

## CASE REPORT

# A Binocular Approach to Treating Amblyopia: Antisuppression Therapy

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### ABSTRACT

**Purpose.** We developed a binocular treatment for amblyopia based on antisuppression therapy.

**Methods.** A novel procedure is outlined for measuring the extent to which the fixing eye suppresses the fellow amblyopic eye. We hypothesize that suppression renders a structurally binocular system, functionally monocular.

**Results.** We demonstrate using three strabismic amblyopes that information can be combined normally between their eyes under viewing conditions where suppression is reduced. Also, we show that prolonged periods of viewing (under the artificial conditions of stimuli of different contrast in each eye) during which information from the two eyes is combined leads to a strengthening of binocular vision in such cases and eventual combination of binocular information under natural viewing conditions (stimuli of the same contrast in each eye). Concomitant improvement in monocular acuity of the amblyopic eye occurs with this reduction in suppression and strengthening of binocular fusion. Furthermore, in each of the three cases, stereoscopic function is established.

**Conclusions.** This provides the basis for a new treatment of amblyopia, one that is purely binocular and aimed at reducing suppression as a first step.

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Key Words: amblyopia, global motion, contrast, binocular summation, dichoptic interaction, treatment of amblyopia

The most common treatment for improving monocular function involves patching the good eye to force the amblyopic eye to improve. Although there is often improvement to monocular function for amblyopic children younger than 12 years,<sup>1</sup> this does not always result in binocular function.<sup>2</sup> There is a need for alternate approaches that might be more effective in children, might be applicable to even adults who have been left permanently visually disabled and whose treatment has been abandoned,<sup>1</sup> might promote cooperation between the two eyes with the eventual hope of establishing some rudimentary form of depth vision, and will not have adverse psychosocial side effects.

Our understanding of the binocular deficit of amblyopes, particularly strabismics, has changed in recent years. We now know that the loss of the binocular responsiveness of cortical cells in strabismic animals is largely reversible<sup>3</sup> by ionophoretic applications of bicuculline (selective blocker of GABAA receptors), suggesting a functional suppression of the input from the strabismic eye rather than a loss of cells driven by that eye's input.<sup>4</sup> Furthermore, there is reason to doubt the claim that humans with ambly-

opia do not possess binocular mechanisms, since Baker et al.<sup>5</sup> showed normal binocular contrast summation in adult strabismic amblyopes when the signal attenuation by the amblyopic eye is accounted for (i.e., using signals whose contrast are normalized to threshold), suggesting that the apparent lack of binocular combination found previously was simply because of an imbalance in the monocular signals before the point of summation. All of these results on amblyopic animals and humans point to the fact that strabismic amblyopes do have intact, but suppressed, binocular mechanisms. In support of this, it has been shown that the reason why binocular combination does not normally occur for suprathreshold motion and orientation tasks in strabismic amblyopia is because of interocular suppression.<sup>6</sup> A reduction in suppression leads to normal levels of binocular combination in strabismic amblyopia, revealing the presence of functioning binocular cortical mechanisms. Finally, it has been shown that the monocular vision of adult amblyopes can be improved after only 10-min application of repetitive transcranial magnetic stimulation to the visual cortex, suggesting that a significant part of the monocular loss may be suppressive in nature.<sup>7</sup> Thus, there is converging evidence for the conjecture that strabismic amblyopes possess cortical cells with binocular connections but that under binocular (and to a lesser extent, monocular) viewing, suppressive mechanisms render their

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cortex functionally monocular. The consequence is that amblyopia is an intrinsically binocular problem and not the monocular problem on which current patching treatment is predicated. Thought of in this way, the binocular problem involving suppression should be tackled at the very outset if one is to achieve a good binocular outcome as opposed to hoping binocular vision will be regained simply as a consequence of acuity recovery in the amblyopic eye, which is the current approach and which is often not found to be the case.<sup>2</sup>

