Disrupted Retinotopic Maps in Amblyopia

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Purpose. The amblyopic visual system exhibits both positional inaccuracy (uncertainty) and systematic biases (distortion). The fidelity of the retinotopic representation of the visual field driven by the amblyopic eye was studied for each of these aspects of position coding by using a dichoptic position-matching task.

Method. Fifteen patients with amblyopia and five normal subjects were tested. The stimuli were luminance-defined Gaussian blobs that were presented within a circle of 15° diameter. Each Gaussian blob was seen only by the amblyopic eye. Moving a mouse marker seen only by the fellow fixing eye (perceptual matching measure), each subject had to localize the position of previously presented targets.

Results. The results confirm previous findings that there is significant distortion in the maps of the central visual field in amblyopic subjects. However, the uncertainty measure did not correlate with the measured distortion in amblyopic maps nor with the visual acuity. Also, regional analysis of the data showed that the distortion occurred heterogeneously in different parts of the visual field and had no relationship to the associated strabismus.

Conclusions. The underlying explanations for these three visual deficits—inaccuracy, distortion, and acuity loss—may be different. (*Invest Ophthalmol Vis Sci.* 2009;50:3218–3225) DOI:10.1167/iovs.08-2914

Amblyopia is a developmental disorder that usually occurs in one eye and is responsible for irreversible monocular impairment in adults. It involves several visual deficits, with acuity and contrast sensitivity being the most studied.[1,2] It also involves positional inaccuracy[3] and positional distortion,[4] important deficits that have received less attention.

Humans with strabismic amblyopia, though not those with nonstrabismic anisometropic amblyopia, display increased uncertainty for positional tasks with their amblyopic eyes that do not follow as a simple consequence of associated deficits in contrast sensitivity.[5] Furthermore, this deficit, unlike their contrast sensitivity deficit, is scale-invariant. Positional uncertainty is elevated to a similar extent for large objects of low spatial frequency as it is for small objects of high spatial frequency.[5] Such a deficit would be expected to produce substantial perceptual consequences.[6] Besides an elevated uncertainty for position, subjects with strabismic amblyopia display fixed spatial biases (i.e., distortions) for positional judgements[4,5,7–17] and perceive spatial distortions in general.[18]

Animal models of amblyopia due to lid suture or strabismus also show a profound loss of positional accuracy. Even though visual acuity recovers when the animal is subjected to normal binocular stimulation[19] or when the fellow eye is reverse occluded, the positional deficit remains.[20] The positional deficit in deprived animals is substantial, there usually being greater than an order of magnitude between the accuracy of the amblyopic and fellow eyes, and, like the human equivalent, it exhibits the property of spatial scale invariance. Although it is true that explanations couched in terms of undersampling[21] or uncalibrated disarray[22] could equally account for the positional uncertainty, the explanation for the spatial distortion is more easily modeled by hypothesizing a spatial disarray.[6] The fact that such comparable positional deficits occur in humans with amblyopia and in animals deprived of vision during the critical period of visual development suggests that our ability to encode the relative position of objects undergoes development and can be easily disrupted with profound perceptual consequences.

Several important questions concerning the positional deficit in amblyopia are yet to be adequately answered. For example: What is the relationship between the deficits for uncertainty, distortion, and acuity? What is the regional distribution of these deficits within the central 30° visual field, and do they bear any simple relationship to the direction of the associated strabismus?

Regarding the first question, there is considerable disagreement. In several studies,[4,7,23,24] investigators have argued that distortions, uncertainty, and acuity loss are correlated, at least in strabismic amblyopia. Other investigators[9,12,17] have also argued for a correlation between the spatial distortions/spatial uncertainty and acuity loss in strabismic amblyopia. On the other hand, some[5,16,25] have found no significant correlation between either spatial measure (i.e., distortions or uncertainty) and the loss of contrast sensitivity. There is also no clear consensus concerning the second question relating to the regional distribution of the positional loss. The distribution of the deficit for distortion was initially reported to be confined to the central field (2.5° radius)[9]; however, later evidence using a different task showed that it was greater in a region beyond a 2.5° radius (but within a 20° radius).[9,12] Other work[16] suggests that the distortion is greater beyond 5° eccentricity but that the distribution of the elevated uncertainty depends on the spatial scale used to measure it.

Our purpose was to examine each of these currently unresolved issues by comparing spatial distortion and spatial uncertainty across the central visual field in a group of subjects mainly having strabismic amblyopia (one with deprivation amblyopia and one with anisometropic amblyopia), to ascertain their relationship to the acuity loss as well as their regional distribution.

Methods

Apparatus

All stimuli were generated by computer (Intel Pentium IV, 2.4-GHz processor equipped with 1-Gb RAM; Intel, Mountain View, CA). Stimuli were displayed by using a linearized look-up table (22-in. NuVision 21 MX-SL CRT driven by a VSG2/5 graphics card; Cambridge Research Systems, Cambridge, UK) with 15-bit gray-scale resolution. Maximum

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TABLE 1. Clinical Details of Amblyopic Subjects

