In individuals with normal binocular function, visual feedback ensures accurate fixation on targets, so that the eyes maintain a state of nearly perfect alignment.\(^1,2\) In strabismus, the inability to fuse images means that one eye is not directed at a target. Without a target, the deviated eye is more unstable in position than the fixating eye.\(^3\) Numerous studies have documented the variability of ocular misalignment in strabismus.\(^4,12\) Reported values depend on observer skill, the method used to measure the deviation angle, the characteristics of the patient population, and the true variability in deviation angle. The Hirschberg, Krimsky, and prism alternate cover tests are relied on for clinical purposes but potentially error prone.\(^13\)\(^-\)\(^15\) When repeated assessment of a patient’s strabismus angle yields variable results, it would be helpful to know whether the variability is likely to represent simple measurement error or real biological fluctuation in the magnitude of the ocular deviation.

Until recently, eye trackers had required patients to wear a scleral search coil. Although topical anesthetic makes the device tolerable, scleral coils are not practical for routine clinical use, especially in children. The advent of video-based eye trackers has made it possible to measure eye position noninvasively, with a resolution of better than 0.5°.\(^16\) In patients with strabismus, one eye shifts over a range of positions when the other eye fixates a target (Figure 1). In this study, we used video eye trackers to measure variability in the position of the fixating eye and the deviating eye in a cohort of patients with strabismus. The data were compared with measurements of eye position during fixation performed in a control population of individuals with normal eye alignment.
Methods

The goal of this study was to compare eye position stability in individuals with normal alignment and those with strabismus. To eliminate confounding effects that might arise from amblyopia, patients with a history of amblyopia were disqualified. Screening assessment included best-corrected visual acuity in each eye, refractive error, pupils, color discrimination (Ishihara plates), eye movements, alignment, and stereopsis. Slitlamp and fundus examinations were also performed. Inclusion criteria were (1) 20/20 Snellen acuity in each eye with refractive correction, (2) exotropia since childhood, (3) no eye disease except strabismus, (4) ability to alternate ocular fixation freely, (5) no pathological nystagmus, (6) normal color vision, (7) absence of diplopia, and (8) less than 4 diopters (D) of myopia, hyperopia, or astigmatism. Testing was performed with no refractive correction.

This study was approved by the institutional review board at the University of California, San Francisco. Adult patients provided written informed consent to participate; minors gave their assent and a parent gave written informed consent.

The 25 patients with strabismus (10 male and 15 female) had a mean (SD) age of 28 (14) years (range, 8-55 years). Their mean (SD) ocular deviation was 14.2° (5.9°) (range, 4.4°-22.4°). The control participants (14 male and 11 female) had a mean (SD) age of 25 (12) years (range, 9-58 years). Participants sat with their head stabilized in a chin/forehead rest, facing a translucent tangent screen at a distance of 57 cm. Stimuli were rear-projected and eye movements were recorded with video trackers.

The variability in eye position signal from video tracker noise was determined by measuring their output during a 180-second epoch while focused on a motionless artificial eye. The artificial eye consisted of a polymethyl methacrylate contact lens (to generate a corneal light reflex) glued onto a black disc placed on a white background (to generate a pupil). The SD in the position of this stationary artificial eye was 0.24°.

Participants wore goggles with a red filter over the right eye and a blue filter over the left eye. The dichroic filters matched the passband properties of the dichroic filters in the projector. A background of random dot noise (each element 0.14° × 0.14°; 50% purple; 50% black) was displayed. The purple elements in the textured pattern, consisting of equiluminant red and blue, were transmitted to both eyes to provide binocular stimulation (Figure 2 in the article by Economides et al).17

For each trial, a cross was presented in the middle of the screen. The cross was either red (visible only to the right eye) or blue (visible only to the left eye). After sustained fixation within a 2°-radius window for between 500 and 2000 milliseconds, a small spot (red, blue, or purple) appeared for 200 milliseconds at a random location. The spot and cross disappeared simultaneously. The participant’s task was to identify the color of the peripheral stimulus. The next trial began with presentation of a fresh cross and a new purple background. The task was not relevant to analysis of eye position stability but kept participants alert and engaged.17

Each random change in cross color induced patients with strabismus to alternate fixation. Control participants could see the cross with only one eye, but fixated its location with both eyes. The textured background allowed them to maintain ocular alignment.

