and binocular deficits. In this study, McKee and colleagues proposed that the severity of binocularity loss may sometimes better predict the nature of the physiological changes in amblyopia than the clinical etiology. In other words, the degree of binocularity may at least partially predict abnormality on monocular tasks. They compared the Vernier acuity of a binocular group with that of a matched “nonbinocular” group and found a significant difference (P < 0.001) between them. Similar ideas have been proposed in animal models of induced amblyopia.19

The present study attempts to replicate the conclusions of the study by McKee et al14 in a hypothesis-driven manner. We determined whether the results of their study could be replicated using a more typical moderate number of subjects, for whom it is not possible to match subjects with binocular and nonbinocular vision according to visual resolution. In addition, we introduced a test not included before, dichoptic contrast masking, so that the degree of interocular inhibition could be directly assessed.

### METHODS

#### SUBJECTS

This study examined 20 subjects, including 7 control subjects, 7 subjects with anisometropia, and 6 subjects with strabismus (Table 1); subject groups were matched for mean age (25.1, 28.0, and 26.3 years, respectively) and mean years of education (13.7, 14.9, and 13.5 years, respectively). Subjects provided informed consent conforming to the Declaration of Helsinki (West Virginia University Institutional Review Board Protocol 14788). Any subject with known or suspected neu-

### Table 1. Characteristics of Clinical Groups

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Snellen Acuity</th>
<th>Deviation in Prism Diopter</th>
<th>Refraction*</th>
<th>Interocular Difference in Spherical Equivalent of Refractive Error</th>
<th>Age at Diagnosis, y</th>
<th>Age at Eye Correction Surgery, mo</th>
<th>Patching Treatment, mo</th>
<th>Binocular Vision</th>
<th>Stereoacuity, arc seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/20</td>
<td>-0.25 + 0.50</td>
<td>0</td>
<td>0.30</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20/16</td>
<td>-2.25 + 0.50</td>
<td>-3.75 + 0.75</td>
<td>1.25</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20/20</td>
<td>0.00</td>
<td>0</td>
<td>0.25</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20/16</td>
<td>-0.25 + 0.25</td>
<td>0</td>
<td>0.25</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>20/16</td>
<td>0.00</td>
<td>0</td>
<td>0.25</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20/20</td>
<td>0.50</td>
<td>0.50</td>
<td>0.25</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20/20</td>
<td>-1.75 + 1.75</td>
<td>-1.50 + 1.25</td>
<td>1.0</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 0.00 indicates no refractive error.
† A score of 7000 arc seconds was assigned to subjects who scored incorrect on every trial.
‡ All esotropic except for exotropic strabismus in subject 6.

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rological conditions was excluded from the study. All subjects completed an ophthalmologic examination to confirm diagnosis. For control subjects, dominant and nondominant assignments were given to the eyes based on acuity measures. Most subjects with amblyopia had a history of patch treatment during childhood (ie, a patch was worn to cover the dominant [fellow] eye). One subject with exotropic strabismus showed equal visual acuity in both eyes at the time of testing.

Diagnosis of anisometropic amblyopia was made on the basis of (1) an interocular refractive difference of hyperopia of at least 1.00 diopter (D), astigmatism of at least 1.00 D, or myopia of at least −2.50 D or (2) a history of anisometropia but no strabismus by clinical alternate cover testing and no history of strabismus or strabismus surgery. Diagnosis of strabismic amblyopia was made on the basis of a history of strabismus or strabismus surgery and no anisometropia. In clinical practice, some subjects with amblyopia have a mixed strabismic and anisometropic diagnosis at initial examination, although little consensus exists regarding additional subtypes. One subject with strabismus might be classified as having a mixed diagnosis because of an interocular refractive error difference of 1.5 D (Table 1).

GENERAL PROCEDURES AND APPARATUS

Except for Snellen acuity and Titmus stereo tests, tests were administered in darkened rooms using calibrated visual display hardware. Stimuli were generated with the use of Psychophysics Toolbox
and MATLAB for Macintosh OS (Natick, Mass). Vernier acuity and grating acuity tests were administered using a high-resolution monitor (Hitachi SuperScan 812; Hitachi, Brisbane, Calif) viewed from 5.87 m. Subjects were tested with (their normal optical correction) with one eye covered by a translucent patch. The amblyopic eye was always tested after the fellow eye.