Recently, we developed a novel way of quantifying suppression.<sup>6</sup> We showed, under a wide variety of conditions, when the signal to the fellow fixing eye is reduced in strength (in this context this is the contrast of the stimuli), strabismic amblyopes can combine information between their two eyes, as normal patients do. Thus, our current notion of suppression is that it reduced the efficiency with which the signal seen by the amblyopic eye is transduced. The extent to which the signal strength to the fellow fixing eye needs to be reduced allows one to quantify the degree of suppression. Here, we report the results of three case studies where continual and intensive measurement of the degree of suppression leads, in itself, to a reduction of the degree of suppression until it is eliminated. In other words, providing artificial viewing conditions under which binocular combination can take place results in a strengthening of binocular vision, so that it can occur under a wider variety of interocular viewing conditions. Eventually, binocular combination can occur under more natural viewing conditions when the eyes view objects of the same physical contrast. This finding provides the basis for a new binocularly based treatment of amblyopia in which the suppressive imbalance is measured and treated as a first step. We found that in many cases, the reduction in suppression led not only to a reestablishment of stereoscopic function but also to a reduction in the monocular acuity deficit, attesting to the primal importance of suppression in the amblyopic syndrome.

## METHODS

### Observers

We discuss the case results of three adult strabismic amblyopes who underwent antisuppression therapy. Refraction in all observers was undertaken, and vision was corrected to best visual acuity. The “Declaration of Helsinki” was followed and informed consent was obtained from all observers before data collection.

### Dichoptic Global Motion

#### *The Measurement of Suppression*

To measure the ability of amblyopic observers to binocularly combine motion information, we used random dot kinematograms and a coherence motion discrimination task (see Ref. 6 for details). These stimuli are constructed of two populations of moving dots. The “signal” population consists of dots that all move in the same direction, termed the “coherent” direction. Conversely, the “noise” population has no common motion direction because all the dots move in random directions. The ratio of signal to noise dots required to determine the coherent motion direction is called the motion coherence threshold. Therefore, by using these stimuli with signal and noise separated dichoptically, one can assess the

degree to which underlying mechanisms combine information from two eyes.

We have previously used this approach to study binocular interactions in normals<sup>8</sup> and strabismic amblyopes,<sup>6</sup> and the test has a high test/retest reliability ( $r = 0.89$ ;  $p < 0.0001$ ). Performance (that is the signal magnitude required to reach the threshold criterion) was quantified by changing the signal to noise ratio in the random dot kinematogram. The extent to which information was combined binocularly was quantified by only allowing one eye to see the signal and the other eye to see the noise (Fig. 1). In a binocularly normal individual, the noise seen by one eye makes the detection of the motion direction of the signal elements seen by the other eye more difficult. However, it does not matter which eye sees the signal and which sees the noise. There is a “dichoptic balance” in the threshold performance. In amblyopes with suppression, it matters which eye sees the signal and which eye sees the noise. In the most extreme case, if the fellow fixing eye sees the signal and the amblyopic eye sees the noise, then owing to the suppression of the amblyopic eye by the fellow fixing eye, performance will be at ceiling. On the other hand, if the amblyopic eye sees the signal and the fellow fixing eye sees the noise, then the performance will be at chance. Thus, one would expect there to be an imbalance in the dichoptic thresholds because of suppression. By suitably imbalancing the strength of the signals seen by the fellow fixing eye (be it signal or noise), we found that balanced dichoptic performance could be obtained, reflecting the fact that the information from the two eyes was being combined binocularly. In other words, imbalancing the input to the amblyopic binocular visual system can result in a balanced output, namely normal binocular combination. The extent of the signal imbalance needed to achieve this balanced performance provides a measure of the degree of suppression.

The dichoptic stimuli were produced using a large, eight-mirror stereoscope to allow signal and noise dots to be presented separately to each eye, and thresholds were measured using a standard up/down staircase procedures. The testing field was circular with a diameter of 7°, having an outer peripheral fusion frame that was used to ensure correct alignment of dichoptic images in the case where strong suppression prevented the central nonius markers from being used. This was the case for the first strabismic amblyope (case 1).

