

Motion Information via the Nonfixating Eye Can Drive Optokinetic Nystagmus in Strabismus

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Submitted: March 20, 2015

Accepted: August 31, 2015

Citation: Agaoglu S, Agaoglu MN, Das VE. Motion information via the nonfixating eye can drive optokinetic nystagmus in strabismus. *Invest Ophthalmol Vis Sci.* 2015;56:6423–6432. DOI:10.1167/iovs.15-16923

PURPOSE. Strabismic patients can perceptually suppress information from one eye to avoid double vision. However, evidence from prior studies shows that some parts of the visual field of the deviated eye are not suppressed. Our goal here was to investigate whether motion information available only to the deviated eye can be utilized by the oculomotor system to drive eye movements.

METHODS. Binocular eye movements were acquired in two exotropic monkeys in a dichoptic viewing task in which the fixating eye viewed a stationary spot and the deviated eye viewed a $10^\circ \times 10^\circ$ stationary patch that contained a drifting grating stimulus moving at $10^\circ/\text{s}$ to the right or left for 20 seconds. Spatial location and contrast of the grating were systematically varied in subsequent trials. For each trial, mean slow-phase velocity of the optokinetic nystagmus (OKN) elicited by grating motion was calculated.

RESULTS. We found that OKN responses can be elicited by a motion stimulus presented to the foveal region of the deviated eye. Optokinetic nystagmus magnitude varied depending on which eye was viewing the drifting grating and correlated well with fixation preference and fixation stability (indicators of amblyopia). The magnitude of OKN increased for increased relative contrast of the motion stimulus compared to the fixation spot.

CONCLUSIONS. Our results show that motion information available only to the deviated eye can drive optokinetic eye movements. We conclude that the brain has access to visual information from portions of the deviated eye (including the fovea) in strabismus that it can use to drive eye movements.

Keywords: strabismus, nonhuman primate, OKN, suppression

Two to five percent of all children are affected by developmental strabismus, a disorder in which the normal development of binocular vision is disrupted and the eyes become permanently misaligned.^{1–3} The misalignment of the two eyes can cause diplopia (double vision) and visual confusion. In diplopia, an object is projected to the fovea of one eye as well as to the peripheral retina of the deviated eye, and visual confusion occurs due to the projection of different objects in the environment to the foveae of the two eyes.⁴ However, patients with developmental strabismus do not experience diplopia and visual confusion because of two adaptive mechanisms adopted by the brain: visual suppression and anomalous retinal correspondence.^{4–6} Visual suppression of the images from one eye (deviated eye) results in temporary blind fields in the retina, known as scotomas, that are present in binocular viewing conditions but not in monocular viewing conditions. It could be that the fovea of the deviated eye is suppressed to avoid visual confusion, and that portions of temporal hemiretina in exotropes and nasal hemiretina in esotropes are suppressed to prevent diplopia.^{1,6–8} However, Economides et al.⁹ mapped areas of visual suppression in exotropic human subjects by using a color discrimination task and found that the fovea and portions of the temporal retina immediately adjacent to the fovea in the deviated eye are not suppressed in exotropes. They also showed that visual confusion is avoided by anomalous retinal correspondence

(ARC), in which the fovea of the viewing eye is paired with a noncorresponding location in the deviated eye.

Strabismic patients with relatively little amblyopia can switch the eye of fixation spontaneously depending on the location of the object they want to fixate, and this fixation-switch feature of strabismus is likely the result of visual suppression of portions of each eye's retina.^{7,10–12} Studies from our lab have replicated fixation-switch behavior in a monkey model for strabismus, and analyzing the spatial patterns of fixation switch in strabismic monkeys has provided insight into how visual information from the two eyes is processed and converted into action in strabismus.^{13,14} Fundamentally our results supported the idea that fixation-switch behavior follows from suppression of a portion of temporal retina in exotropes and a portion of nasal retina in esotropes. However, the fovea and portions of the temporal retina immediately adjacent to the fovea (portions of the nasal retina adjacent to the fovea in esotropes) were apparently not suppressed because the animals switched fixation when the target appeared in these retinal locations, thereby in agreement with the suppression maps of Economides et al.⁹ A novel finding was that the transition zone between preference for right eye fixation and preference for left eye fixation was “fuzzy” in that the animals could choose either eye to fixate the target appearing at certain spatial locations, suggesting that visual suppression can be partial. Agaoglu and colleagues¹³ proposed a framework for fixation-switch behavior wherein the oculomotor system has

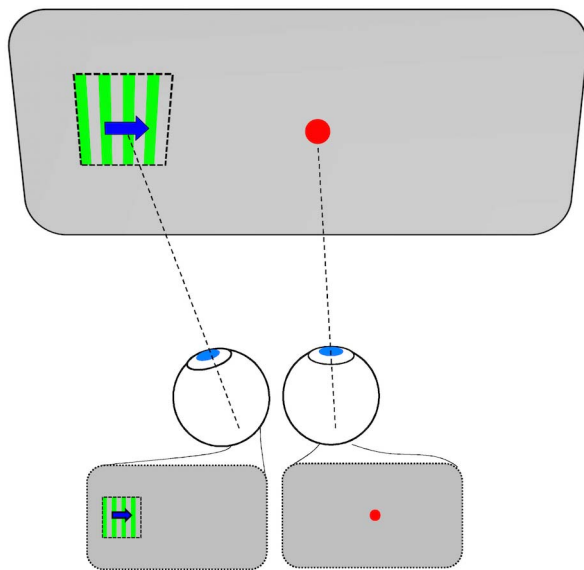


FIGURE 1. Dichoptic stimulus configuration. One eye is presented a 2° red fixation spot at the center of the screen, and the other eye is presented a square-wave green drifting grating at various eccentric locations. In the condition illustrated in this figure, the drifting grating is shown only to the deviated left eye while the fixating right eye is only viewing the red fixation spot (represented by the images below each eye). Each grating patch covered an area of 10° by 10° , and its drift velocity and spatial frequency were $\pm 10^\circ/\text{s}$ and 0.5 cyc/deg, respectively. The location of the grating on the display was varied across trials from left 30° to right 30° in the horizontal axis, and from up 10° to down 10° in the vertical axis.

retinal error information from both eyes, and the choice of fixating eye is made according to the strength of retinal error representations from each eye. Economides et al.¹⁵ also examined fixation-switch behavior in human exotropes and showed a coupling between perceptual state and spatial patterns of fixation-switch behavior.

The overall motivation for the current study was to continue to investigate the nature of the visual information available to the brain from the two eyes that it can use to drive eye movements. Specifically, we asked whether motion information available only to the deviated eye could be used by the oculomotor system to drive eye movements. Similar to studies that employed dichoptically presented drifting grating stimuli with motion in opposite directions to assess eye dominance or interocular suppression from optokinetic motor responses,^{16–22} our strategy was to present an optokinetic stimulus (a drifting grating) only to the deviated eye of the strabismic monkeys and determine whether it was sufficient to generate an optokinetic nystagmus (OKN). Our investigation suggests that optokinetic oculomotor responses can indeed be generated by a stimulus that falls on/around the fovea of the deviated eye, supporting the overall hypothesis that the oculomotor system has retinal information available from both eyes in strabismus. Some of these data have been presented before (Agaoglu S, et al. *IOVS* 2014;55:ARVO E-Abstract 2573).