Binocular motion integration and dichoptic contrast masking tests achieved dichoptic stimulation using a device from Avotec, Inc (SV 4021; Stuart, Fla). This system offers dual independent fiberoptic periscopes with built-in optical correction and provides a real-time feedback image of each eye. We took the following steps to ensure correct alignment of stimuli in the 2 eyes: (1) The position of each eyepiece was adjusted to bring each eye to the center of the screen. (2) Subjects’ perception of nonius cues was determined, and fine adjustment of the stimulus was performed using software to achieve alignment. Nonius cues were composed of green angles for the left eye. One subject with exotropic strabismus showed equal childhood (ie, a patch was worn to cover the dominant [fellow] eye). One subject with exotropic strabismus showed equal childhood (ie, a patch was worn to cover the dominant [fellow] eye).

**MONOCULAR TESTS**

**Snellen Acuity**

This test was performed at the West Virginia University Eye Center as part of a clinical examination. A standard chart (Lambert Instrument, Norfolk, Va) was used.

**Grating Acuity**

For each trial, the subject saw 2 temporally sequenced screens; 1 contained a vertical sinusoidal grating (80% contrast, subtending 8° of visual angle). The subject identified the grating epoch (2-alternative forced-choice paradigm). Spatial frequency was varied by a staircase procedure that increased spatial frequency following 1 correct response and decreased spatial frequency after 1 error. Approximately one third of trials were blanks. The staircase was terminated after 7 reversals. The threshold value was the mean of the last 4 reversals.

**Vernier Acuity**

Five high-contrast (90%) offset pairs of horizontal lines, each 2.5-mm wide and 15-cm long (7.5 cm each half), were separated vertically by 2.5 cm. Subjects first adjusted the stimulus offset until the relative position of the left side was visibly different from that of the right side. The mean offset obtained from 4 adjustments was used as a starting offset for a 2-alternative forced-choice paradigm (1 down–1 up). Four search reversals were used with a step size of 1 pixel, followed by 6 test reversals with a step size of 0.125 pixel. Subpixel resolution was achieved using luminance dithering. The threshold value was the mean of 6 test reversals. Feedback was provided.

**Contrast Sensitivity**

Each eye was tested separately using the Avotec device. Monocular functions were assessed as the nontested eye viewed a mean-level gray screen. For each trial, the subject saw 2 temporally sequenced screens, one of which contained 2-cycles per degree (cpd) vertical sinusoidal grating (7.5°). A 2-alternative forced-choice paradigm procedure was used (2 down–1 up) to approach the threshold (71%). Three search reversals (6 dB) preceded 4 test reversals (2 dB). The threshold obtained was used to compute the suprathreshold stimuli for the dichoptic contrast masking test.

**BINOCULAR TESTS**

**Titmus Stereo Test**

This test (Titmus Optical, Inc, Petersburg, Va) was included in the clinical examination. Subjects wore polarized lenses and distinguished between raised circles and distracter circles with no stereo offset. Nine trials of increasing difficulty are associated with stereocuity from 40 to 800 arc seconds. This test assesses crude stereopsis with an image of a housefly (3500 arc seconds). For subjects who could not perceive the fly, a (doubled) score of 7000 arc seconds was assigned (Table 1).

**Binocular Motion Integration**

Each eye viewed a vertical grating patch in which contrast was modulated sinusoidally at 2 Hz. The stimuli shown to the left vs the right eye were spatially and temporally out of phase by 90°. The direction of phase shifts produced an illusion in which the binocularly summed signal appeared to move left or right, as described by Carney and Shadden. The contrast in one eye was set at 65%. The subject adjusted the contrast for the other eye to
match. Once the nonius cues were aligned, observers were given 20 trials in which they saw the stimuli for 2 seconds and judged the direction of movement. Feedback was provided. Five blocks of 20 trials were used to test 5 spatial frequencies (0.312, 0.625, 1.25, 2.5, and 3.0 cpd). The percentage of correct trials was scored.

Dichoptic Contrast Masking

Once the nonius cues were aligned, each eye was tested separately. Each trial consisted of 2 temporally sequenced epochs. The nontested eye viewed a vertical masking grating (2 cpd) in both epochs shown at 1.0 log unit above the monocular contrast sensitivity threshold (of that nontested eye). The eye being tested viewed a vertical grating stimulus (2 cpd) in 1 of the epochs. The subject decided which epoch contained a grating with the most contrast (2-alternative forced-choice paradigm). The starting contrast was 40%, and a 2 down–1 up staircase procedure was used to find the dichoptic increment contrast detection threshold.

STATISTICAL ANALYSIS

The analyses of variance (ANOVAs) were performed using JMP software (SAS Institute Inc, Cary, NC). Two factors, diagnosis (control, strabismic, or anisometropic) and eye tested (amblyopic and fellow eyes), were used. For binocular motion integration, spatial frequency was also a factor. Subsequently, we subdivided our subjects according to the results in values of $R^2$. Significant deficits were seen (Table 1). ANOVAs for Snellen acuity, subjects with anisometropia showed a main effect of diagnosis, eye tested, and their interaction. Subjects with strabismus showed a main effect of diagnosis, but no significant effect of eye tested or interaction between the factors was observed. For Vernier acuity, subjects with anisometropia showed a main effect of diagnosis, but no significant effect of eye tested or interaction between the factors was observed. However, subjects with strabismus showed a main effect of diagnosis, eye tested, and their interaction.