Subj.	Age	Type	Refraction	Acuity	Strab	History, Stereo (Randot Test)
ED	43	LE strab	R: +0.75 DS L: +0.75 DS	20/16 20/63	ET 5 PD	Detected at age 6 years, patching for 1 year, stereo 40 seconds
EF	56	LE strab	R: +2.00 + 1.00×180° L: +2.00 + 1.00×130°	20/32 20/250	ET 10.5 PD	Detected at 6 years, patching for 1 to 2 years, no surgery, no stereo
GN	30	RE mixed	R: +5.00 − 2.00× 120° L: +3.00 − 1.00×75°	20/70 20/20	ET 14 PD	Detected at 5 years, patching 3 months, no glasses, strabismus surgery RE × 2 age 10–12 years, no stereo
PH	33	LE strab	R: −1.00 + 0.50×10° L: plano	20/25 20/63	ET 9 PD	Detected at 4 years, patching for 6 months; surgery age 5 years, no stereo
LS	22	BE depr	R: −2.00 + 0.50×90° L: +0.50 DS	20/20 20/125	Ortho	Detected at 5 years, left denser than right bilateral cataract surgery ages 5 (RE), 6 (LE) years; patching (RE) 4 months at 8 years, no stereo
MA	22	LE aniso	R: −0.25 DS L: +3.50 − 0.50×180°	20/15 20/200	Ortho	Detected at 3 years, patching for 4 years, and glasses for 8 years, no stereo
MB	50	RE strab	R: −1.00 DS L: +0.50 DS	20/32 20/80	ET 5 PD	No surgery, first glasses at 32 years, no stereo
MG	30	RE strab	R: +1.50 DS L: +1.50 DS	20/100 20/15	ET 2 PD	Detected at 4 years, patching for 6 months, no surgery, no
ML	20	RE mixed	R: +1.0 − 0.75×90° L: −3.25 DS	20/80 20/25	ET 10.5 PD	Detected at 5 years, patching for 2 years, no stereo
OA	21	RE mixed	R: −4.50−5.00×30° L: −1.75/−1.75×150°	20/80 20/20 20/32	ET 9 PD	Detected at 3 years, patching at 3 years, no surgery, no stereo
RA	49	LE strab	R: +3.50 DS L: +4.75 − 0.75×45°	20/15 20/40	XT 4 PD	Detected at 6 years, glasses since 6 years, no other therapy, stereo 400 seconds
VD	23	LE mixed	R: +0.25 DS L: +2.75 − 1.25×175°	20/20 20/40	ET 4 PD	Detected at 5–6 years, patching for 6 months, no surgery, stereo 50 seconds
VE	69	LE mixed	R: +4.5−5.00×30° L: −1.75−1.75×150°	20/80 20/25	ET 9 PD	Detected at 10 years, no treatment, no stereo
XL	31	LE mixed	R: −2.50 D L: −2.75 D	20/20 20/400	ET 27 PD	Detected at 13 years, no treatment, no stereo
YC	31	LE strab	R: +2.00 D L: +2.00 D	20/15 20/40	ET 18 PD	Detected at 2 years, patching for 4 years, glasses for 16 years, no stereo

strab, strabismic amblyopia; DS, ; ET, : PD, ; depr, deprivation amblyopia.

luminance was 80 cd/m^{-2}, the frame rate was 120 Hz, and the resolution was 1024 × 768 pixels. Single pixels subtended 0.053° visual angle (i.e., 3.18 arc minutes) as viewed from 27 cm. For the eye-tracking portion of the study, eye position was monitored using a monocular infrared tracking system (Videox Eye-Tracker Toolbox; Cambridge Research Systems) that samples eye positions every 20 ms with a resolution of 0.1° and a tracking accuracy of 0.25 to 0.5°.

Participants

Thirteen observers with strabismus, one with anisometropia and one with form-deprivation amblyopia, participated in the mapping experiment.

Details of the amblyopic observers can be found in Table 1. Stereo acuity was measured with the Randot test (Stereo Optical Co. Inc., Chicago, IL), and the angle of squint was determined with an amblyoscope (Major; Clement Clarke, Harlow, UK). Five control observers took part in the mapping experiment. Refraction was undertaken, and any ametropia corrected to the best optotype acuity by using a logMAR chart in all observers. All studies were performed with the informed consent of participants, were approved by the Research Ethics board of the Montreal Neurologic Institute, and adhered to the tenets of the Declaration of Helsinki.

Stimulus Construction

The stimulus consisted of a 2-D Gaussian blob subtending 0.5° visual angle (full width at half height) constructed with the following equation:

$$g(x_i, y_j) = 0.5 + (0.5 * e^{-\left[\frac{(x_i - x_{peak})^2}{\sigma_x^2}\right]} e^{-\left[\frac{(y_j - y_{peak})^2}{\sigma_y^2}\right]}) \quad (1)$$

where x_i and y_j represent the pixel location in an image matrix with dimensions corresponding to the desired visual angle, x_{peak} and y_{peak} represent the spatial coordinates of the center of the 2-D Gaussian function, s_x and s_y represent the SD of the 2-D Gaussian, and finally, $g(x_i, y_j)$ is the 2-D Gaussian function itself. The 2-D Gaussian function modulated between 0.5 (i.e., mean luminance) and 1.0 on a normalized (0, 1) pixel luminance scale; thus the luminance at the peak of the function was 80 cd/m^{-2} (Fig. 1).

Psychophysical Procedure

Viewing was dichoptic, each participant wore a pair of polarized glasses so that each eye could be presented with separate stimuli (e.g., one eye was presented with a Gaussian blob, and the other was presented with a mean luminance display; Fig. 2A). By the use of a polarizing sheet in front of the monitor that could be switched at the frame rate (MacNaughton, Inc., Beaverton, OR), different stimuli could be presented to each eye on a frame-by-frame basis. Sessions were balanced such that each eye would be tested an equal number of times in random order. The general psychophysical task involved presenting each observer's stimulated eye (the affected eye for those with amblyopia and the nondominant eye in normal subjects) with a sharp-edge fixation dot placed at the center of the display for 500 ms. This task was followed by the presentation of a Gaussian blob at one of 32 possible locations (500 ms), while the observers continued to fixate the circular fixation dot, which remained present during the presentation of the Gaussian blob (Fig. 2A). After the Gaussian blob was extinguished, the mouse cursor (previously hidden) was replaced with a Gaussian blob (always starting at the center of the display) visible only to the other eye (the fellow fixing eye of the amblyopic subjects and the dominant eye of normal subjects) at which time observers were required to move it (via the mouse) to the location at which they had just perceived the previously presented Gaussian blob and click one of the mouse buttons to indicate the response (Fig. 2B). The duration