METHODS

Subjects

Eye movement data were recorded from two juvenile rhesus monkeys (*Macaca mulatta*) with an exotropic strabismus (age 5–6 years, weight 8–9 kg). Strabismus was induced by rearing the animals under special viewing conditions (optical prism

viewing) for the first 4 months of their life. Prism strabismus or optical strabismus^{23,24} is based on the premise that the visual axes are separated due to prism viewing (noncorresponding binocular visual input) to an extent that sensory fusion cannot be achieved during development.^{25,26} Viewing through prisms for the first 3 months of life in a monkey can induce a permanent esotropia²⁷ or exotropia.²⁸ In the optical prism viewing procedure that we employed, infant monkeys viewed through a 20D base-down prism placed in front of one eye (left eye in one monkey [M1] and right eye in another monkey [M2]) and a 20D base-out prism placed in front of the other eye (right eye in M1 and left eye in M2). These horizontal and vertical Fresnel prisms were fitted in a lightweight helmet-like device that the animal wore for the first 4 months of life starting from 1 to 2 days after birth. Disruption of binocular vision due to prism viewing during this initial period leads to strabismus, as it is the critical period for development of eye alignment, stereopsis, and binocular sensitivity.²⁹

Surgical Procedures

After prism rearing, the monkeys grew normally (unrestricted vision) until ~ 4 years of age before starting the experiments. A head stabilization post was implanted by a sterile surgical procedure that was carried out under aseptic conditions using isoflurane anesthesia (1.25%–2.5%).³⁰ In a second surgery, a scleral search coil was implanted in one eye using the technique of Judge and colleagues.³¹ Later, in another surgery, a second scleral search coil was implanted in the other eye. All procedures were performed in strict compliance with National Institutes of Health and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the protocols were reviewed and approved by the Institutional Animal Care and Use Committees of the University of Houston.

Eye Movement Measurements

Binocular eye positions were measured using the magnetic search coil method (Primelec Industries, Regensdorf, Switzerland). Calibration of the eye coil signal was achieved while rewarding the monkey with a small amount of juice when the animal looked at a bright fixation target on a dark background that was rear projected on a tangent screen 57 cm away from the animal. The fixation target was shown at several horizontal and vertical positions to adjust the gain and offset values required to map eye coil signals to gaze positions. Calibration of each eye was performed independently during monocular viewing. The animals had previously participated in other oculomotor projects in the lab and were therefore trained to fixate on small high-contrast targets for substantial periods of time prior to their participation in this study.

Stimulus Presentation and Experimental Procedure

Visual stimuli were generated using the BITS# visual stimulus generator (Cambridge Research Systems, Cambridge, UK) and Psychtoolbox 3³² operated under computer control and presented using a DepthQ projector running at 120-Hz frame rate (Lightspeed Design, Inc., Bellevue, WA, USA). In the main experimental paradigm, a dichoptic visual stimulus was presented to the strabismic animals. In each trial, one eye was presented with a 2° diameter red fixation spot at the center of the tangent screen (57 cm away from the monkey), and the other eye was presented with a green drifting grating at various locations on the screen (Fig. 1). The background was otherwise gray. For every trial, the eye that was viewing the red fixation spot was the fixating eye and the eye viewing the

grating was the deviated eye, and the monkey was rewarded for continuing to maintain fixation on the red fixation spot. Grating size was $10^\circ \times 10^\circ$, spatial frequency was 0.5 cyc/deg, and drift velocity was $10^\circ/\text{s}$ rightward or leftward. The grating was presented at 21 gaze locations with respect to the fixating eye (7 horizontal locations from -30° to 30° and 3 vertical locations from -10° to 10°). The total duration of each trial was 40 seconds. The drifting grating was shown in the first 20 seconds (the "ON" period) along with the fixation spot in each trial; however, only the fixation spot was presented during the last 20 seconds in each trial (the "OFF" period).

In order to present the dichoptic stimulus, the fixation spot and drifting grating were shown in a frame-sequential presentation to each eye in sync with liquid crystal display (LCD) goggles (Micron Technology, Boise, ID, USA) that the animal wore during the experiment. We determined empirically that the LCD goggles lowered the luminance of stimuli to 28% of the actual value when open and 0.7% of actual value when closed. Therefore to prevent the small amount of light leakage that was present when the goggles were closed, we additionally placed dichroic filters in front of the goggles. Measurements showed 1.2% transmission of green light through the red filter and 0.9% transmission of red light through the green filter. Therefore with the combination of frame-sequential presentation and the dichroic filters, we are confident that the animals were indeed presented with a dichoptic stimulus (i.e., one eye views only the fixation spot and other eye views only the drifting grating). In order to additionally make sure that OKN responses were not elicited due to stimulus leakage through the LCD goggles, we ran a control condition in which the fellow eye, which would normally be presented a drifting grating, was physically patched with an opaque occluder, and no OKN response was elicited in this condition. In the presence of open LCD goggles and the red filter, the luminance of the fixation spot was 2.3 cd/m^2 . The luminance of the gray background was 0.84 cd/m^2 through the green filter and 0.56 cd/m^2 through the red filter for all conditions except when the contrast ratio was 0.96. In that condition, the luminance of the background was 0.08 and 0.06 cd/m^2 through the green and red filters, respectively. In the presence of open LCD goggles and the green filter, the luminance of the dark stripes of the grating was the same as background while the luminance of the bright stripes varied from 2.2 to 15.9 cd/m^2 .

In subsequent trials, we varied the contrast of the drifting grating, the drift direction, and the eye that was presented with the fixation spot. Seven different contrast ratios, defined as the ratio of Michelson contrast values of the fixation spot and the grating, were applied during the experiments (0.68, 0.71, 0.84, 0.96, 0.97, 1.18, 1.37). Therefore the entire experiment consisted of 588 trials (21 stimulus locations, 7 contrast ratios, either left or right eye viewing the red fixation spot, and two drift directions) for each monkey. In any particular block of trials, stimulus location was randomized but contrast ratio, eye of fixation, and drift direction were kept constant.

In order to examine any potential relationship between OKN response strength and possible relative unilateral amblyopia, we measured the fixation stability to use as an indicator of presence of amblyopia.³³⁻³⁵ Fixation stability was quantified by computing the bivariate contour ellipse area (BCEA) metric from the OFF section of data (i.e., only the red fixation spot is present on the screen).³⁶ In addition, to minimize the possibility of increased instability due to any charging up of the optokinetic system due to the previous motion stimulus, we included only data files corresponding to the lowest contrast ratio. Therefore we were able to analyze fixation data from 21 experimental conditions, each of which included 20 seconds of data. Saccades, blinks, and any other

sections of data during which the monkey was not on target were removed for the analysis.

We were also able to train one of the monkeys (M1) in a psychophysical task to measure a monocular contrast sensitivity function for each eye. The animal was first trained to discriminate between two grating orientations.³⁷ Each training trial began with central fixation followed by a 1-second presentation of a central 8° Gabor pattern (1 cyc/deg; 100% contrast) oriented at 45° clockwise (+) or counterclockwise (-). In the response phase, the animal was required to make a saccade in $<300 \text{ ms}$ to one of the response targets located on the left and right side of central fixation depending on grating orientation (e.g., rightward saccade for $+45^\circ$ and leftward saccade for -45°). Once the animal was trained ($>95\%$ correct for training parameters), grating contrast and spatial frequency was modulated in an adaptive 1-up-1-down staircase paradigm to identify contrast sensitivity thresholds for each spatial frequency.³⁸⁻⁴¹ Within a block of trials, several staircases for each spatial frequency were interleaved. Multiple staircases were averaged to obtain contrast sensitivity (1/threshold contrast) at each spatial frequency.

