Can Misalignments in Typical Infants Be Used as a Model for Infantile Esotropia?

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PURPOSE. To investigate the nature of early ocular misalignments in human infants to determine whether they can provide insight into the etiology of esotropia and, in particular, to examine the correlates of misalignments.

METHODS. A remote haploscopic photorefraction system was used to measure accommodation and vergence in 146 infants between 0 and 12 months of age. Infants underwent photorefraction immediately after watching a target moving between two of five viewing distances (25, 33, 50, 100, and 200 cm). In some instances, infants were tested in two conditions: both eyes open and one eye occluded. The resultant data were screened for instances of large misalignments. Data were assessed to determine whether accommodative, retinal disparity, or other cues were associated with the occurrence of misalignments.

RESULTS. The results showed that there was no correlation between accommodative behavior and misalignments. Infants were more likely to show misalignments when retinal disparity cues were removed through occlusion. They were also more likely to show misalignments immediately after the target moved from a near to a far position in comparison to far-to-near target movement.

DISCUSSION. The data suggest that the prevalence of misalignments in infants of 2 to 3 months of age is decreased by the addition of retinal disparity cues to the stimulus. In addition, target movement away from the infant increases the prevalence of misalignments. These data are compatible with the notion that misalignment are caused by poor sensitivity to targets moving away from the infant and support the theory that some forms of strabismus could be related to failure in a system that is sensitive to the direction of motion. (Invest Ophthalmol Vis Sci. 2004;45:714–720) DOI:10.1167/iovs.03-0454

Infants' eyes are broadly aligned from birth.1–10 Nevertheless, parents often notice that their newborn infant shows short periods of fleeting misalignment when one eye looks as if it is pointing in the wrong direction. Parents most often report these misalignments as inward turning.8,11 Fleeting esotropic misalignments are usually considered to be typical neonatal behavior and rarely are presented to ophthalmologists or featured in the literature, except in passing.10,12–14 If an abnormality does not develop, the infant's neonatal squint is quickly forgotten or discounted as insignificant.15 Only if infantile strabismus later develops can early misalignment be considered definitely pathologic.16,17

Neonatal misalignments have been shown to be a useful predictor of later visual abnormalities by Horwood.8 Studies of both the newborn infants of orthoptists8 and a large cohort11 have been used to determine the amount of time that typical infants spend with misaligned eyes in the first months of life. Neonatal misalignments, defined as intermittent, fleeting, large-angle, usually convergent deviations have been found to occur in the first weeks of life in most typical infants. The prevalence of misalignments was 75.2% in 1-month-old infants, reduced to 49% in 2-month-old infants, and had disappeared in typical infants by 4 months of age.18 In children with infantile esotropia, the prevalence of early misalignment appears to increase over the period when similar behavior is disappearing in typical infants.19,20 The large prevalence of esotropia in neonates reported by Archer et al.20 and others in the same laboratory21,22 was not found in these studies. Other studies, where the effect of angle λ has been controlled have also failed to find this.9,10,25

To determine the relationship between the prevalence of misalignments early in development and later visuomotor problems, Horwood et al.18,19,24 followed up participants from previous studies to identify which infants went on to develop strabismus and refractive errors. They found that the prevalence of visual problems was higher in infants at either end of the frequency distribution—that is, those who either never showed misalignment or those who spent much of the day with misaligned eyes during the first weeks of life. In contrast, few abnormalities were found in those infants who had occasional misalignment. In addition, infants who showed frequent misalignments were significantly more likely to show an exodeviation (esotropia or significant esophoria), but not an exodeviation, than were infants who showed few.11

Estimates of the prevalence of essential infantile esotropia vary from 0.09%20 to 1%,25 and its relative rarity makes the development of the condition difficult to study. The cited studies, however, demonstrate a predictive link between the frequency of neonatal misalignments found during early infancy and later-developing esodeviation. Because these deviations are indistinguishable in infants in whom esotropia develops and those in whom it does not, the study of misalignments in typical neonates may provide a larger data source for the study of correlates of this behavior than would be available if we were restricted to studying only infants who have infantile esotropia.

In a study of the development of accommodation and vergence in typical infants, we used photorefraction to demonstrate that most infants aged between 0 and 12 months align their eyes appropriately to targets placed at different distances.25 However, the task occasionally induced large misalignments similar to those reported by parents. It is these large neonatal misalignments that were the subject of the current study. In particular, we were interested in determining which cues to the position of targets in depth were implicated in the production of these misalignments.

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Adult participants are capable of using many cues to depth, including blur, disparity, motion, and other proximal cues. Blur is the main cue that is used to drive accommodation in adults. Research, however, has indicated that, during the first month of life, many infants maintain a fixed plane of focus at approximately 30 cm and fail to relax their accommodation appropriately for distant targets. Some types of strabismus, in older children, are accommodative in nature: in these, the deviation is caused or influenced by the state of accommodation. Thus, it is possible that neonatal misalignments could be associated with overaccommodation early in life.