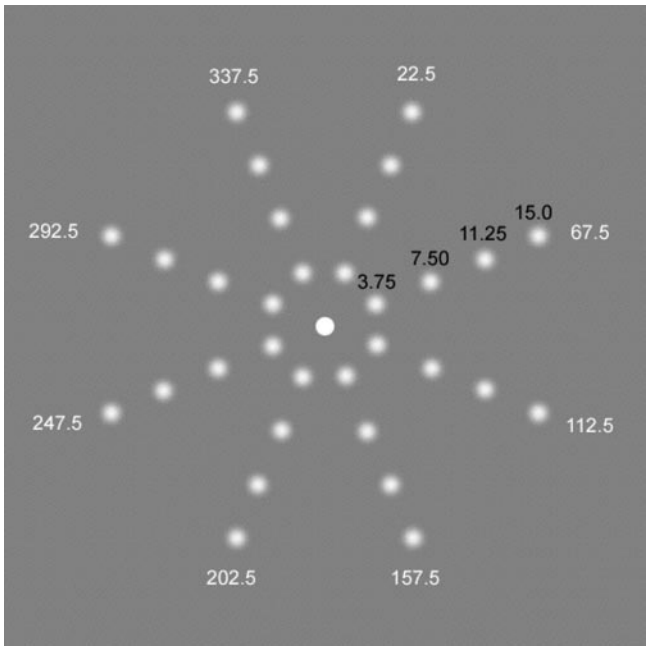

FIGURE 1. The 32 possible locations at which the Gaussian blob was presented. On any given trial, only one Gaussian blob was presented at one of the locations. At the center is the fixation point where observers were required to fixate during the presentation of the Gaussian blob. *Black numbers*: distance from the fixation in degrees of visual angle; *white numbers*: the location of the Gaussian blobs across θ in degrees (i.e., in polar coordinates).

of the response interval was unlimited. This procedure was repeated 64 times (twice for each of 32 locations of the Gaussian blob), and the entire session was repeated 10 times, with five of the sessions run for the amblyopic eye and five for the fellow fixing eye. The identical procedure was performed in the control observers on the dominant and nondominant eyes. An example of the 32 different locations at which the Gaussian blob could be presented is shown in Figure 1. The stimulation space was in polar coordinates, with distance from the center indicated in degrees of visual angle; four different eccentricities (3.75°, 7.50°, 11.25°, and 15.0°) were investigated (see Fig. 1 for further details).

Analysis

To quantify the degree of positional uncertainty and distortion in amblyopia we computed three measures termed, accuracy, resolution, and distortion. These quantities are measured at local regions in the field, and an index measure is computed for different regions of interest within the visual field as a whole.

Accuracy is quantified by the distance between the average of the matched locations and the true location, while resolution is quantified by the variability of the matched locations (i.e., SD). Distortion is quantified by the ratio of accuracy divided by resolution. Low values of the accuracy measure means good accuracy, and low values of the resolution measure means good resolution. In the plotted figure, red dots denote true locations where accuracy is worse than resolution, that is where the true location is outside the area defined by the average location and its SD, in other words locations where distortion is significant (based on 1 SD).

A region of interest (ROI) analysis is performed by computing for each region an index of distortion based on the above criterion (accuracy measurement $>$ resolution measurement). The above criterion defines a binary entity at each location that is summed over the ROIs and divided by the number of locations that compose the ROIs. This results in an index between 0 and 1 that quantifies the level of distortion across the visual field. This index (called the distortion index) is independent of the ROI's size, and allows comparison of the distortion among different ROIs for a given subject. An index of 0 means that no location in the ROI under consideration shows a significant distortion. An index of 1 means that all locations in the ROI under consideration show a significant distortion.

The ROIs considered in the analysis are hemifields and quadrants and also defined along the radial and angular dimensions: top, bottom, left, and right hemifields and top-left, top-right, bottom-right, bottom-left, center-top, center-left, center-bottom, and center-right quadrants.

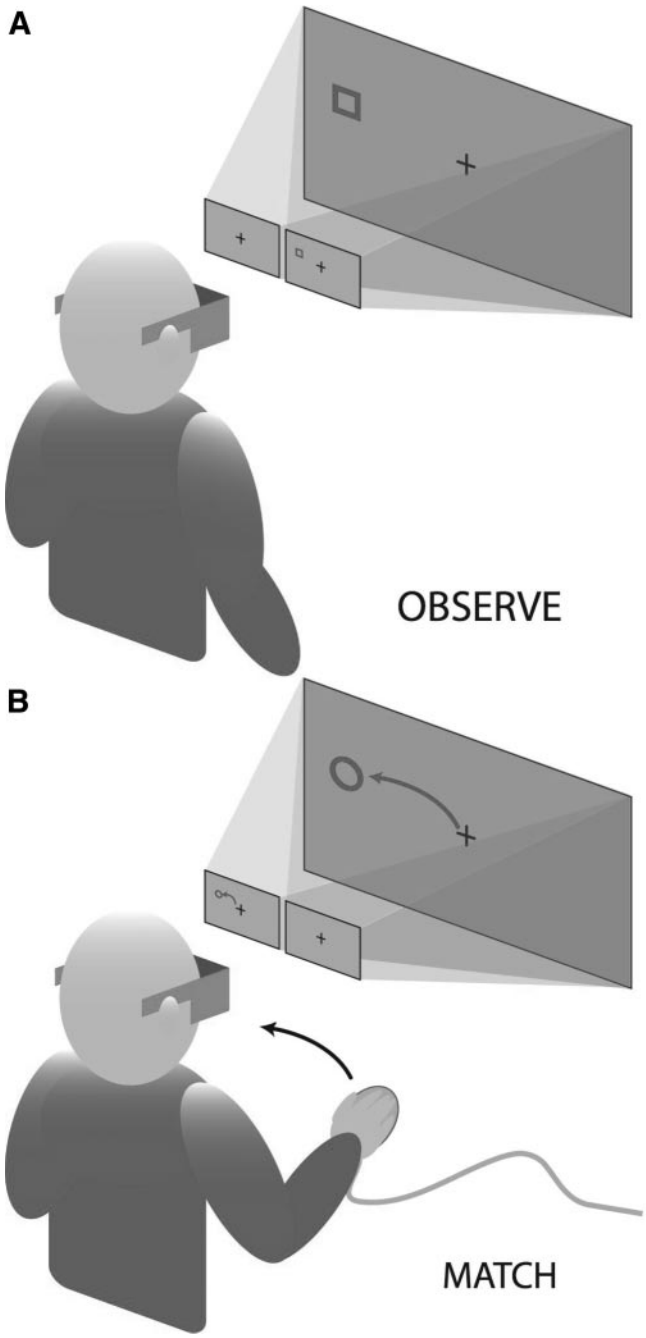

FIGURE 2. Viewing arrangement for the dichoptic presentation of test (**A**) and matching (**B**) stimuli (interocular matching). The fixation point, illustrated here as a *plus*, was actually a *circle*, as shown in Figure 1.