Data Analysis

Analysis was performed using custom programs developed in MATLAB (Mathworks, Natick, MA, USA). For each trial, the magnitude of OKN slow-phase velocity elicited by the drifting grating was analyzed and the mean slow-phase velocity was calculated. The strabismic monkeys showed latent/manifest latent nystagmus (fusion maldevelopment nystagmus) during monocular or binocular viewing with both horizontal and vertical components as do most humans and monkeys who have disrupted binocular fusion in the first months of life.⁴² The horizontal components of the nystagmus are problematic because they potentially interfere with the analysis of the OKN response. Therefore, to eliminate the effect of the inherent horizontal latent nystagmus, we used a form of common-mode rejection wherein for any particular combination of fixating eye, grating location, and contrast ratio, we subtracted OKN responses obtained when the grating drifted leftward from those obtained when the grating drifted rightward. This analytical method effectively isolates the OKN response to the drifting grating because the inherent nystagmus is always in one direction (since fixating eye, grating location, and contrast ratio are fixed) but the OKN responses depend on the grating drift direction. Although we obtained eye traces from both eyes, we considered only the data from the eye viewing the red fixation spot because eye traces of the fixating eye were more robust (fewer drifts) compared to those of the deviated eye in the strabismic monkeys.

RESULTS

Figure 2 illustrates eye misalignment as assessed during horizontal or vertical smooth pursuit with either the left eye viewing (left column) or right eye viewing (middle column) from monkey M1 (top row) and monkey M2 (bottom row). Both animals showed exotropia, as indicated by the abducted position of the left eye (blue trace) during right eye viewing and the abducted position of the right eye (red trace) during left eye viewing. Each animal also had a smaller vertical hypotropia/hypertropia depending on the fixating eye. The horizontal strabismus angles are different depending on which eye is viewing the target (dissociated horizontal deviation), and this strabismus property proved to be fruitful in our experiment as it served as a marker to identify the fixating eye (i.e., eye viewing the spot target) at any specific time

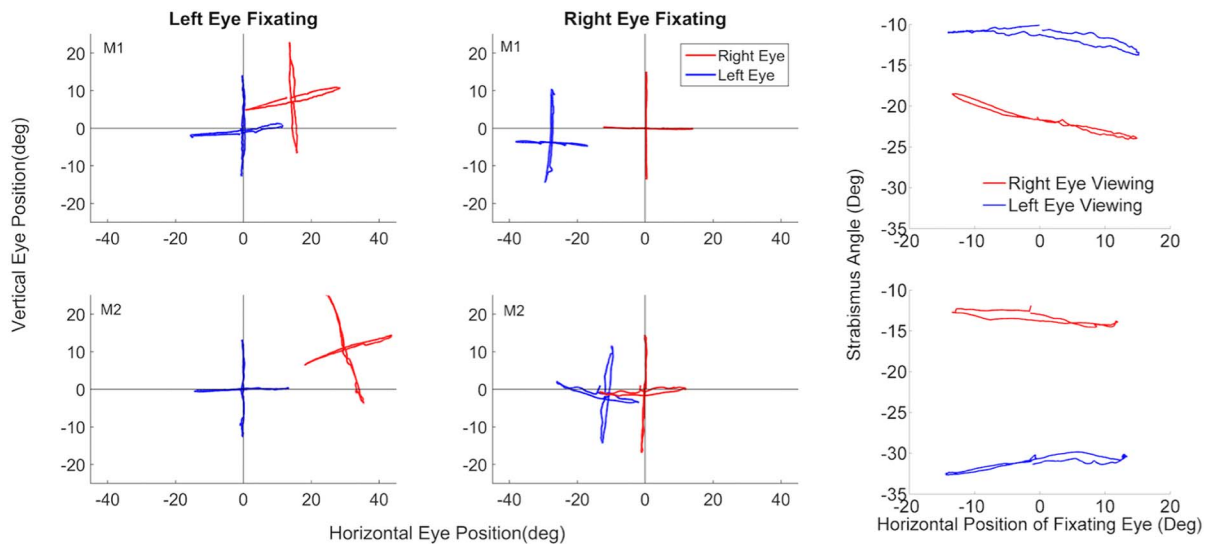


FIGURE 2. Eye misalignment patterns of exotropic monkeys M1 (*top row*) and M2 (*bottom row*) as assessed during horizontal and vertical smooth pursuit under monocular left eye (*left column*) or right eye (*center column*) viewing conditions. Target was a 2° optotype moving at 0.3 Hz, ±15°. Upward and rightward eye positions are positive. Strabismus angle as a function of horizontal position of the fixating eye in M1 (*top*) and M2 (*bottom*) is shown in the *rightmost column*.

instant. One point to be noted is that the strabismus angle remains more or less constant over the range of horizontal eye positions (*rightmost column* in Fig. 2). Therefore the change in strabismus angle between right and left eye viewing conditions occurs only upon fixation switch and not due to eccentric fixation.

OKN Responses Elicited by Stimulating the Fovea of the Deviated Eye

A major finding in both monkeys was that OKN responses were elicited when the drifting grating was presented within a region that included the fovea of the deviated eye. Figure 3

shows examples of a robust OKN response from each monkey (*top row*: M1; *bottom row*: M2) when the grating was presented (ON periods) to the deviated eye. The left column shows the eye traces when the left eye was fixating; that is, the left eye is viewing the red fixation dot, and the right eye is presented with the green drifting grating. The right column shows the eye position traces when the monkeys were fixating the red fixation spot with right eye. In each case, the grating was presented around the fovea of the deviated eye. In these sample plots, grating drift direction was rightward for M1 and leftward for M2. As specified in Methods, both rightward and leftward drifting grating were tested at all spatial locations. Both monkeys demonstrated a latent nystagmus when the grating stimulus was OFF. As is typical, the velocity of latent

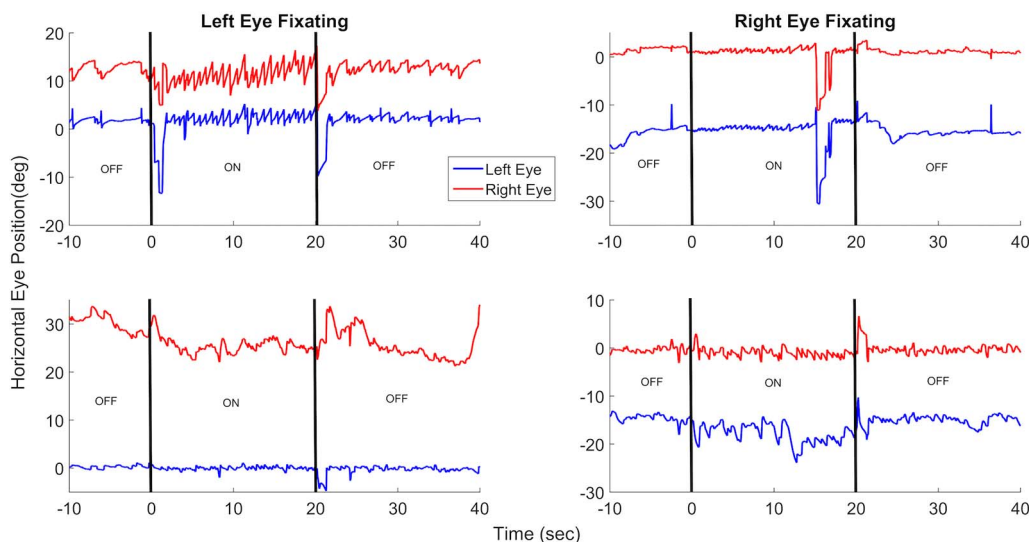


FIGURE 3. Optokinetic nystagmus elicited while monkeys (M1: *top row*; M2: *bottom row*) were presented with a stationary spot to the fixating eye and a drifting grating to the deviated eye (*left column*: left eye fixating and right eye deviated; *right column*: right eye fixating and left eye deviated). In each case, the drifting grating was located around the fovea of the deviated eye. In these sample data, grating drift direction was rightward for M1 and leftward for M2. Grating stimulus onset is depicted by the first vertical black line at the 0-second mark. The grating stimulus was ON for the first 20 seconds and OFF for the last 20 seconds. The grating stimulus offset is depicted by the *second vertical black line* at the 20-second mark. Significant OKN responses were observed during both right eye and left eye viewing of the drifting grating during the stimulus ON times.