Pearson product-moment correlation between Snellen acuity and Vernier acuity (amblyopic and fellow eyes) was calculated separately by diagnosis. Subjects with anisometropia ($R^2=0.64$; $P=.001$) showed a much stronger correlation than subjects with strabismus ($R^2=0.48$; $P=.01$). When grating acuity was compared with Vernier acuity, no significant correlation was found for subjects with anisometropia ($R^2=0.15$; $P=.17$) or for subjects with strabismus ($R^2=0.27$; $P=.08$).

**BINOCULAR TESTS**

**Titmus Stereo Test**

Significant deficits were seen (Table 1). ANOVAs for subjects with anisometropia ($P<.001$; $F=147.5$) and for subjects with strabismus ($P<.001$; $F=207.3$) were significant for the effect of diagnosis. These results were confirmed by nonparametric statistics using ranked categories in which failure to detect any target is the lowest rank.

**Binocular Motion Integration**

Control subjects showed the expected spatial frequency dependency, with best performance at low spatial frequencies and performance approaching 50% at 5.0 cpd (Figure 1). Comparison of their performance at 0.312 cpd with that at 1.25, 2.5, and 5.0 cpd using paired $t$ tests results in values of $P=.02$, $P=.01$, and $P<.001$, respectively. ANOVA performed to compare subjects with anisometropia and control subjects showed a significant effect of diagnosis ($P<.001$; $F=10.1$) and spatial frequency ($P<.001$; $F=36.6$), with no interaction. Comparison of subjects with strabismus and control subjects showed a significant effect of diagnosis ($P<.001$; $F=70.1$), spatial fre-
Amblyopic Eye Performance. Figure 2B shows the effect of masks in the fellow (dominant) eye on the increment thresholds of the amblyopic (nondominant) eye. Again, all subjects demonstrated inhibition (ie, stimulation of the dominant eye reduced the performance of the non-dominant eye). However, the amblyopic eyes were not significantly abnormal.

RELATIONSHIP BETWEEN MONOCULAR AND BINOCULAR DEFICITS

Next, we reclassified our subjects with amblyopia based on residual binocularity, and 67% of subjects with strabismus and 29% of subjects with anisometropia were classified as having nonbinocular vision (Table 1). Using ANOVA, we compared monocular acuities of control subjects with those of subjects with amblyopia using the new classification. The factors were subject group (control, binocular, or nonbinocular) and eye tested (Table 3). The binocular and nonbinocular groups were impaired for all 3 tests, except that Vernier acuity for the binocular group missed significance. Therefore, the nonbinocular group is distinguished from the binocular group by abnormal Vernier acuity, reinforcing the idea that binocular functions can predict loss of this “hyperacuity.”

Pearson product-moment correlation between Snellen acuity and Vernier acuity was significant for the binocular group ($R^2=0.38; P=.001$) but was reduced for the nonbinocular group ($R^2=0.45; P=.02$) (Figure 3A). This suggests that additional factors are needed to explain the Vernier acuity deficit in subjects with nonbinocular amblyopia. The correlation between grating acuity and Vernier acuity was significant for neither the binocular group ($R^2=0.31; P=.04$) nor the nonbinocular group ($R^2=0.15; P=.2$) (Figure 3B).

We compared dichoptic contrast masking for the binocular and nonbinocular groups (Figure 2). The nonbinocular group showed the most suppression of the amblyopic eye and the least suppression of the fellow eye ($P=.004; t=3.6$). These effects might be attributed to a history of strong interocular suppression. Finally, we did not observe any clear correlation between the difference in monocular contrast sensitivity and the degree of interocular contrast suppression among our subjects with amblyopia.24,25

We performed multiple measures of monocular acuity in subjects with strabismic and anisometropic amblyopia. As is typical for subjects with amblyopia, the visual resolution demonstrated by grating acuity is finer than that demonstrated by Snellen acuity:14,15 likely because of crowding, interference between multiple spatial frequencies, or stimulus size. Nevertheless, grating acuity generally correlates with Snellen acuity. On the other hand, Vernier acuity is a hyperacuity, sensitive to different factors. The ratio of Vernier acuity to grating acuity is frequently used to de-
scribe the difference between the 2 functions and has been reported to be 7.5:1 for healthy subjects. The higher ratio among our control subjects (12:1) can be attributed to stimulus-related factors (horizontal vs vertical offsets, number, and length of bars). We might have expected a higher ratio for subjects with anisometropia (5.8:1) than for subjects with strabismus (6.1:1), but our subjects with anisometropia included 2 very impaired subjects (who were later categorized as having nonbinocular vision). Nevertheless, we found a better correlation between Snellen acuity and Vernier acuity for subjects with anisometropia than for subjects with strabismus, as expected.