For each trial, the time between the participant’s acquisition of the fixation cross and the peripheral target’s appearance yielded 500 to 2000 milliseconds of steady fixation for analysis. Approximately 800 trials were analyzed, recorded during approximately 45 minutes. After removal of blinks, tracking error, or saccades outside the fixation window, horizontal and vertical positions were plotted for each eye. The SD of the horizontal and vertical components of the eye position was calculated. Stability of eye position was defined by measuring the area of the smallest ellipse that encompassed 95% of the cloud of data points. The common logarithm of ellipse areas was used as the final measurement unit.18-20 The Wilcoxon rank test was used for statistical analysis.

Variation in eye position over time was examined by computing the mean ellipse area for each eye’s data points over different epochs (0.1, 1, 10, 100, and 1000 seconds). A sliding window equal to each time scale was stepped through each participant’s record in single video frame (16.7 milliseconds) steps. An ellipse area was computed from eye position points recorded within each time window at each step in the data record. The areas of the family of ellipses generated by each sliding window were averaged to derive a measure of eye stability for each time scale. The ellipse areas for the fixating eye were subtracted from those of the nonfixating eye to assess how variability in the angle of ocular deviation changed with time.

Results

In a typical control participant with normal fusion, eye tracker data recorded over an hour showed tight clouds of eye position points during sustained fixation on the target cross (Figure 1A). Ellipses containing 95% of the fixation points were nearly circular, with a major axis of about 2.5°. In contrast, eye position was more variable in patients with esotropia (Figure 1B) or exotropia (Figure 1C). In these 2
examples, the patients showed marked variability in the position of the deviated eye, which wandered over a range of 12° horizontally and 6° vertically. The fixating eye in these patients with strabismus also showed more position variability than observed in the control individuals, with major ellipse axes measuring 3.5°.

A, Participant with normal alignment showing positions of the left eye (blue dots) and the right eye (red dots) while fixating on a cross. Points for the deviating eye (the eye to which the fixation cross is invisible) are plotted on top of those for the fixating eye. B, Patient with esotropia showing positions of the deviating eye and fixating eye; ellipses contain 95% of points. C, Patient with exotropia. In both patients with strabismus, there is increased scatter in the position of the deviating eye compared with the fixating eye. The numbers equal the log of the ellipse area. For illustration, only 1/50 position points is plotted.
It is unknown whether eye position stability is different in patients with esotropia vs exotropia. To avoid additional variability that might stem from the type of strabismus, this study was limited to patients with exotropia. About half the patients had intermittent exotropia, with intact stereopsis while aligned orthotropically. They were referred because their eyes were usually deviated; during testing, their eyes remained deviated. The remaining patients had constant exotropia, without stereopsis.

For both patients with strabismus and participants with normal eye alignment, the fixating eye and the nonfixating eye demonstrated a wide range in position variability (Figure 2).

This was an unexpected feature for the control group. It probably reflected differences in individuals’ ability to concentrate on the task for an hour. Some participants were children, who tended to have more variable fixation because of distractibility.

In those with strabismus, the mean ellipse area was 1.80 log units (95% CI, 1.66-1.93) for the deviating eye (Figure 2). This was greater (P < .001) than the mean position variability of the fixating eye (1.26 log units; 95% CI, 1.17-1.35). Although the fixating eye of patients with strabismus was more stable than the deviated eye, it was more variable in position (P < .005) than the fixating eye of participants with normal alignment (0.98 log units; 95% CI, 0.88-1.08). For control participants, the nonfixating (“deviated”) eye was defined as the eye to which the fixation cross was invisible. Despite the absence of a target, the deviated eye (1.06 log units; 95% CI, 0.94-1.18) was nearly as stable (P > .10) as the fixating eye (0.98 log units; 95% CI, 0.88-1.08). Fixation disparity was minimized by the presence of the textured purple background pattern.