In adults, retinal disparity information is the main cue to vergence eye movements. It is known that infants less than 4 months of age have not developed mature stereopsis and therefore are less likely to be able to use retinal disparity as a cue to target distance. Thus, neonatal misalignments may be associated with cortical immaturities and disappear with the onset of cortical binocularity.

A third possible immaturity in infant vision is the response to moving stimuli. Adult subjects show symmetrical tracking responses to target movement in each direction across the retina when viewing monocularly. In comparison, infants show asymmetrical responses demonstrated by both optokinetic nystagmus (OKN) and visual evoked potentials (VEPs). Neonates show a more vigorous OKN response to targets moving in the temporal-to-nasal direction than in the nasal-to-temporal direction. This suggests that infants should be better at tracking targets (either binocularly or monocularly) when the target is moving toward them (temporal-to-nasal movement in each eye) than when the target is moving away from them (nasal-to-temporal movement in each eye). This asymmetry disappears with development but is apparent in older children who have esotropia. For instance, Birch et al. demonstrated that by 2 to 3 months of age, a similar response to targets at different depths, infants underwent photorefraction with a remote haploscopic photorefractor (Fig. 1, designed by Israel Abramov and Louise Hainline, Infant Study Center, Brooklyn College of the City University of New York). The apparatus has been described in detail elsewhere. It consists of a conventional off-axis photorefraction system as described by Abramov et al. The camera used in this system (Fig. 1, J) views the infant’s eyes through a periscope arrangement consisting of a beam splitter (Fig. 1, F) and a first surface mirror (Fig. 1, G).

The target is presented on a flat-screen monitor that can be moved to positions between 2 and 0.25 m from the infant along a motorized beam. In this study, the target moved among five viewing distances (2, 1, 0.5, 0.33, and 0.25 m). Infants viewed the target at each distance in the same pseudorandom order (0.33, 2, 0.25, 1, and 0.5 m). The target monitor moved between each new depth position at a constant velocity of 0.4 m/s. Thus, transitions between targets took between 0.2 and 0.7 second. Photographs were usually taken within 0.5 second of the target reaching its final position. This took longer only if the infant was inattentive. Infants were very interested in the movement of the target between positions, however, and maximum attention was usually obtained during and immediately after target movement.

The target in this study was a colored picture of a clown’s face subtending 4.2° by 2.8° at 2 m (the farthest distance tested) and containing a range of spatial frequencies. The optical pathway for target viewing was separate from the optical pathway used for photorefraction. The target was viewed through two concave mirrors (Fig. 1; C, D) positioned so that a virtual image of the target appeared directly in front of the infant. The infant saw the approaching and receding target, immediately followed by the camera flash. Enough time was given after each flash for any initial after-image of the flash to subside. Each infant viewed the target while sitting on his or her caregiver’s lap, and a photograph of the infant’s eyes was taken by the photorefractor immediately after target stopped moving and when the infant was seen to be attentive (through a separate video monitor of the infant’s face).

The optical pathway of the fixation target was arranged so that occlusion of one eye could take place remote from the subject, in front of the remaining eye.
of the upper concave mirror (Fig. 1, C). An image of the infant’s face was projected onto this mirror through the virtual image (Fig. 1, E), resulting in a virtual infant. Occluding one eye of the virtual infant is identical with occluding the infant’s eye directly; however, both of the real infant’s eyes could still be photographed by the photorefractor. This setup is particularly suitable for working with infants, because the occluder is invisible to the participant and is not close to the infant’s face. This allows us to test for changes in vergence position when no retinal disparity cues are available to the infant.

Photographs were measured with image-analysis software (Photoshop; Adobe Systems, Mountain View, CA). An estimation of the accommodative response of the infant was obtained by measurement of the size of the fundal crescent in relation to the pupil (for details of calibration, seeRefs. 23,24). Measurement accuracy in our laboratory for this method, accounting for interobserver reliability, is ±0.3 D of accommodation, with a ‘dead zone’ around 0 D of approximately ±0.5 D where no crescents are detectable. Vergence was calculated from the position of the corneal reflection of the flash in relation to the pupil center. As convergence occurred, the pupil center moved nasally in relation to the corneal reflection. By applying the Hirschberg ratio (1-mm corneal reflection change per 1° of vergence change),10,39) we derived an angular estimate of vergence. An average value for the Hirschberg ratio was used because the number of infants who did not complete testing would increase if we attempted to obtain individual Hirschberg ratios. Vergence angle was adjusted for angle λ, with account taken of the developmental change in this value.39 Measurement accuracy for vergence in our laboratory is ±1.1° (approximately ±Δ) of vergence change. In this study, vergence was measured in meter angles (MA: 1/distance at which the eyes are converged) to be directly comparable to accommodation measured in diopeters (1/distance to plane of focus).