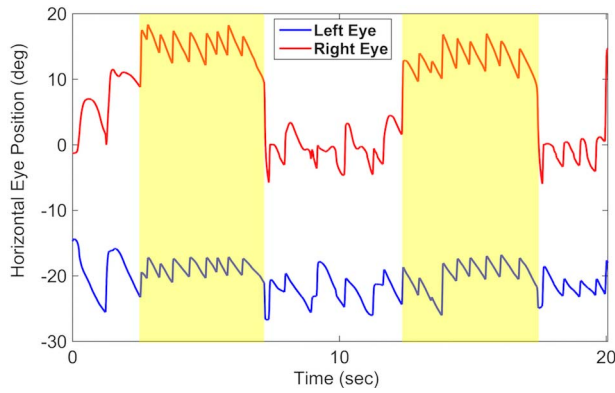


FIGURE 4. Control data from monkey M2 showing a trial in which the animal viewed the fixation spot with his right eye and the drifting grating was presented to the left eye. The figure shows that OKN responses and strabismus angle vary depending on whether the drifting stimulus is viewed via the deviated eye (*unshaded region*: fixating right eye position directed at 0°) or the animal switches fixation to the left eye and directly view the drifting grating stimulus (*yellow shaded regions*: right eye moves away from 0° leading to an increase in strabismus angle). Therefore *outside the yellow shaded regions*, the monkey is fixating the red spot with its right eye, whereas *inside the shaded regions* the animal fixates the grating with the left eye.

nystagmus varied depending on which eye was viewing. We suggest that the nystagmus observed during the OFF intervals was latent nystagmus and not optokinetic after-nystagmus because the duration of grating stimulation was short (only 20 seconds) and also the red fixation spot was still present in the OFF interval. Comparison of the nystagmus during the ON (first 20 seconds of a trial) and OFF (last 20 seconds of a trial) intervals reveals that the sawtooth pattern in the ON epoch was not just due to the latent nystagmus of the monkeys but an actual OKN response. Note also that the OKN responses were more robust when the direction of the horizontal component coincided with the direction of the latent nystagmus slow phase (top left and bottom right), representing the nasotemporal asymmetry often observed in developmental strabismus.^{43,44}

It is reasonable to question whether the elicited OKN was simply because the animal switched fixation from the red fixation spot to the green drifting grating. We are convinced that the animal did not switch fixation and that the OKN was in fact elicited by presenting the motion stimulus to the strabismic eye, for two reasons. The first reason is that the angle of strabismus remained the same for the duration of the grating presentation. As shown in Figure 2, a switch in fixation is accompanied by a significant change in strabismus angle, and so if the animal were to switch fixation to directly view the eccentric grating stimulus, we would have observed an accompanying change in strabismus angle. The second reason is that when the animal directly viewed the drifting grating

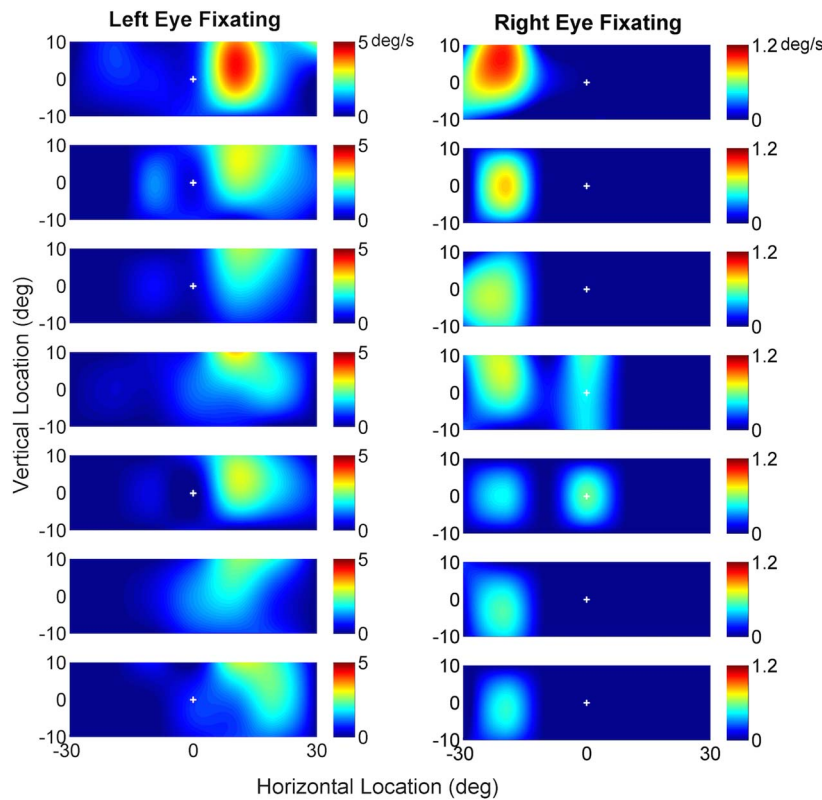


FIGURE 5. Magnitude of OKN slow-phase velocity in monkey M1 as a function of spatial location of drifting grating and relative contrast of fixation spot compared to the drifting stimulus. The *x*-axes represent horizontal grating center locations and *y*-axes represent vertical grating center locations. *Left and right columns* show the OKN magnitudes when monkey is fixating the stationary spot with left and right eyes, respectively. In each case, the position of the fixating eye, depicted by *plus sign*, is located at 0° because the monkey is fixating a straight-ahead stationary spot. The *color bar scale* represents slow-phase velocity (°/s), with warmer colors indicating higher velocity. From the *top* to the *bottom*, contrast ratio (fixation/grating contrasts) increases from 0.68 to 1.37. We observed measurable OKN responses when the drifting stimulus was around the fovea of the deviated eye. There is a decrease in OKN amplitude with increasing contrast ratio. Please note that the OKN response (color) scales are different in *left and right* columns.

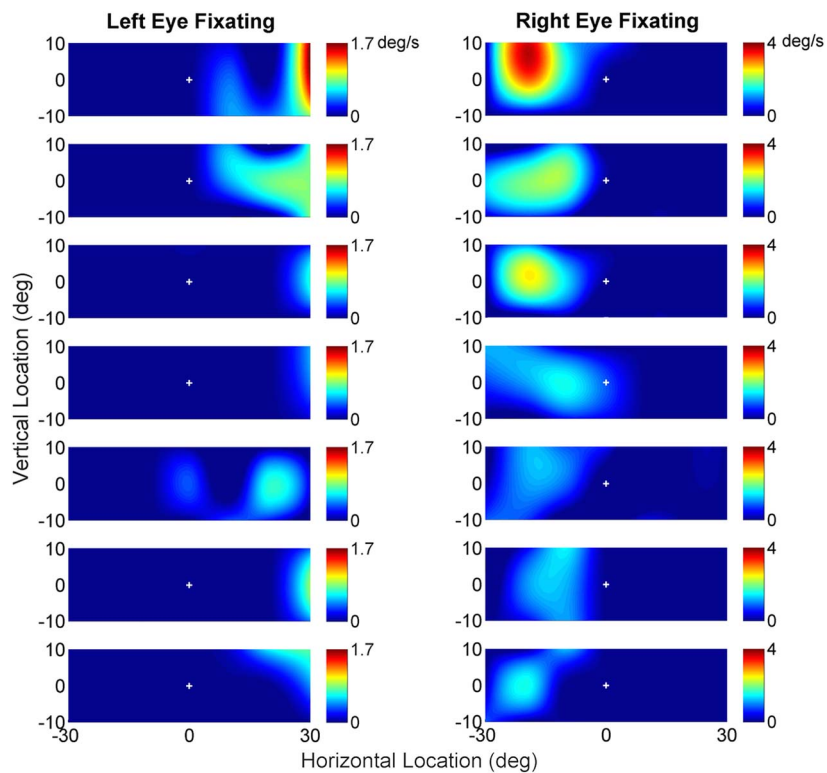


FIGURE 6. Magnitude of OKN slow-phase velocity in monkey M2 as a function of spatial location of drifting grating and relative contrast of fixation spot compared to the drifting stimulus. All legends and description same as in Figure 5.