The ellipse area is a useful metric; however, the SD in eye position is easier to relate to a patient's angle of strabismus. For patients with strabismus, the mean horizontal SD of the nonfixating eye's position was 2.43° (95% CI, 1.99°-2.86°) compared with 0.75° (95% CI, 0.61°-0.90°) in control participants (Figure 3A). This value means that 95% of deviating eye positions would fall within ±4.86°, which corresponds to a range of 17.0 prism diopters (Δ). For the deviating eye in strabismus, the vertical SD averaged only 1.7° (95% CI, 1.38°-2.09°), which was less (P < .01) than the horizontal SD. For the fixating eye, the mean SD in eye position was 1.0° for the patients with strabismus and 0.8° for the control individuals (Figure 3B). No difference was identified between the horizontal and vertical SDs for the patients with strabismus or control participants.

To explore variability in the angle of deviation between the eyes over time, the ellipse area formed by the fixating eye was subtracted from the ellipse area formed by the deviated eye. This was done over a range of time scales (Figure 4). For control participants, the difference in area between the ellipses formed by the 2 eyes was small because there was essentially
no ocular deviation. The value remained unchanged across time windows. For patients with strabismus, the deviation angle showed far more variability, mainly because of instability in the position of the deviating eye. This variability increased with longer measurement epochs, especially between the window of 1 second to 100 seconds.

For these experiments, the testing conditions were artificial in many respects: participants wore color filters to control which eye was exposed to the fixation target, the target never changed position, and the background consisted of a random noise pattern. Real-life conditions are simulated more closely when a participant explores an image freely. An example is shown for an individual who had a right exotropia averaging 22° and a right hypertropia averaging 5° (Figure 5A). She had a strong preference for left eye fixation. Her right hypertropia was larger when fixating with the left eye than with the right eye, allowing one to determine which eye was engaged in fixation. While viewing the picture for 10 seconds, she fixated at 30 different locations, each for a mean of 266 milliseconds (Figure 5B), using the left eye most often (25 of 30 fixations). During each left eye fixation, there was instability in the position of the deviated right eye, represented by a small ellipse of points (Figure 5C). Each saccade resulted in a slight change in the amplitude of her ocular deviation, producing a separate ellipse for each fixation. After 10 seconds, the family of 25 ellipses comprising each fixation epoch gave rise to a large ellipse. This ellipse resembled the ellipse of deviated eye position points that the participant generated while alternating fixation on a cross (Figure 5D). This comparison shows that the simple task of alternating fixation on a cross captures accurately the variability in ocular deviation that is present while freely viewing images, at least for individuals without a pattern deviation. Findings were similar in 3 other participants tested during free viewing and the fixation cross task.

Discussion

Video eye trackers allow highly accurate assessment of patients’ ocular deviation. They permit one to measure variability in the position of each eye and in the angle of ocular deviation by recording data over long intervals. When ocular alignment is assessed using the prism and alternate cover test, the observer makes multiple determinations by swinging the paddle back and forth repeatedly. Prism strength is varied until no refixation movement is seen. To evaluate each prism, the examiner averages the eye movements seen on each alternate paddle occlusion to arrive at a verdict. Small fluctuations in ocular deviation that occur on a brief time scale (milliseconds to seconds) are not usually detected. Fluctuations are also present on a longer time scale (seconds to minutes), which means that 2 prisms of a slightly different power may both abolish the refixation movement because of a change in the deviation angle. Consequently, when measurements differ, one is uncertain whether the discrepancy is from measurement error, a true change in strabismus angle, or a combination of both.

Hatt et al made repeated prism and alternate cover test measurements in children with intermittent exotropia over the course of a day. The 95% repeatability coefficient was 7.3° (12.8Δ) for near deviation (33 cm) measurements in patients with deviations greater than 20Δ. This corresponds to an SD of 3.7°. We measured a horizontal SD of 2.43° in ocular deviation over 45 minutes in our cohort. Therefore, our results showed that a substantial portion of the variability measured using the prism and alternate cover test represents true biological variability in the deviation angle, not measurement error. Because of this variability, it makes sense to report a range, rather than a single value, for a patient’s strabismus angle.

In our experiments, the target was located at a fixed distance, so participants did not need to shift vergence tone during the task. However, in patients with exotropia, the angle of deviation is sensitive to vergence tone and more variable when viewing at near than at far. Therefore, the values we obtained for variability in the angle of strabismus would have been lower if measurements had been performed during distance viewing.