### Stimulus

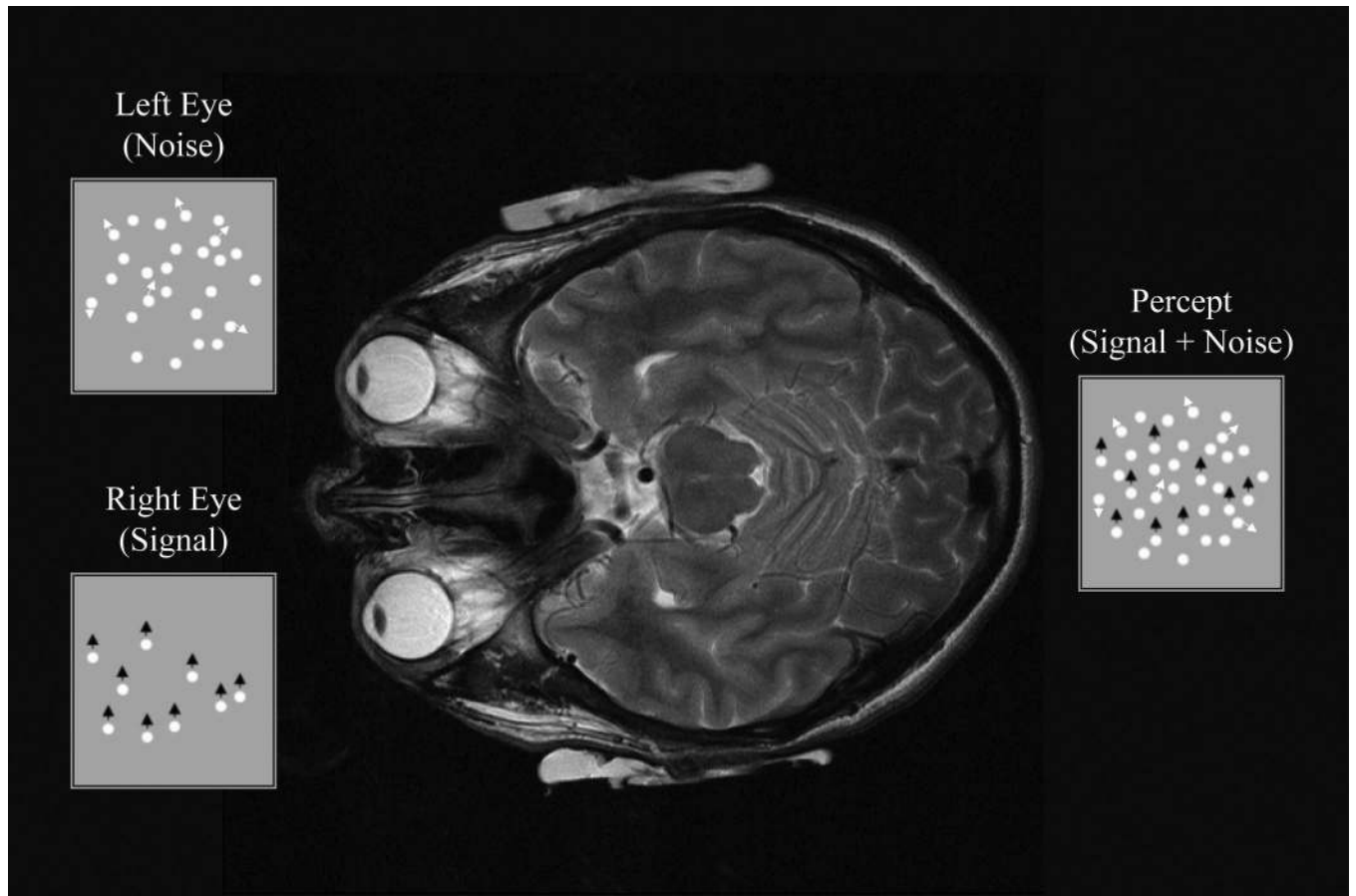
#### *Visual Acuity and Stereo Acuity*

Visual acuity was measured with a Snellen letter chart at 6 m, and stereo acuity using the preschool Randot test at 30-cm viewing distance.

## RESULTS

### Case 1

Case 1, a 44-year-old man, who was an emmetrope, presented with a constant 20° left esotropia and grossly reduced acuity (20/400) in the left eye that could not be improved with a refractive correction. He had a history of strabismic amblyopia from the age of 4 years, when the strabismus was first detected but had not