(i.e., drifting grating presented to the fixating eye), the OKN response was significantly more robust than the OKN response elicited when the grating stimulus was presented to the deviated eye. Figure 4 shows an example of a single continuous section of data from monkey M2 illustrating both of these points. In this trial, the red fixation spot was presented to the right eye, and a leftward drifting grating (drift velocity of $10^\circ/s$; spatial location left 20°) was presented to the left eye. Although OKN responses are observed throughout the trial, two differences are noted between the shaded regions (marked in yellow) and the unshaded regions. In the unshaded regions, the right eye position ($\sim 0^\circ$) is appropriate for fixating on the red fixation spot, and the left eye position is appropriate for viewing the drifting grating. In the shaded regions, however, while the left eye positions remain on the drifting grating, the right eye position moves away from the red fixation spot—indicating that a switch in fixation occurred, resulting in the left eye directly viewing the grating. This movement also results in an increase in strabismus angle. The second difference between the shaded and unshaded regions is with regard to the “quality” of the OKN. As can be seen in Figure 4, the OKN response in the shaded regions is significantly more robust than in the unshaded regions. Quantitative analysis of OKN slow phases in the shaded and unshaded regions of Figure 4 showed increased OKN frequency and decreased variability in slow-phase velocities in the shaded (direct viewing) region compared to the unshaded (deviated eye viewing) region (unshaded region left eye OKN frequency = 1.16 Hz, slow-phase velocity = $-6.0 \pm 2.0^\circ/s$; shaded region left eye OKN frequency = 1.90 Hz, slow-phase velocity = $-6.5 \pm 1.1^\circ/s$; difference in variability of slow-phase velocities statistically significant, *F*-test, $F(17,10) = 3.3058$; $P = 0.03$). Therefore observations of the strabismus angle, position of the eyes, and the OKN characteristics together allowed us to

identify data where the animal was viewing the fixation spot and the drifting grating was being presented to the deviated eye; and all further analysis of OKN properties was focused only on these sections (i.e., corresponding to the unshaded regions in Fig. 4).

Effect of Varying Contrast and Stimulus Location on OKN Response

In our experiments, we also examined whether varying the contrast of the grating with respect to the fixation spot or varying the stimulus location with respect to the fovea of the fixating or deviated eyes would influence the OKN slow-phase velocity. Figures 5 and 6 summarize these results for the two animals. The left column shows spatial OKN response slow-phase velocities when the monkey was fixating with the left eye, and the right column shows spatial OKN response slow-phase velocities when the monkey was fixating with the right eye. The *x*-axis represents the horizontal position of the grating center, and the *y*-axis represents the vertical position of the grating center. From top to the bottom, the contrast ratio, defined as the ratio of Michelson contrasts of the fixation and drifting grating stimuli, increases (contrast ratio values tested: 0.68, 0.71, 0.84, 0.96, 0.97, 1.18, 1.37). In other words, the saliency of the drifting grating decreases from top to bottom. The color scale bar on the right illustrates the magnitude of OKN slow-phase velocity, with the red color representing the highest OKN slow-phase velocities and the cooler colors representing lower OKN velocities. Note that the OKN response scales are different for different monkeys and different eye fixating conditions. The grating stimulus was presented at discrete horizontal and vertical locations as

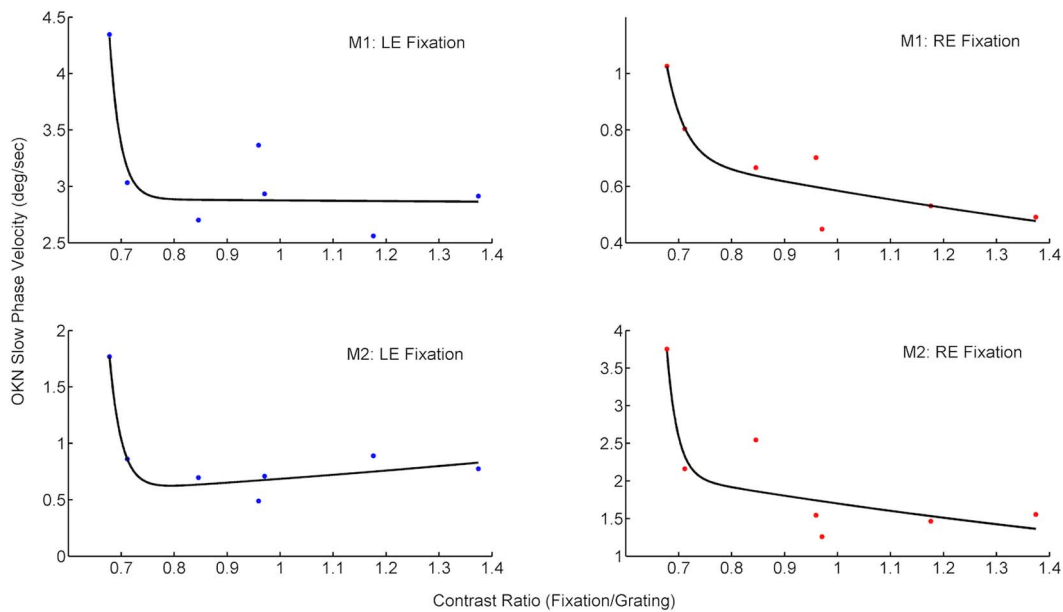


FIGURE 7. Maximum OKN slow-phase velocity plotted as a function of contrast ratio. The *x*-axes represent contrast ratio, calculated as the ratio between fixation and drifting grating stimuli contrast values. Data points are the highest OKN velocity obtained at each contrast ratio from Figures 5 and 6. *Black line* shows the exponential fit to the data.

described in Methods, and we used cubic interpolation to generate the spatial maps of Figures 5 and 6.

The highest OKN amplitudes are observed when the motion stimulus is on/around the fovea of the deviated eye. Therefore, the peak OKN response occurs at different distances from the center for right and left eye viewing conditions (different strabismus angles for right and left eye viewing conditions). Not much OKN is elicited when the grating is presented away from the fovea of the deviated eye. In M2, strabismus angle when viewing with the left eye is $\sim 30^\circ$, and so the peak OKN response appears at the far right edge of the plot. However, since the grating is 10° in width, it is likely that the motion stimulus is indeed on or very close to the fovea of the deviated eye. Unfortunately, due to limitations in the angular subtense of our projection setup, we were unable to present the motion stimulus at further eccentric locations in the nasal retina of the deviated right eye of M2 as was possible for the other three conditions. Another

observation from Figures 5 and 6 is a decrease in OKN slow-phase velocity with increasing contrast ratio for both left and right eye viewing conditions in both monkeys. However, a deviation from this general observation is that we also observed OKN responses in a secondary region that corresponds to the fovea of the fixating eye in some cases. We suspect that this observation is due to ARC (discussed further later).