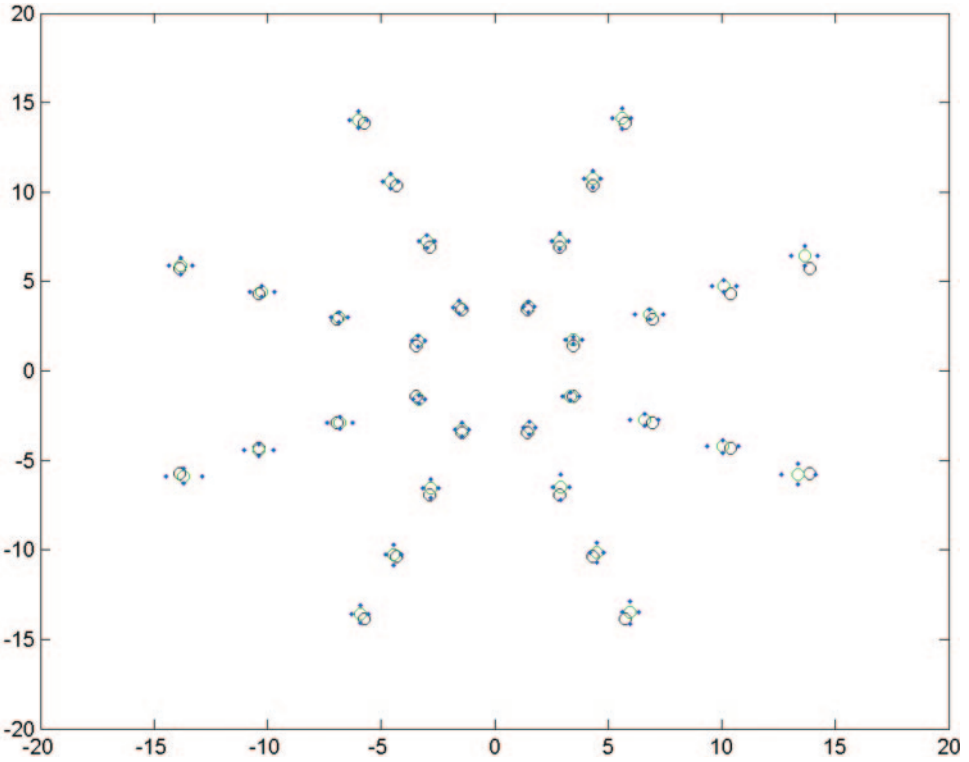

FIGURE 3. A sample-matching result using perceptual matching is presented for a normal subject (BH). *Black circles*: the position where the blobs were presented to the dominant eye. *Green circles*: the actual matched positions by the nondominant eye. *Red circles* (not shown) indicated the locations where significant distortion was observed. *Blue dots*: 1 SD around the average matched positions.

The average resolution per location in each given ROI is also provided by the analysis (called resolution). This index is a quantitative measure of the resolution across the visual field. It is independent of ROI's size.

RESULTS

Figures 3 to 6 show sample results from three amblyopic subjects (two with strabismus and one mixed) and one normal subject (Fig. 3). Stimuli were presented individually at several visual field locations to the amblyopic eye (while the fellow fixing eye viewed a mean luminance) and matched (interocular matching) by using a fixation dot seen only by the fellow fixing eye (while the amblyopic viewed a mean luminance). The test was performed similarly for the dominant and nondominant eyes of the normal observer. The grid positions on which individual stimuli were presented are marked in black. The