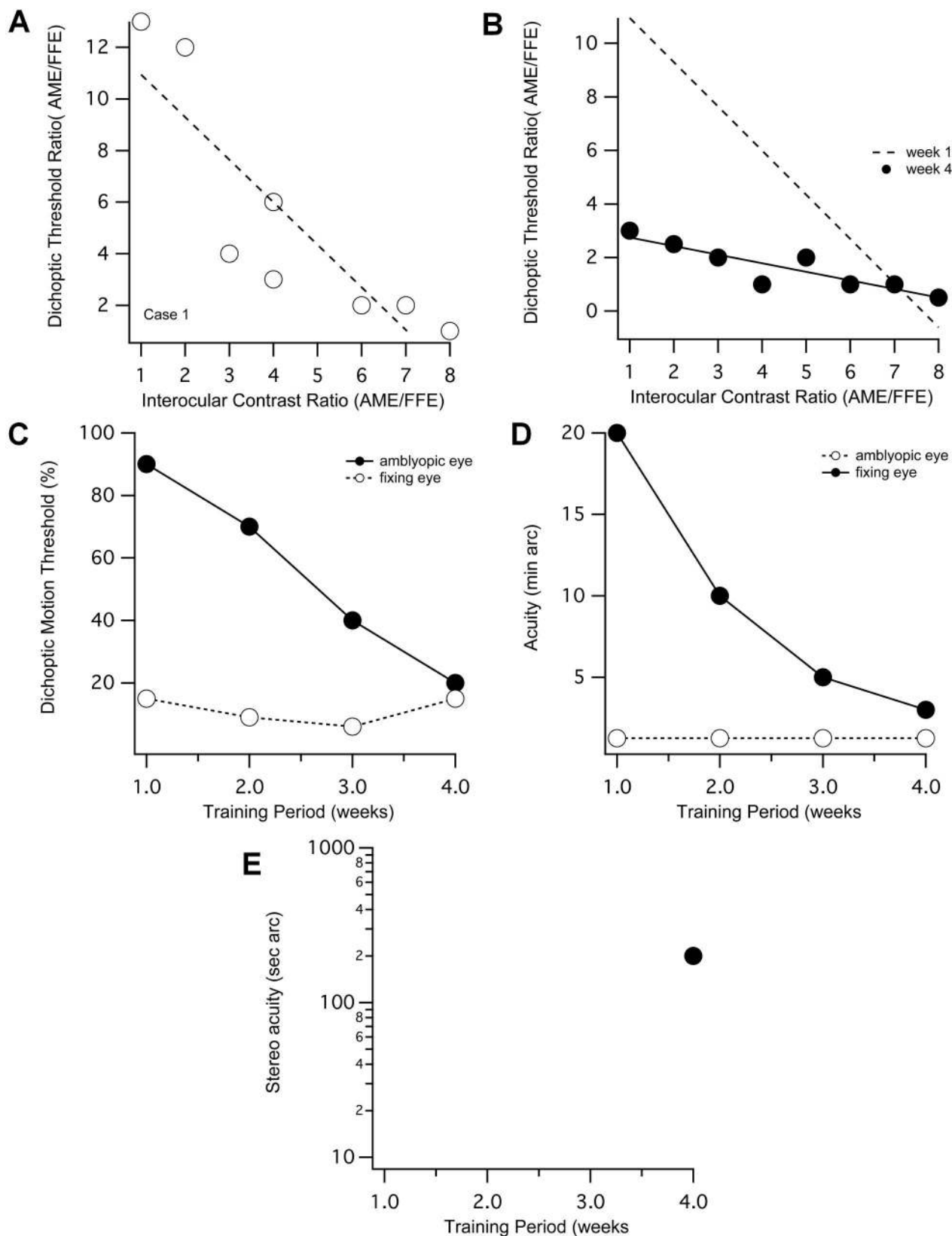
**FIGURE 1.**

Schematic presentation of the random dot kinematogram shown to each eye during dichoptic viewing. Black arrows show the signal dots schematically, which were moving in the same direction (up vs. down) within a trial. White arrows represent the noise dots schematically, which were moving in random directions. In different trials, signal dots were shown to the fixing eye and noise dots to the fellow amblyopic eye and vice versa. The ratio of the thresholds obtained for these two types of dichoptic presentations was computed as the dichoptic threshold ratio.