In order to quantify the OKN responses as a function of contrast ratio, we took the largest OKN magnitudes from the primary region of response (i.e., region on/around the fovea of the deviated eye) and correlated this value with the contrast ratio. Figure 7 shows these data for each of the four conditions along with an exponential fit, and in each case, we found excellent R^2 values (M1, left eye fixating: 0.82; right eye fixating: 0.86; M2, left eye fixating: 0.94; right eye fixating: 0.83).

Finally, we also performed a control experiment wherein we evaluated the magnitude of the OKN when each eye directly viewed the same drifting stimulus as used at the lowest contrast ratio (M1, right eye, $7^\circ/s$; left eye: $4^\circ/s$; M2, right eye: $4^\circ/s$; left eye: $8^\circ/s$). In each case this value was significantly greater than the magnitude of OKN when the drifting stimulus was presented to the fovea of the deviated eye (Fig. 7), additionally proving that the motion information is indeed being processed via the deviated eye and that partial interocular suppression is present.

Correlation Between amplitude of elicited OKN and amblyopia

As we found that the OKN magnitude was different for right eye and left eye viewing of the drifting grating for each monkey (Fig. 7), we wondered whether this was influenced by the presence of an unilateral amblyopia. For example, in M1, a relative amblyopia in the left eye could have resulted in reduced OKN velocity when the left eye viewed the drifting stimulus compared to when the right eye viewed the identical

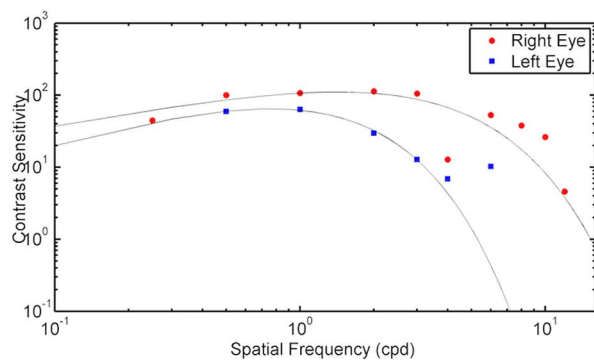


FIGURE 8. Contrast sensitivity function for monkey M1. The *x*-axis represents spatial frequency and *y*-axis represents contrast sensitivity. *Red and blue symbols* are data points for right and left eye, respectively. *Black lines* show the double exponential fits to data for each eye.

drifting stimulus. The presence of relative amblyopia was verified in two ways.

In M1, we were able to directly measure a monocular contrast sensitivity function for the two eyes using a psychophysical testing method (see Methods). Figure 8 shows the monocular contrast sensitivity function for monkey M1 and shows that indeed his left eye is relatively amblyopic compared to his right eye. Unfortunately, attempts to train M2 on the contrast sensitivity task were unsuccessful. Therefore a direct measure of the presence and depth of amblyopia in M2 could not be made.

However, another, admittedly indirect, way to assess presence of amblyopia is to examine fixation instability.³³⁻³⁵ In the current study, we assessed fixation stability by calculating the BCEA metric (see Methods). In M1, the mean BCEA was 0.56 deg² during right eye viewing and 5.14 deg² during left eye viewing. In M2, mean BCEA was 5.60 deg² during right eye viewing and 2.95 deg² during left eye viewing. This suggests that in M1 the left eye is relatively amblyopic (agreeing with the contrast sensitivity function results of Fig. 8) and in M2 the right eye is relatively amblyopic. Accordingly, for both the monkeys, the magnitude of elicited OKN was less when the suspected amblyopic eye was viewing the drifting stimulus.

DISCUSSION

Our overall goal with this line of research is to investigate whether the brain has access to visual information from the deviated eye in strabismus that it can use to drive eye movements. In this particular study, we investigated whether motion information available only to the deviated eye is read by the oculomotor system and used to drive optokinetic eye movements. Our main finding was that OKN responses could be elicited by a motion stimulus presented in the foveal region of the deviated eye. Further, the magnitude of the OKN depended on the relative contrast of the motion stimulus compared to the fixation spot and also depended on which eye was presented with the motion stimulus. Below we discuss each of our findings in greater detail.

OKN Driven Through the Deviated Eye

A principal finding was that a drifting grating motion stimulus applied to the fovea of the deviated eye was able to drive OKN in both eyes. Our methodological controls (use of frame-sequential display and red-green filters) and our experimental and analytical controls (Fig. 2 incoherence plots and Fig. 4) are sufficient, in our view, to prove that the OKN is indeed driven from the visual motion information to the deviated eye.

Our finding supports the finding of Economides and colleagues^{9,15} that the fovea of the deviated eye is in fact not fully suppressed. Maps of suppression scotomas in human exotropes and also the spatial patterns of fixation switch in exotropic monkeys^{13,14} further suggested that the nasal retina of the deviated eye, and also portions of the temporal retina immediately adjacent to the fovea of the deviated eye, were not suppressed. So one prediction for the current study might have been that OKN responses will be elicited when the drifting stimulus is placed in any location within the aforementioned regions that are not fully suppressed. We propose that the reason we obtained OKN response only in a limited region involving the fovea of the deviated eye is likely related to properties of OKN rather than properties of visual suppression.⁴⁵ Although generally OKN stimuli occupy the whole visual field, it is known that stimulating the fovea and the

surrounding 10° is almost as effective as a full-field stimulus. On the other hand, stimulating only the periphery (i.e., no stimulus in central 10°) results in a weak or absent OKN response.⁴⁶⁻⁴⁸ Further, as shown by Cynader and Harris⁴⁹ in strabismic cats, responsiveness to full-field OKN stimuli might be overall depressed in strabismus even during binocular viewing. We suggest therefore that when the drifting grating was placed in locations that were eccentric to the fovea of the deviated eye, the weak motion stimulus was insufficient to overcome the partial interocular suppression imposed by the fixating eye. Therefore the inability to drive OKN due to stimuli presented in the nasal/temporal retinal regions outside of the fovea of the deviated eye should not be interpreted as the presence of complete visual suppression in those regions. One noteworthy point is that although the fovea of the deviated eye is visually active, it is still under the influence of partial interocular suppression because the OKN magnitudes when stimulating the deviated eye were significantly less than when stimulating the fixating eye.

Fries and colleagues²² also used drifting gratings in a dichoptic presentation and OKN responses to investigate perceptual selection and suppression in surgically strabismic cats. In their study, the strabismic cats dichoptically viewed full-field gratings that drifted in opposite directions in each eye. The strabismic cats showed OKN, the direction of which could be manipulated by manipulating the contrast of the grating displayed to one or the other eye. Our fundamental finding of driving OKN via information available to only the deviated eye is therefore consistent with these results. However, one important difference in our study is that we applied the grating stimulus to only one specific portion of the visual field of the deviated eye and therefore were able to show that the fovea of the deviated eye was not completely suppressed.

Also generally consistent with the findings of Fries and colleagues²² is our finding that OKN magnitude was different for right eye and left eye viewing of the drifting grating for each monkey (Fig. 7). Interocular differences in visual sensitivity measured in a variety of ways have been considered as indicators of amblyopia.^{6,9-14,21,50-55} To address the interocular difference within the context of our OKN results, we measured contrast sensitivity of each eye in M1 and also fixation stability (BCEA) in both monkeys to assess the presence of amblyopia. At least in our small sample, we found that interocular OKN magnitude differences for the deviated eyes could be due to a relative amblyopia of one of the eyes. However, Fries and colleagues did not find a consistent relationship between amblyopia measured using a behavioral method and the interocular difference measured in their version of the OKN paradigm; and data from some other studies suggest that the relationship between amblyopia and an overall reduction of OKN gain may not be consistent.⁵⁶⁻⁵⁸ Regardless of the presence of relative amblyopia, the fundamental finding of this study is that with either eye viewing, an OKN response was always elicited when the fovea of the deviated eye was stimulated.