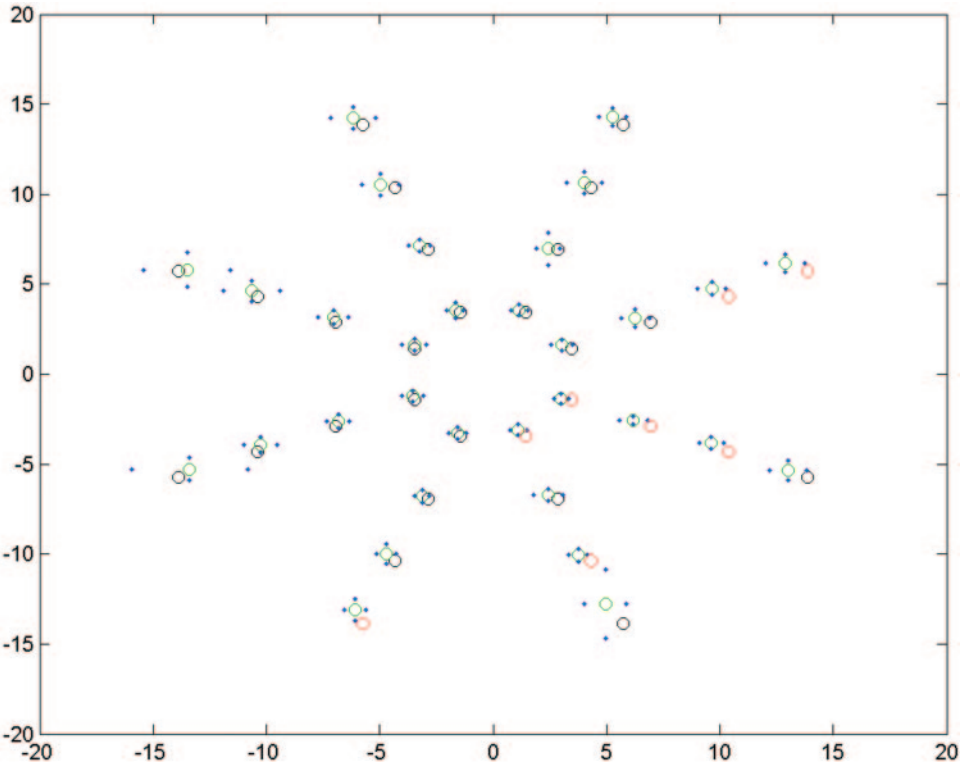

FIGURE 4. A sample-matching result using the perceptual matching is presented for one amblyopic subject (GN) who had anisometropia and a postsurgical 14-PD esotropia. *Black circles*: the position where the blobs were presented to the amblyopic eye. *Green circles*: the actual matched positions by the fellow fixing eye. *Red circles*: the locations where significant distortion was observed. In the areas where there are significant distortions, *red circles* replaced *black circles*, denoting stimulus position. *Blue dots*: 1 SD around the average matched positions.

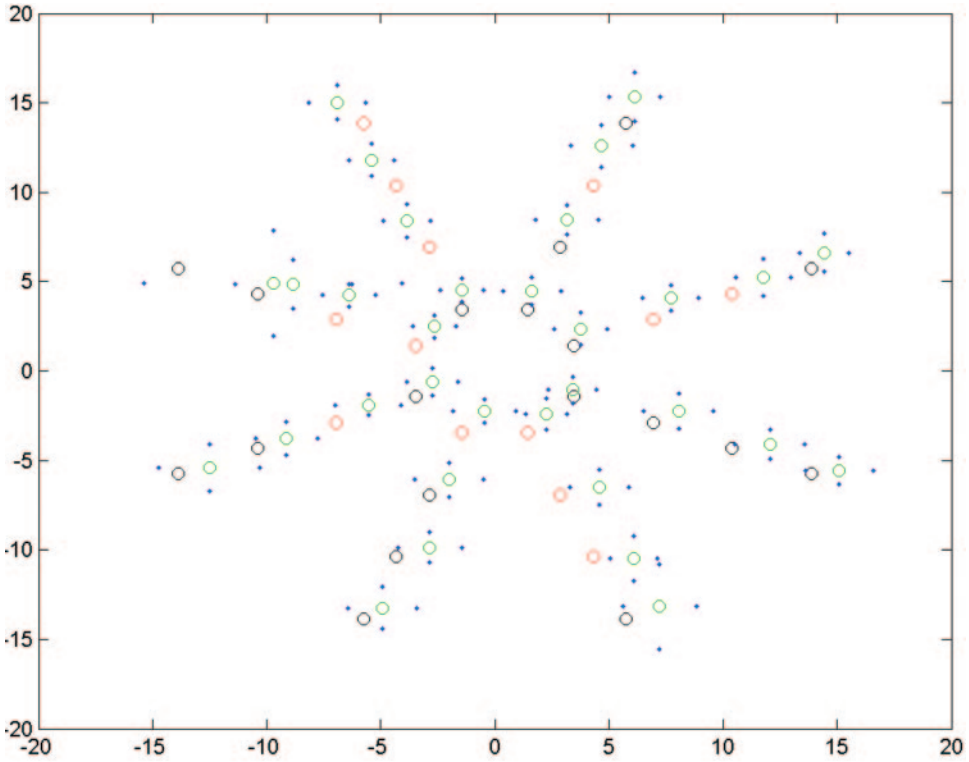

FIGURE 5. A sample-matching result using the perceptual matching is presented for one amblyopic subject (PH) who had a postsurgical 9-PD esotropia. *Black circles*: the position where the blobs were presented to the amblyopic eye. *Green circles*: actual matched positions by the fellow fixing eye. *Red circles*: locations where significant distortion was observed. *Blue dots*: 1 SD around the average matched positions. In the areas where there were significant distortions, *red circles* replace *black circles* denoting stimulus position.

green circles indicate the equivalent matches made by the fellow fixing eye (or dominant eye of normal subjects). The red circles indicate the locations where there were significant mismatches (i.e., the distortion measure). Where there are significant positional mismatches, the red circles replace the black circles in denoting the stimulus position. The blue dots represent one SD around the average matched positions (i.e., the resolution measure). It can be seen that these amblyopic eyes exhibited small but significant losses in accuracy and resolution. The distortion measure was computed from accuracy/resolution and is significant in some parts of the field. Losses in accuracy and resolution measures can occur in different regions within the central field of view and are not tightly correlated. For example, GN (Fig. 4) exhibited loss of