Deficits were observed for all subjects with amblyopia on our binocular tests. The categorization into binocular and nonbinocular vision was based on residual function measured using Titmus stereo test and binocular motion integration. Titmus stereo test categorization was based on the presence of gross stereovision (the binocular group achieved acuity ≥800 arc seconds). Similarly, for binocular motion integration, performance at low spatial frequencies (0.3 cpd) was the discriminating factor. Most subjects with strabismus (and by definition all of the nonbinocular group) were impaired at this lowest spatial frequency. This ability may be commonly spared in subjects with anisometropia because lower spatial frequencies are less affected by spatial blur. In addition, sensitivity for low spatial frequencies develops earlier than that for higher spatial frequencies and may be less vulnerable to the effects of abnormal experience.

We further characterized the nonbinocular group by measuring dichoptic contrast masking, and our results were generally consistent with previous reports. Harrad and Hess used a paradigm similar to ours, although they used a range of contrast masking, whereas we tested one contrast level (tailored to each subject’s monocular sensitivities). They found abnormally weak masking by amblyopic eyes and abnormally strong masking by fellow eyes. However, only subjects with strabismus showed this effect; subjects with anisometropia were less impaired. We did not find a consistent difference between clinical subgroups, but a similar distinction was seen after categorizing subjects based on residual binocularity. The nonbinocular group displayed strong asymmetry in interocular masking, whereas the binocular group showed little asymmetry. This result seems to be consistent with the theory that a history of strong amblyopic eye suppression distinguishes the nonbinocular group and is an important etiological determination of their constellation of deficits. Even with monocular view-

### Table 3. Analysis of Variance Results for the 3 Monocular Tests According to Binocularity Classification

<table>
<thead>
<tr>
<th>Test</th>
<th>Group</th>
<th>Mean Acuity</th>
<th>P Value (F Distribution)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Amblyopic Eye</td>
<td>Fellow Eye</td>
</tr>
<tr>
<td>Snellen acuity, minimum angle of resolution</td>
<td>Control</td>
<td>1.01</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Binocular</td>
<td>2.25</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>Nonbinocular</td>
<td>3.68</td>
<td>1.10</td>
</tr>
<tr>
<td>Grating acuity, arc minutes</td>
<td>Control</td>
<td>0.79</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Binocular</td>
<td>1.35</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Nonbinocular</td>
<td>1.27</td>
<td>0.87</td>
</tr>
<tr>
<td>Vernier acuity, arc minutes</td>
<td>Control</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Binocular</td>
<td>0.23</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Nonbinocular</td>
<td>0.36</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Only statistically significant differences are given.
ing, spatial localization abilities such as Vernier acuity may be particularly impaired because subjects with nonbinocular vision suppress or ‘neglect’ the amblyopic eye input.29 The hypothesis that Vernier acuity relies on neural pathways that overlap with binocular integration pathways is attractive.30,31 Both functions may depend on cortical regions beyond the primary visual cortex, and there is evidence for extrastriate abnormalities in amblyopia from animal studies.19,32,33 and from human neuroimaging.14-30. The correlation between Vernier acuity and binocularity might also be explained developmentally. Vernier acuity reaches adult levels at age 10 years,17 and binocular acuity reaches adult levels at age 9 years.38 In contrast, gratting acuity develops rapidly in the first year of life and then continues to develop more slowly, reaching adult levels at age 3 to 6 years.39

These results reinforce the theory that achieving residual binocularity is desirable in the treatment of subjects with amblyopia, regardless of clinical subtype. In this study of treated adults, we cannot determine whether residual binocularity is achieved because of more favorable etiological factors or because of effective treatment. The age at diagnosis was late for some subjects with nonbinocular amblyopia (Table 1). This is consistent with suggestions that early treatment results in better stereocuity (at least in the case of esotropia).30 Treatment regimens that incorporate sufficient binocular vision would be important in this context. Although stereopsis may generally improve during treatment along with visual acuity,40 regular testing of stereopsis is desirable and might be considered a separate factor for treatment optimization. Residual stereocuity has been associated with reduced risk of recurrent esotropia after surgery41 and is associated herein with more symmetrical interocular inhibition and with better Vernier acuity.14

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