We found that reducing the relative contrast of the motion stimulus (presented to the deviated eye) with respect to the fixation spot (shown to the viewing eye) results in an exponential decrease in OKN slow-phase velocity (Fig. 7). This is perhaps to be expected because OKN scales with contrast.^{59,60} Further, a lower-strength motion stimulus to the deviated eye likely cannot overcome any partial interocular suppression applied by the fixating eye.⁶¹ Therefore, our results are consistent with the view that interocular suppression is not absolute but rather relative and stimulus dependent.

OKN and Perception

It is reasonable to ask what the monkey is actually seeing in our experiments. Although we do not have a direct readout of the perceptual state of the animal (perhaps better approachable in human studies by adding a perceptual component along with the OKN analysis), we can make some inferences. There are two possibilities. One is that the animal is not “perceiving” the motion stimulus. In this case, only the oculomotor system has access to retinal information from both eyes and can therefore drive OKN via information from the deviated eye. This would also imply that visual suppression acts independent of oculomotor mechanisms to eliminate perception of the motion stimulus. However, OKN has been shown to strongly correlate with perception in normal cats,^{16,17} normal monkeys,²⁰ and normal humans.^{19,62} This tight relationship allowed the use of OKN as an indicator of perceptual state in studies that investigated eye dominance, depth of suppression in rivalry situations, and their neural correlates.

The second possibility is that there is some sort of binocular combination wherein visual information from both eyes is being combined to drive both perception and eye movements. Although it was once believed that strabismic amblyopes were essentially monocular (i.e., no binocular combination possible), there is now mounting evidence supporting binocular combination effects even in strabismic amblyopia and in strabismus without amblyopia.^{61,63} Goodman and colleagues⁶¹ used a dichoptic viewing task in two patients with alternating strabismus to show that ability to perceive coherent motion was affected by the amount of signal or noise presented to the nonfixing eye compared to the fixing eye. They further showed that varying the contrast of the stimulus presented to the nonfixing eye could influence the thresholds to perceive coherent motion, which fits in nicely with our finding of OKN magnitudes scaling with contrast.

A curious finding was that we observed OKN responses in a secondary region corresponding to the fovea of the fixating eye at certain contrast levels. This was prominent in M1 (Fig. 5, right eye fixating, rows 4 and 5) but also present in M2 (Fig. 6, left eye fixating, row 5). One possibility is that this unusual OKN response is a manifestation of ARC; that is, the extrafoveal region of the deviated eye corresponding to the fovea of the fixating eye is driven by the presence of the drifting grating.⁵ It is not clear why this unusual response would manifest only at certain contrast levels. Also note that, in each case, this unusual OKN response was present when the amblyopic eye was viewing the drifting stimulus, although the significance of this observation is also not clear.

Acknowledgments

The authors thank Ernest Baskin for technical assistance with the animals.

Supported by National Institutes of Health Grants R01-EY015312 and R01-EY022723 and University of Houston, College of Optometry Core Grant P30 EY 07551. The authors alone are responsible for the content and writing of the paper.

Disclosure: **S. Agaoglu**, None; **M.N. Agaoglu**, None; **V.E. Das**, None

References

1. von Noorden GK, Campos EC. *Binocular Vision and Ocular Motility: Theory and Management of Strabismus*. 6th ed. St. Louis: Mosby; 2002.
2. Govindan M, Mohny BG, Diehl NN, Burke JP. Incidence and types of childhood exotropia: a population-based study. *Ophthalmology*. 2005;112:104–108.
3. Greenberg AE, Mohny BG, Diehl NN, Burke JP. Incidence and types of childhood esotropia: a population-based study. *Ophthalmology*. 2007;114:170–174.
4. Serrano-Pedraza I, Clarke MP, Read JC. Single vision during ocular deviation in intermittent exotropia. *Ophthalmic Physiol Opt*. 2011;31:45–55.
5. Herzau V. How useful is anomalous correspondence? *Eye (Lond)*. 1996;10(pt 2):266–269.
6. Joosse MV, Simonsz HJ, de Jong PT. The visual field in strabismus: a historical review of studies on amblyopia and suppression. *Strabismus*. 2000;8:135–149.
7. Sireteanu R. Binocular vision in strabismic humans with alternating fixation. *Vision Res*. 1982;22:889–896.
8. Sireteanu R, Fronius M. Different patterns of retinal correspondence in the central and peripheral visual field of strabismics. *Invest Ophthalmol Vis Sci*. 1989;30:2023–2033.
9. Economides JR, Adams DL, Horton JC. Perception via the deviated eye in strabismus. *J Neurosci*. 2012;32:10286–10295.
10. van Leeuwen AE, Collewijn H, de Faber JT, van der Steen J. Saccadic binocular coordination in alternating exotropia. *Vision Res*. 2001;41:3425–3435.
11. Dickey CF, Metz HS, Stewart SA, Scott WE. The diagnosis of amblyopia in cross-fixation. *J Pediatr Ophthalmol Strabismus*. 1991;28:171–175.
12. Steinbach MJ. Alternating exotropia: temporal course of the switch in suppression. *Invest Ophthalmol Vis Sci*. 1981;20:129–133.
13. Agaoglu MN, LeSage SK, Joshi AC, Das VE. Spatial patterns of fixation in monkeys with strabismus. *Invest Ophthalmol Vis Sci*. 2014;55:1259–1268.
14. Das VE. Alternating fixation and saccade behavior in nonhuman primates with alternating occlusion-induced exotropia. *Invest Ophthalmol Vis Sci*. 2009;50:3703–3710.
15. Economides JR, Adams DL, Horton JC. Eye choice for acquisition of targets in alternating strabismus. *J Neurosci*. 2014;34:14578–14588.
16. Enoksson P. A method for investigation of ocular dominance based on optokinetic nystagmus. *Acta Ophthalmol (Copenh)*. 1961;39:115–140.
17. Enoksson P. Binocular rivalry and monocular dominance studied with optokinetic nystagmus. *Acta Ophthalmol (Copenh)*. 1963;41:544–563.
18. Fox R, Todd S, Bettinger LA. Optokinetic nystagmus as an objective indicator of binocular rivalry. *Vision Res*. 1975;15:849–853.
19. Hayashi R, Tanifuji M. Which image is in awareness during binocular rivalry? Reading perceptual status from eye movements. *J Vis*. 2012;12(3):5.
20. Logothetis NK, Schall JD. Binocular motion rivalry in macaque monkeys: eye dominance and tracking eye movements. *Vision Res*. 1990;30:1409–1419.
21. Fries P, Roelfsema PR, Engel AK, König P, Singer W. Synchronization of oscillatory responses in visual cortex correlates with perception in interocular rivalry. *Proc Natl Acad Sci U S A*. 1997;94:12699–12704.
22. Fries P, Schroder JH, Singer W, Engel AK. Conditions of perceptual selection and suppression during interocular rivalry in strabismic and normal cats. *Vision Res*. 2001;41:771–783.
23. Smith EL III, Bennett MJ, Harwerth RS, Crawford ML. Binocularity in kittens reared with optically induced squint. *Science*. 1979;204:875–877.
24. Crawford ML, von Noorden GK. Optically induced concomitant strabismus in monkeys. *Invest Ophthalmol Vis Sci*. 1980;19:1105–1109.
25. Crawford ML. Animal models in strabismus: sensory aspects of a comitant strabismus. In: Lennerstrand G, Ygge J, eds.