Refractive error and accommodative effort could also potentially affect eye position stability. We excluded participants with a refractive error of more than 4 D; 18 of 25 participants with strabismus had less than 2 D of refractive error. Accommodative fatigue might contribute to variability in the position of the deviated eye, especially in hyperopes. However, position stability for the deviated eye was not correlated with spherical equivalent of refractive error (r = 0.11).

Several previous studies have shown that the amblyopic eye is less stable than the fellow eye while fixating a target. Our data showed that patients with strabismus, even without amblyopia, fixate targets less accurately than individuals with normal eye alignment (Figure 2). That result seems puzzling given that fixation does not require binocular vision. However, strabismus has effects that extend beyond binocular vision. For example, smooth pursuit is impaired.

González et al used video eye trackers to measure the stability of each eye during near fixation in 12 patients with amblyopia. Most of the participants had strabismus or a combination of strabismus and anisometropia. The eye with normal acuity exhibited significantly better fixation stability than the
amblyopic eye when viewing a fixation cross under binocular conditions. Presumably, the amblyopic eye was deviated in most of the participants while viewing the fixation target, although this point was not stipulated. Our data suggest that strabismus alone, even without amblyopia, results in greater instability in the position of the deviated eye compared with the fixating eye. In most studies, fixation stability and ocular alignment have been assessed over a single time interval. We monitored eye position over an average of 45 minutes, allowing us to determine how variability in ocular deviation changes over a timescale spanning 4 log units. After about a minute, variability in the amplitude of the ocular deviation reaches a maximum. On a short time scale, high-frequency tremor and microsaccades are the main sources of variability.25,26 Over a longer time scale, slow drifts, oscillatory eye movements, vergence efforts, and blink-induced position errors come into play.2,27 Saccades are also a major source of variability in ocular deviation because the act of making a saccade contributes to disconjugacy and position drift (Figure 5). Saccadic disconjugacy has been documented previously in humans and monkeys.15,28,29

In strabismus, individual patients differ in their mean deviation angle. It is unknown what mechanism governs the angle of strabismus in a given patient. We found a horizontal SD of 2.43° in the position of the deviating eye. This value may be greater than in other forms of strabismus because deviation angle is particularly variable in intermittent exotropia.6,22,30,31 In patients with a small deviation, the position of the deviated eye is likely to be more stable, particularly if some binocular function is preserved.23-34 It would be worthwhile to test whether occlusion of the deviating eye affects the stability of its position. If so, it would imply that sensory feedback via the deviating eye is used by the visual system to control its position. González and colleagues19 found only a small effect on position stability when an amblyopic eye is covered. Occlusion of a nonamblyopic eye might have a greater impact on position stability because in alternating exotropia, the deviated eye remains perceptually active.17

Conclusions

An instrument has been developed to identify individuals with strabismus by detecting whether each eye is engaged in foveal fixation on a target.35,36 It might be possible to develop an instrument for screening purposes based on stability of eye position. Instability of the fixating eye has been reported in children with reduced or absent stereopsis.17 We also found instability of the fixating eye in strabismus (Figure 3B), but there

Figure 5. Variability of Eye Alignment While Viewing a Natural Scene

A, Fixations of a patient with exotropia recorded while scanning a picture of a deer; each white line pairs left eye position (blue dot) and right eye position (red dot) during a single fixation. B, Horizontal left eye (blue) and right eye (red) positions and horizontal deviation angle (right eye – left eye) recorded while the patient viewed the picture in panel A. C, Ellipses containing 95% of position points for each eye during the 25 individual left eye fixations. The ellipses for the left eye have been centered at the origin, and each corresponding ellipse for the right eye shifted by the same amount. The large red dashed ellipse encompasses 95% of right eye positions during the 10-second viewing period. D, Ellipses containing 95% of positions recorded while the patient performed the task of alternating fixation on a central cross. Only left eye fixations are shown and, for clarity, only 1/50 points is plotted.
was considerable overlap with the values for individuals with normal eye alignment. The best separation between patients with strabismus and control individuals was provided by the horizontal SD of the nonfixating eye’s position (Figure 3A). An instrument that could detect abnormal variability in the relative horizontal position of the 2 eyes, even if not calibrated to measure precisely the actual eye deviation, might be useful for mass strabismus screening.

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