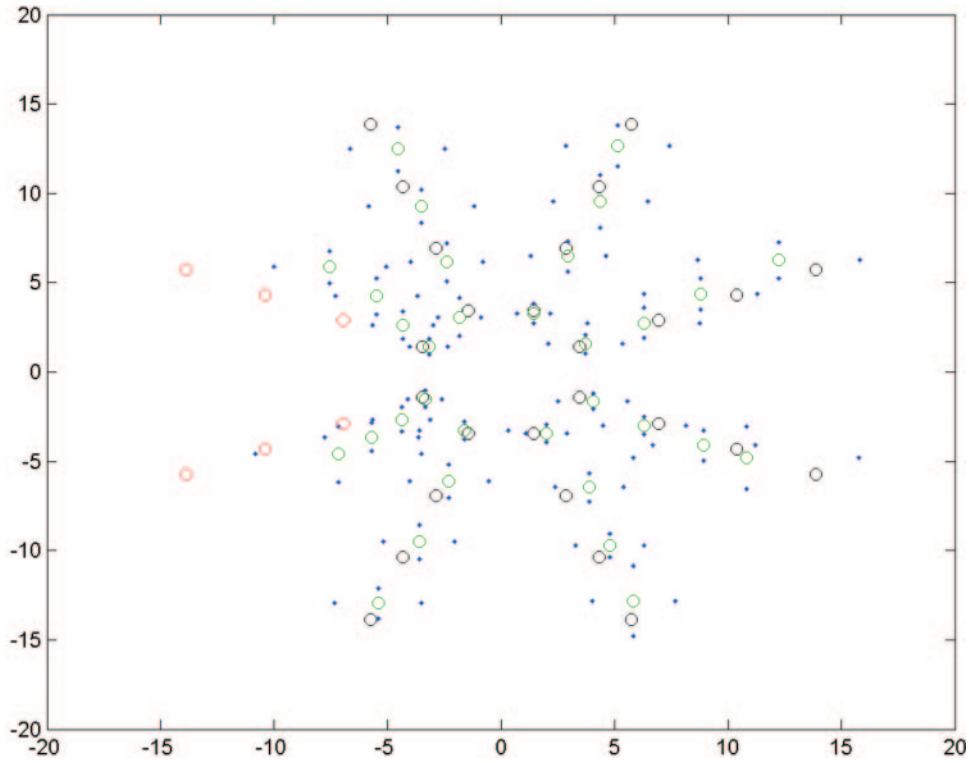

FIGURE 6. A sample-matching result using the perceptual matching is presented for one amblyopic subject (RA) who had 4-PD exotropia (no surgery). *Black circles*: the position where the blobs were presented to the amblyopic eye. *Green circles*: the actual matched positions by the fellow fixing eye. *Red circles*: locations where significant distortion was observed. *Blue dots*: represent one SD around the average matched positions. In the areas where there are significant distortions, *red circles* replace *black circles* denoting stimulus position.

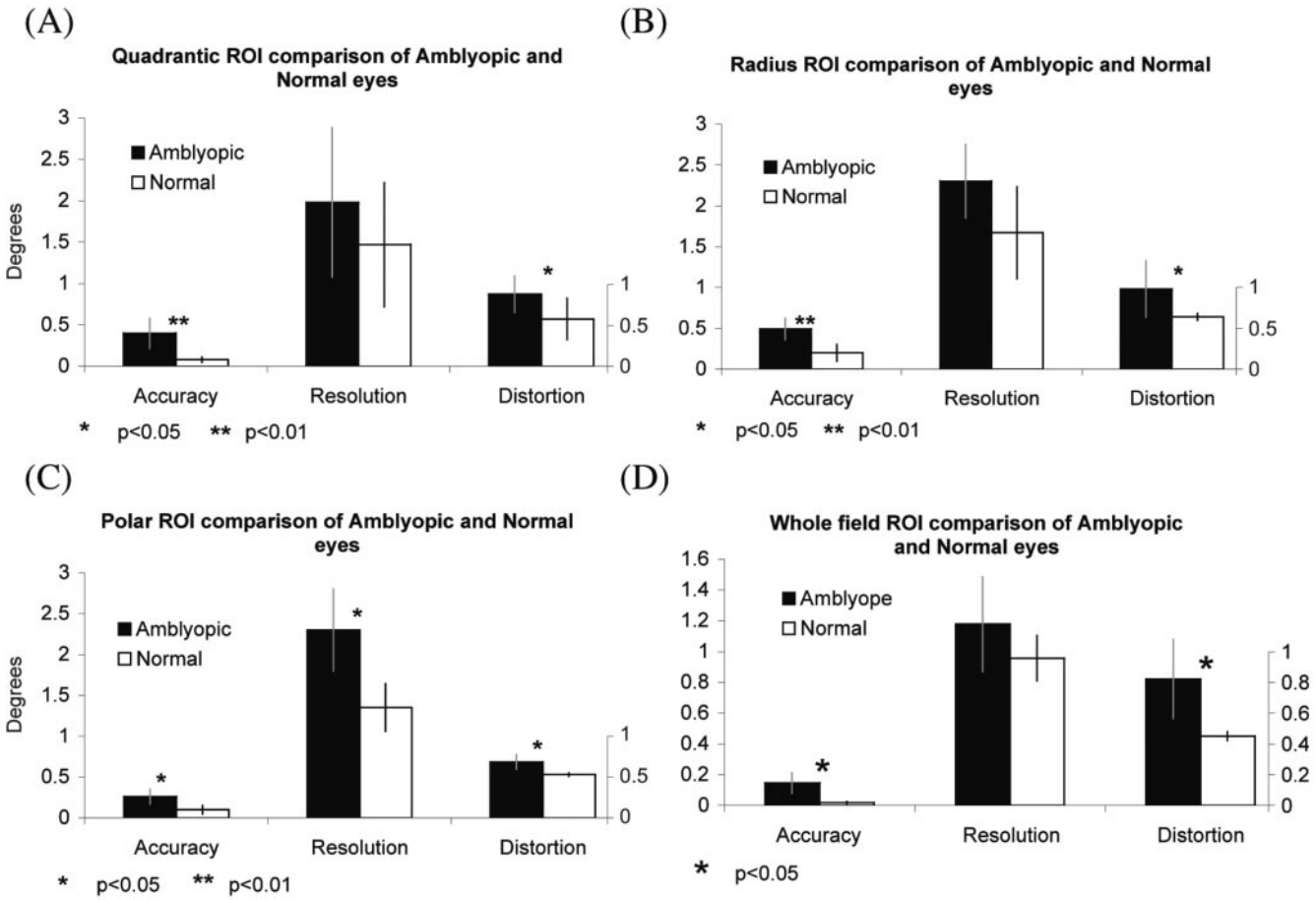

FIGURE 7. Accuracy, resolution, and distortion measures are compared in amblyopic (■) and normal observers (□) for (**A**) quadrantic, (**B**) radius, (**C**) polar, and (**D**) whole-field ROIs. Accuracy and resolution are measured in degrees, and distortion is a ratio.

accuracy without a loss of resolution whereas RA (Fig. 6) had resolution loss over much of the field only a part of which exhibited accuracy loss.