undertaken any patching and had not had surgery. He did not show fusion on the Worth 4 dot test (distance and near) and had no measurable stereopsis on the preschool Randot test (near). Our measurement of his suppression using our dichoptic global motion stimulus is shown in Fig. 2A. Here, we are plotting the dichoptic threshold ratio, which is the ratio of the performance when the amblyopic eye sees the noise and the fellow eye the signal compared with vice versa. In a binocularly normal observer, it does not matter whether the right eye sees the signal and the left eye sees the noise or vice versa because the information from the two eyes is combined and the binocular signal to noise ratio is the same in these two situations. In this case, we would expect the dichoptic threshold ratio as expressed in Fig. 1A, B to be at unity. The extent to which the dichoptic ratio is above unity signifies that there is an imbalance in the combination of binocular information, and in the case of strabismus, this is because of suppression. We quantify the degree of suppression by seeing how much we have to offset the contrast (i.e., reduce it in the fellow fixing eye) to establish equal performance (i.e., a dichoptic threshold ratio of unity). The abscissa is the contrast ratio of the stimulus (be it signal or noise) seen by each eye. The contrast of his fellow fixing eye had to be reduced by a factor of  $\sim 8$  before there was evidence that information was being combined between his two eyes (the balance point is indicated

by the interocular contrast ratio that corresponds to a dichoptic threshold ratio of unity, i.e., x axis intercept). This indicates a strong level of suppression exerted on the amblyopic by the fixing eye under binocular viewing conditions.

This subject came in for 3 weeks, (4 days a week, average of 350 threshold measurements per week) repeating this measurement of the balance point under the assumption that by providing conditions over an extended time where the suppression by the fixing eye is reduced (by reducing the contrast of the signal and noise seen by the fixing eye) that this would lead to a strengthening of the binocular connections that underlay the combination of left and right eye information. Summary measurements of the balance point after the first (dashed line) and last (filled symbols) week of training are shown in Fig. 2B. It is clear that after a substantial amount of binocular training, the degree of suppression is reduced, as reflected in the fact that the contrast of stimuli shown to the fixing eye now needed to be reduced to a much lesser extent. In this case, the balance point (i.e., the contrast ratio at which the dichoptic threshold ratio was unity) only changed a little (i.e., from a contrast ratio of eight before treatment to one of five after treatment); however, large changes occurred in the extent to which the fellow fixing eye's signal needed to be reduced in contrast for binocular combination to take place (i.e., for stimuli of equal contrast, the



**FIGURE 2.**

Results are shown for Case 1 in terms of (A) the initial measurement of suppression (see text), (B) how this changed with prolonged artificial binocular viewing, (C) how the dichoptic threshold for both eyes changed with prolonged artificial binocular viewing, (D) how visual acuity changed for each eye as a function of the training, and (E) the reinstating of stereopsis after training.

dichoptic threshold ratio was 11 before treatment, and three after treatment). The fact that it took 1 or 2 weeks before improvements were seen was probably because of the limited treatment duration.

Another way of quantifying the extent to which suppression is reduced, and as a consequence binocular combination is strengthened, is to compare results where each eye receives stimuli of the same contrast (conditions where suppression is maximal). This is relevant to everyday viewing where the physical contrast of stimuli impinging on the retinae is of identical contrast. This corresponds to the condition where dichoptic motion thresholds (e.g., Fig. 2A, B) are most different (leftmost data in these figures, i.e., an interocular contrast ratio of unity) owing to the strong suppression that occurs from the fellow fixing eye to the amblyopic eye under these conditions. In Fig. 2C, we plot the dichoptic motion thresholds of each eye (from which the ratios were computed for Fig. 2A, B) as a function of the weeks of training. Our binocular training regime improves the dichoptic motion threshold of the amblyopic eye (i.e., when the amblyopic eye sees the signal and the fixing eye the noise) although having much less impact on the dichoptic motion thresholds of the fixing eye (i.e., when the fixing eye views the signal and the amblyopic eye the noise). Over time, the threshold of the amblyopic eye approaches that of the fixing eye (i.e., the ratio of the dichoptic thresholds is approaching unity in Fig. 2A, B). What this means is that, over time, suppression is being reduced and the two eyes of this strabismic amblyope are now successfully combining information of comparable contrasts between the two eyes. The improved binocular combination that results was reflected in the establishment of stereoscopic function. Stereoscopic sensitivity was limited to 200 arc secs but was present for the first time (Fig. 2E).

We were surprised to find that monocular acuity of the amblyopic eye improved as a result of our antisuppression therapy. These results are shown in Fig. 2D where Snellen line letter acuity is plotted against the period of training. A significant improvement accompanies the reduction of suppression even in this adult amblyope.