- Advances in Strabismus Research: Basic and Clinical Aspects*. London: Portland Press; 2000:121-130.
26. Chino YM. Developmental visual deprivation. In: Kaufman P, ed. *Adler's Physiology of the Eye*. 11th ed. New York: Elsevier; 2011:732-749.
 27. Wong AM, Foeller P, Bradley D, Burkhalter A, Tychsen L. Early versus delayed repair of infantile strabismus in macaque monkeys: I. ocular motor effects. *J AAPOS*. 2003;7:200-209.
 28. Narasimhan A, Tychsen L, Poukens V, Demer JL. Horizontal rectus muscle anatomy in naturally and artificially strabismic monkeys. *Invest Ophthalmol Vis Sci*. 2007;48:2576-2588.
 29. Boothe RG, Dobson V, Teller DY. Postnatal development of vision in human and nonhuman primates. *Annu Rev Neurosci*. 1985;8:495-545.
 30. Adams DL, Economides JR, Jocson CM, Horton JC. A biocompatible titanium headpost for stabilizing behaving monkeys. *J Neurophysiol*. 2007;98:993-1001.
 31. Judge SJ, Richmond BJ, Chu FC. Implantation of magnetic search coils for measurement of eye position: an improved method. *Vision Res*. 1980;20:535-538.
 32. Brainard DH. The Psychophysics Toolbox. *Spat Vis*. 1997;10:433-436.
 33. Subramanian V, Jost RM, Birch EE. A quantitative study of fixation stability in amblyopia. *Invest Ophthalmol Vis Sci*. 2013;54:1998-2003.
 34. Gonzalez EG, Wong AM, Niechwiej-Szwedo E, Tarita-Nistor L, Steinbach MJ. Eye position stability in amblyopia and in normal binocular vision. *Invest Ophthalmol Vis Sci*. 2012;53:5386-5394.
 35. Chung ST, Kumar G, Li RW, Levi DM. Characteristics of fixational eye movements in amblyopia: limitations on fixation stability and acuity? *Vision Res*. 2015;114:87-99.
 36. Timberlake GT, Sharma MK, Grose SA, Gobert DV, Gauch JM, Maino JH. Retinal location of the preferred retinal locus relative to the fovea in scanning laser ophthalmoscope images. *Optom Vis Sci*. 2005;82:177-185.
 37. Newsome WT, Pare EB. A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J Neurosci*. 1988;8:2201-2211.
 38. Zhang B, Tao X, Wensveen JM, Harwerth RS, Smith EL III, Chino YM. Effects of brief daily periods of unrestricted vision during early monocular form deprivation on development of visual area 2. *Invest Ophthalmol Vis Sci*. 2011;52:7222-7231.
 39. Wensveen JM, Smith EL III, Hung LF, Harwerth RS. Brief daily periods of unrestricted vision preserve stereopsis in strabismus. *Invest Ophthalmol Vis Sci*. 2011;52:4872-4879.
 40. Wensveen JM, Harwerth RS, Hung LF, Ramamirtham R, Kee CS, Smith EL III. Brief daily periods of unrestricted vision can prevent form-deprivation amblyopia. *Invest Ophthalmol Vis Sci*. 2006;47:2468-2477.
 41. Levitt H. Transformed up-down methods in psychoacoustics. *J Acoust Soc Am*. 1971;49(2, suppl 2):467+.
 42. Tychsen L, Richards M, Wong A, Foeller P, Bradley D, Burkhalter A. The neural mechanism for latent (fusion maldevelopment) nystagmus. *J Neuroophthalmol*. 2010;30:276-283.
 43. Tychsen L, Richards M, Wong A, et al. Spectrum of infantile esotropia in primates: behavior, brains, and orbits. *J AAPOS*. 2008;12:375-380.
 44. Yildirim C, Tychsen L. Disjunctive optokinetic nystagmus in a naturally esotropic macaque monkey: interaction between nasotemporal asymmetries of versional eye movement and convergence. *Ophthalmic Res*. 2000;32:172-180.
 45. Fuchs AF, Mustari MJ. The optokinetic response in primates and its possible neuronal substrate. *Rev Oculomot Res*. 1993;5:343-369.
 46. Van Die GC, Collewijn H. Control of human optokinetic nystagmus by the central and peripheral retina: effects of partial visual field masking, scotopic vision and central retinal scotomata. *Brain Res*. 1986;383:185-194.
 47. Dubois MF, Collewijn H. Optokinetic reactions in man elicited by localized retinal motion stimuli. *Vision Res*. 1979;19:1105-1115.
 48. Schor C, Narayan V. The influence of field size upon the spatial frequency response of optokinetic nystagmus. *Vision Res*. 1981;21:985-994.
 49. Cynader M, Harris L. Eye movement in strabismic cats. *Nature*. 1980;286:64-65.
 50. Singer W, von Grunau M, Rauschecker J. Functional amblyopia in kittens with unilateral exotropia. I. Electrophysiological assessment. *Exp Brain Res*. 1980;40:294-304.
 51. von Grunau MW, Singer W. Functional amblyopia in kittens with unilateral exotropia. II. Correspondence between behavioural and electrophysiological assessment. *Exp Brain Res*. 1980;40:305-310.
 52. Mitchell DE, Ruck M, Kaye MG, Kirby S. Immediate and long-term effects on visual acuity of surgically induced strabismus in kittens. *Exp Brain Res*. 1984;55:420-430.
 53. Harrad RA, Hess RF. Binocular integration of contrast information in amblyopia. *Vision Res*. 1992;32:2135-2150.
 54. Li J, Hess RF, Chan LY, et al. Quantitative measurement of interocular suppression in anisometropic amblyopia: a case-control study. *Ophthalmology*. 2013;120:1672-1680.
 55. Zhou J, Jia W, Huang CB, Hess RF. The effect of unilateral mean luminance on binocular combination in normal and amblyopic vision. *Sci Rep*. 2013;3:2012.
 56. Westall CA, Schor CM. Asymmetries of optokinetic nystagmus in amblyopia: the effect of selected retinal stimulation. *Vision Res*. 1985;25:1431-1438.
 57. Valmaggia C, Proudlock F, Gottlob I. Optokinetic nystagmus in strabismus: are asymmetries related to binocularity?. *Invest Ophthalmol Vis Sci*. 2003;44:5142-5150.
 58. Knapp CM, Proudlock FA, Gottlob I. OKN asymmetry in human subjects: a literature review. *Strabismus*. 2013;21:37-49.
 59. Leguire LE, Zaff BS, Freeman S, Rogers GL, Bremer DL, Wali N. Contrast sensitivity of optokinetic nystagmus. *Vision Res*. 1991;31:89-97.
 60. Schor CM, Levi DM. Disturbances of small-field horizontal and vertical optokinetic nystagmus in amblyopia. *Invest Ophthalmol Vis Sci*. 1980;19:668-683.
 61. Goodman LK, Black JM, Phillips G, Hess RF, Thompson B. Excitatory binocular interactions in two cases of alternating strabismus. *J AAPOS*. 2011;15:345-349.
 62. Naber M, Frassle S, Einhauser W. Perceptual rivalry: reflexes reveal the gradual nature of visual awareness. *PLoS One*. 2011;6:e20910.
 63. Hess RF, Thompson B, Baker DH. Binocular vision in amblyopia: structure, suppression and plasticity. *Ophthalmic Physiol Opt*. 2014;34:146-162.