Regional Nature of the Deficit

We were surprised to find that the distortion was not evenly distributed across the central field of view, as was evident in the example results displayed in Figures 4 to 6. We found regional losses in some subjects that involved quadrants of the visual field. For example, GN (Fig. 4) and RA (Fig. 6) exhibited distortion over only limited regions of the temporal field, whereas PH (Fig. 5) showed a more even distribution. Such a varied pattern of loss cannot be solely determined by the present angle of strabismus, since GN and PH had a similar sized esotropic deviation and yet had very different regional distributions of distortion, and GN and RA had similar regional distribution of distortion and yet very different strabismus (i.e., exo- versus esotropia). However, such a conclusion must be qualified by the fact that comparing results solely in terms of the strabismus potentially ignores other important differences in the orthoptic status among these subjects. Figure 7 shows an analysis of the computed index measures of accuracy, resolution, and distortion across the population of amblyopic and normal observers for different ROI analyses (e.g., quadrantic, radial, polar, and whole-field).

For all these different ROIs, the magnitude of each of our three derived measures (i.e., accuracy, resolution, and distortion) are raised in the amblyopic eye, because different amblyopic subjects displayed different regional distributions of positional loss. The measure of distortion was significantly raised for all ROIs, suggesting that across a population of persons with amblyopia a variety of different regions can be affected. That the positional anomalies showed such regional variation, including circumscribed quadrantic deficits, makes it less likely that they developed as a direct consequence of the type of strabismus. However, our lack of information on the sensory and motor status of these patients during early visual development makes it difficult to come to a firm conclusion.

Relationship between Accuracy, Resolution, and Acuity

The results in Figures 4 to 6 suggest that subjects with amblyopia can have elevated positional variability (reflected in the resolution measure) in regions where the average position estimates are normal (the accuracy measure) and vice versa. Regardless of the regional distribution, do subjects with loss of accuracy also have loss of resolution and is this because of their poorer letter acuity?

The results in Figure 8A show the accuracy measure derived for each subject (within the appropriate ROI for each subject) with subjects arranged in ascending order of anomaly. Figures 8B and 8C maintain the same subject order for the resolution (i.e., variability) and acuity measures, respectively. It is immediately obvious that there is no tight correlation between accuracy and resolution (i.e., variability) or between either of these measures and acuity. The correlations between each of these three measures is given in Table 2. More severe ambly-

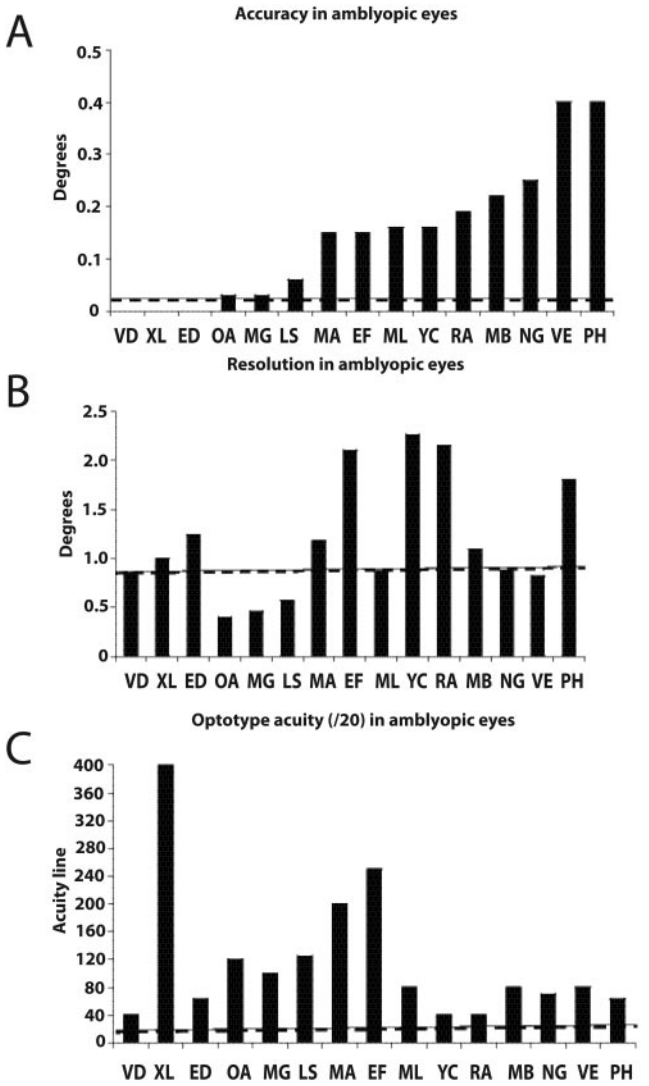

FIGURE 8. (**A**) Accuracy (i.e., average position estimate), (**B**) resolution (i.e., variability), and (**C**) optotype acuity are presented for 12 amblyopic observers. *Dashed lines*: normal average. Accuracy (**A**) correlated with neither the resolution (i.e., variability) nor the optotype acuity.

opia, as determined by acuity, does not necessarily cause more positional variability or more distortion. A similar lack of significant correlation for each of these parameters was obtained when we computed the correlations for just strabismic amblyopia (excluding deprivation and anisometropic amblyopia).

TABLE 2. Group Correlations and Associated Significance Levels for the Measures of Accuracy, Resolution, and Visual Acuity

	Accuracy	Resolution	VA
Accuracy			
Pearson correlation	1.000	0.396	−0.268
Significance (two-tailed)		0.144	0.334
Resolution			
Pearson correlation	0.396	1.000	0.062
Significance (two-tailed)	0.144		0.827
VA			
Pearson correlation	−0.268	0.062	1.000
Significance (two-tailed)	0.334	0.827	

In all groups, $n = 15$.