## Case 2

Case 2 was a 45-year-old man who had a history of anisometropic amblyopia [R,  $-1.75$  diopter (D)/ $+0.50 \times 90^\circ$ ; L,  $+1.25$  D] which had been first detected at the age of 11 years and treated with a mixture of patching for 1 to 2 years and refractive correction at the age of 11 years. No surgery had been undertaken. He presented with a 3-D anisometropia, a  $6^\circ$  constant esotropia (also detected at the age of 11 years), a mild degree of amblyopia (20/63), no fusion on the Worth 4 dot test, and no measurable stereopsis at near.

Using our global motion measurement of suppression, we found a degree of suppression that could be nullified when the contrast of the stimuli viewed by the fixing eye were reduced by a factor of 4 (Fig. 3A).

Over the antisuppression treatment period of 5 weeks (4 days a week, average of 350 threshold measurements per week), there was a steady change in the degree of suppression exerted by the fixing eye. This is reflected in a change in the derived balance point (i.e., the interocular contrast ratio where the dichoptic threshold ratio between the fixing and amblyopic eyes is unity, x axis intercept in

Fig. 3B) or by the progressive improvement in the dichoptic motion threshold for the amblyopic eye for stimuli of equal contrasts in the two eyes (Fig. 3C). Monocular acuity improved in the amblyopic eye from 20/63 to 20/30 (Fig. 3D), and stereopsis was established with an acuity of 20 arc secs (Fig. 3E).

## Case 3

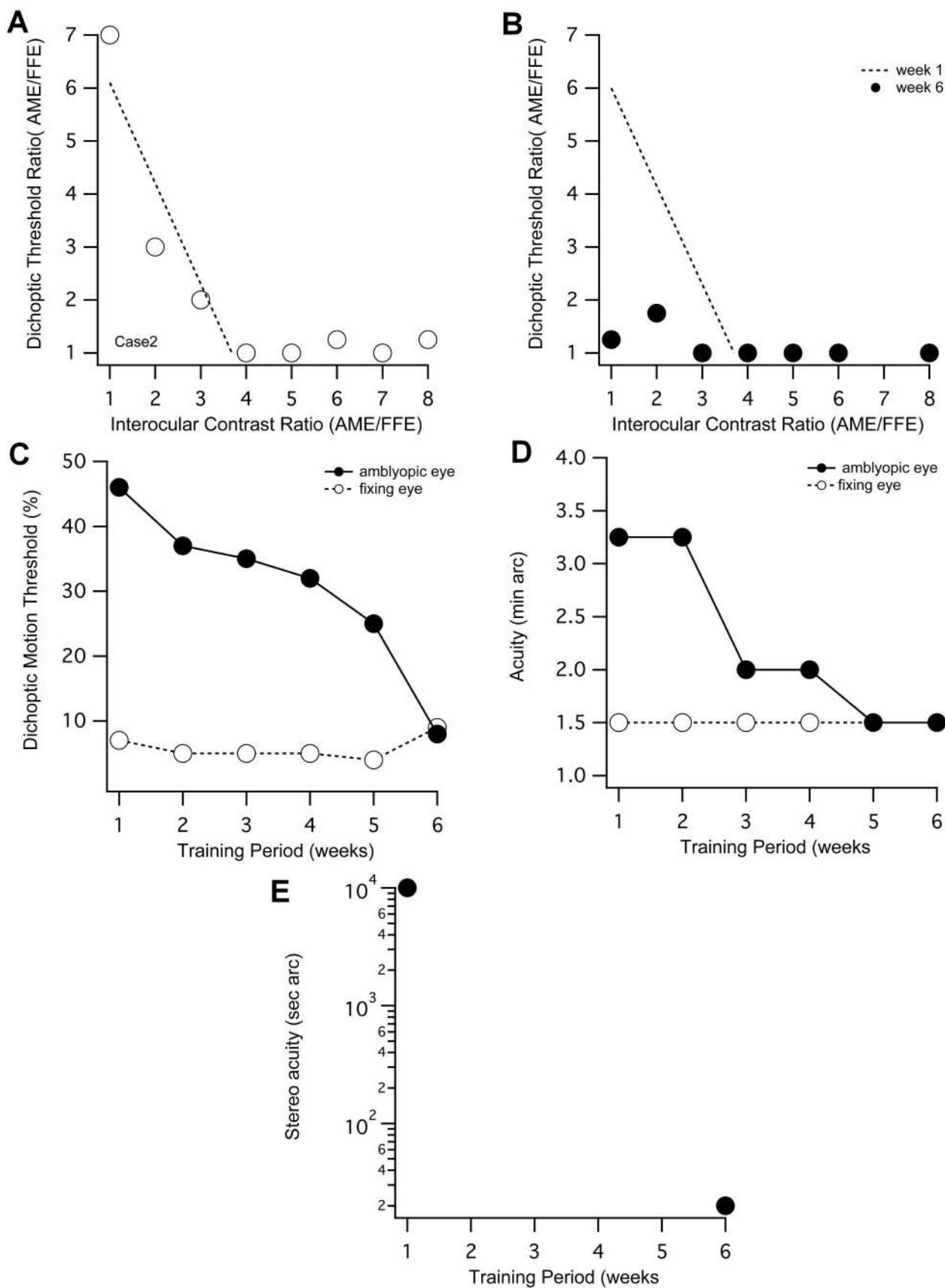
Case 3 was a 33-year-old woman with a history of strabismic amblyopia (R,  $-1.00$  D; L,  $-0.50$  D) having been first detected at the age of 5 years. Two years of constant patching was undertaken, but there had been no surgical intervention (visual acuity at the end of this patching was not available). She presented with a small but bilaterally equivalent amount of myopia, a small angle ( $4^\circ$ ) constant esotropia with intermittent fusion on the Worth 4 dot (distance and near) test but no measurable stereopsis (near). The acuity in the deviating eye was 20/80. The measurement of suppression using the balance point determination with the dichoptic motion stimulus showed a mild suppression by the fixing eye that could only be neutralized by reducing the contrast in the fellow fixing eye by a factor of 3 (Fig. 4A).

During a period of 5-week training (3 days a week, average of 100 threshold measurements per week), using our antisuppression therapy, the degree of suppression gradually disappeared (indicated by a dichoptic ratio of 1 for equal interocular contrasts in Fig. 4B). Another reflection of this reduction in suppression is the improvement that occurred in her dichoptic motion thresholds for her amblyopic eye (signal to amblyopic eye, noise over the training period). Stereopsis (near) was established with an acuity of 30 arc secs (Fig. 4E), and monocular acuity in the amblyopic eye improved from 20/80 to 20/25 (Fig. 4D).

## DISCUSSION

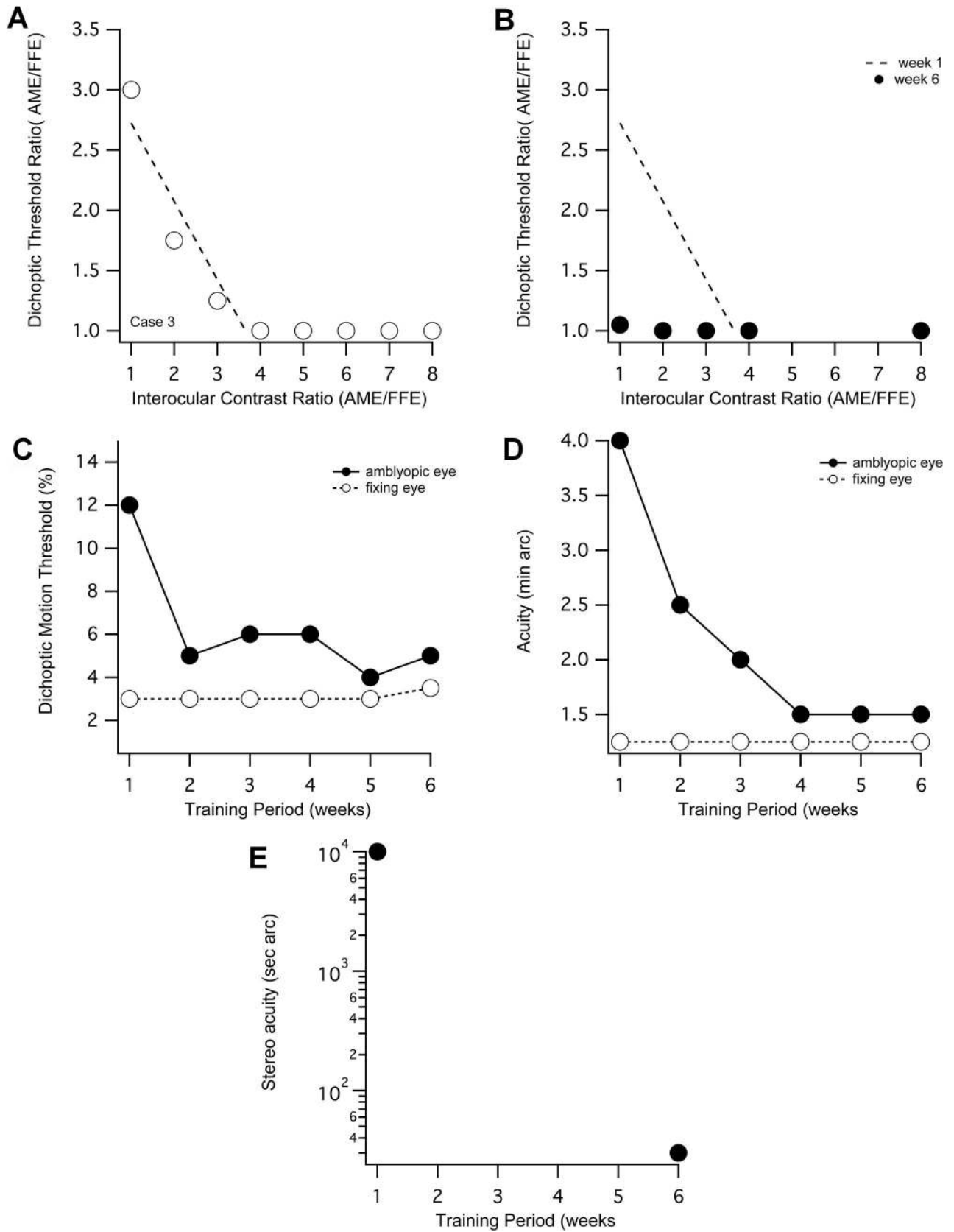
We describe a new quantitative method for the clinical measurement of suppression, something that is done in either a binary fashion (i.e., worth 4 dot test) or using methods that are coarse (i.e., the Sbis Bar) or uncalibrated (i.e., reducing illumination for one eye on the synoptophore) in the clinic at present. The method is based on a signal to noise approach but applied within the context of dichoptic stimulation. This allowed us to demonstrate, for the first time, that threshold and suprathreshold information can be combined between the eyes of strabismic amblyopes under suitable, albeit artificial, viewing conditions.<sup>5-7,9</sup> Suppression is a well-known clinical entity, but it is rarely measured quantitatively and rarely used to direct the treatment approach. We believe this is unfortunate because the current animal<sup>3,4,10,11</sup> and human<sup>5,6</sup> research on amblyopia suggests that it is primarily a binocular problem with suppression being the key feature. We strongly recommend that suppression is measured in a quantitative way along the lines suggested here.