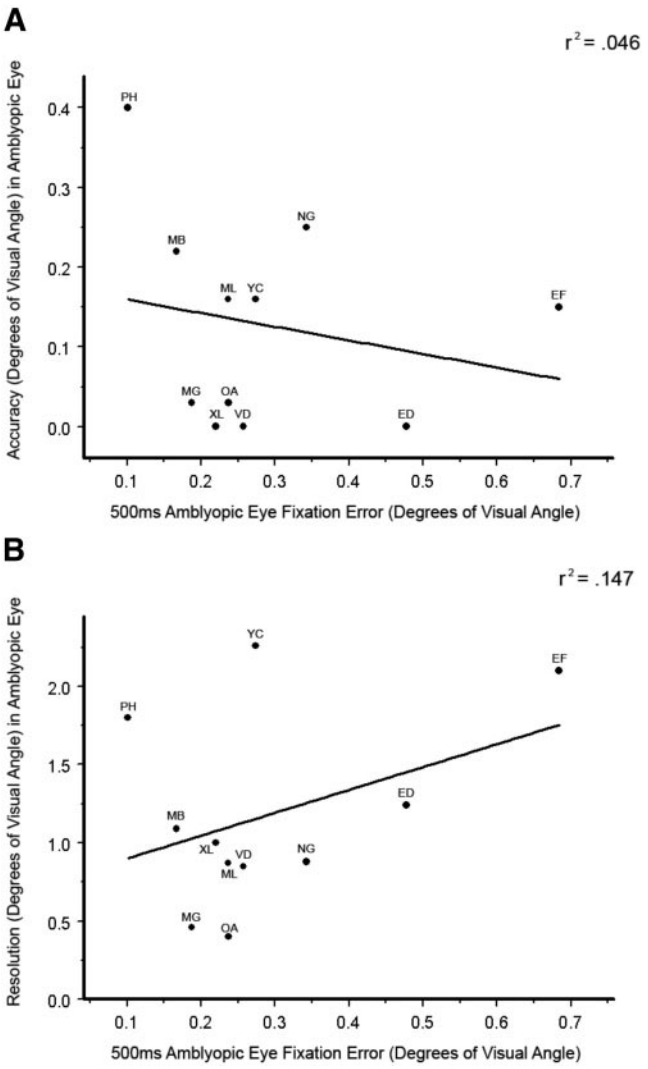

FIGURE 9. Relationship between measured oculomotor instability during fixation by the amblyopic eye and the key positional measures of accuracy (**A**) and resolution (**B**). Neither correlation is significant.

In the present study, local reference stimuli were not used, and so a possible reason for the lack of correlation between the deficits of variability and distortion may be oculomotor inaccuracy of the amblyopic eye during the 500-ms pretrial fixation period. In 11 of the 15 subjects, we monitored oculomotor accuracy during the first 500 ms of fixation. Specifically, occulomotor stability (i.e., fixation stability) was assessed by taking the SD of the observed fixation differences (in degrees of visual angle) from the center of the fixation dot over the 500-ms pretrial fixation period (i.e., an estimate of fixation error for which smaller estimates indicate higher fixation stability and vice versa). The relationship between fixation stability and either distortion (the accuracy measure) or positional variability (the resolution measure) is plotted in Figure 9. No significant correlation was found between either distortion ($r^2 = 0.046$, accuracy measure) or positional variability ($r^2 = 0.147$, resolution measure). The form of the results regarding resolution is suggestive of a relationship but it failed to reach significance.

DISCUSSION

In this study, we sought to provide answers to two currently unresolved questions concerning the positional deficits in ambly-

opia: Is there a relationship between the deficits for distortion, variability, and acuity? What is the regional distribution of these deficits? We did not find any relationship between variability (quantified by the resolution measure), distortion (quantified by the accuracy measure), and acuity (optotype acuity) in our group who are mainly subjects with strabismic amblyopia. Not only were the correlations low in any one part of the field, but also they often exhibited an entirely different regional distribution.

Previous measurements showing that the amblyopic eye exhibits increased positional variability have all involved the use of reference stimuli with which any effect of fixation instability would have had little or no influence on relative position judgment.[4,5,26] This conclusion receives support by the finding in normal subjects that spatiotemporal instability does not affect positional uncertainty for such targets unless it differentially affects the reference and test stimuli.[27] In the present study, local reference stimuli were not used, and so a possible reason for the lack of correlation between the deficits of variability and distortion may be the oculomotor inaccuracy of the amblyopic eye during the 500-ms pretrial fixation period. In 11 of the 15 subjects, we monitored oculomotor accuracy during the first 500 ms of fixation (Fig. 9) and did not find a significant correlation between the accuracy of fixation and either positional variability or distortion.

In terms of the regional distribution, we were surprised to find such a diversity of field deficits within the central 30°. The positional deficits are not evenly distributed across the central 30° of the visual field in most patients with strabismic amblyopia. Such a finding means that these deficits are less likely to have occurred on the basis of anomalous retinal correspondence secondary to a fixed strabismus, as such a deficit would not only bear a definite relationship to the direction of the strabismus but also be evenly distributed over the central field. We have no explanation for why the positional deficits, in some cases, should be localized to quadrants of the visual field.

The nature of the neural disturbance responsible for the elevated positional variability and distortion in amblyopia is not well understood. The suggestion that it could be due to there being fewer cells (sometimes loosely termed, undersampling)[21] is a possible explanation for the increased positional inaccuracy, but it is less clear without a specific model how this could account for distortions. The other suggestion involves a disarray in cellular connections as the result of a lack of calibration during development.[22] Such a distortion could account for both inaccuracy and distortion. To date, the only evidence to support this theory is the finding that the retinotopic map in several early visual areas is represented with less fidelity for the input from the amblyopic eye.[28] To qualify for an adequate explanation, such a mapping deficit should show the same regional distribution as shown here for the psychophysics. Since this varies from subject to subject (Figs. 4–6) and from one field location to another (Fig. 7), such a comparison would need to be made not only on a subject-by-subject basis but also on a field location-by-field location basis.

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