Furthermore, we show here, for three subjects, that intensive training using this suppression measurement approach leads to a progressive strengthening of binocular vision in strabismic amblyopes such that they can eventually operate under natural viewing conditions where the left and right image contrast is equal. We found this to be the case in 8/10 amblyopes tested so far, and it should be emphasized that all subjects were adult amblyopes well



**FIGURE 3.**

Results are shown for case 2 in terms of (A) the initial measurement of suppression (see text), (B) how this changed with prolonged artificial binocular viewing, (C) how the dichoptic threshold for both eyes changed with prolonged artificial binocular viewing, (D) how visual acuity changed for each eye as a function of the training, and (E) the reinstating of stereopsis after training.



**FIGURE 4.**

Results are shown for case 3 in terms of (A) the initial measurement of suppression (see text), (B) how this changed with prolonged artificial binocular viewing, (C) how the dichoptic threshold for both eyes changed with prolonged artificial binocular viewing, (D) how visual acuity changed for each eye as a function of the training, and (E) the reinstating of stereopsis after training.

beyond the accepted “critical period” for patching therapy.<sup>1</sup> Concurrent with this improvement in the efficacy of binocular combination, we also found that stereopsis in all three cases presented here, and in a majority of cases studied so far, was established and the monocular acuity also improved. These improvements were significant, stable, and in some cases large.

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