At each visit, the parents were also asked about the ocular misalignments that they had seen at home. Questions were identical with those used by Horwood10 so that direct comparisons could be made with previous data. Infants were given basic orthoptic tests including cover test, ocular motility, fixation behavior, convergence to near point, and 20Δ base-out prism test.40

Participants

The present study was performed in compliance with the Declaration of Helsinki. One hundred forty-six healthy infants attended the Infant Vision Laboratory as part of a longitudinal study into the development of vergence and accommodation.25 Infants were recruited through antenatal classes and healthcare professionals and varied in corrected gestational age from ~2 to 7 weeks at the first visit. Any infant who showed significant manifest refractive error (≥1.0 DS or DC in this study), manifest strabismus, or heterophoria over 4Δ (by prism cover test) by 1 year of age was excluded from the analysis. Four infants were excluded on this basis. The remaining infants produced data on 658 visits (mean, 4.47 visits per infant; range, 1–9 visits). Each visit produced between 3 and 7 photographs of the infant viewing with both eyes (mean, 5.2 photographs) resulting in a total of 3691 photographs. Infants were assessed in the monocular condition only when bilateral deviations. To define misalignment, all vergence errors were first expressed as vergence error in relation to fixation demand (actual vergence position in MA — required vergence position in MA).

For the infants in this study, these errors were found to be distributed normally (Kolmogorov-Smirnov statistic = 0.043, P < 0.001). Because neonatal ocular misalignments are large angles, they represent the extremes of the distribution of vergence errors. We therefore defined a convergent misalignment as any deviation that was more than 2 SD more convergent than target demand (11.5°, or 20Δ). This is larger than the limit for detecting vergence errors visually and so is likely to concord with the types of errors detected by untrained parents. Divergent misalignments were defined as errors that were more than 2 SD divergent from orthotropia. The definitions used for convergent and divergent misalignments are purposely conservative to avoid overreporting due to individual variations in angle λ or the Hirschberg ratio. These definitions were used to define misalignments in both binocular and monocular conditions. Note that in the monocular condition, a misalignment could not be produced as a result of the infant’s fixating the target with the nonoccluded eye and then making a following movement with the occluded eye, because this would result in a divergent movement in the occluded eye. Thus, convergent misalignments in the monocular condition must result from overactivation of the vergence system.

Results

Using our conservative definition, misalignments were found in 102 photographs (2.7% of the total photographs) on 65 visits (9.87% of visits) in 42 infants (27.45% of infants). Figure 2 shows a steady decrease in the percentage of misalignments detected with increasing age. Between 20% and 30% of infants up to 8 weeks of age were found to have ocular misalignment, whereas, by 16 weeks of age, less than 5% showed misalignment.

To determine whether the misalignments observed in the laboratory were similar to those reported by the parents, we compared the parental reports of misalignments among three groups of infants: (1) those in whom misalignment was never seen in the laboratory (Non-NM); (2) those in whom it was seen only one occasion in the laboratory (One NM); and (3) those in whom it was seen on more than one occasion in the laboratory (>One NM). Parents were asked to report neonatal misalignments at home on a scale from 0 (never squinted) to 7 (constantly squinting) on a scale from 0 to 7 (constantly squinting). Mean score for all infants was 1.8 (i.e., infants showed misalignment fleeting, approximately once a day). Figure 3 shows a comparison of misalignments in the laboratory and at home. It is clear that there is an association between observation of misalignment at home and in the laboratory. Infants who showed no misalignment in the laboratory had the lowest mean score on home observations, whereas infants showing one misalignment in the laboratory had a significantly higher than average score at home (Mann-Whitney test = 1408.5, P = 0.021). The 15 infants who showed more than one misalignment in the laboratory were even more likely to be seen to squint at home (Mann-Whitney = 381.5, P = 0.003).
Do Misalignments Result from Accommodative Errors?

To determine whether misalignments are due to accommodative errors, we looked at the simultaneous accommodation response recorded at the time of vergence misalignments. If vergence misalignments result from accommodative errors, we would expect accommodation to have changed in the same direction as the misalignments. To test whether this was the case, we created a 4-point rating scale for links between accommodation and vergence. A “good” link on this scale was defined as accommodation within 1 D of the vergence response in MA during the misalignment. A “fair” link was scored as a change in accommodation that was more than 1 D greater than demand, but was less than the vergence response in MA during the misalignment. A “poor” link was scored as a small change in accommodation that was less than 1 D greater than demand during the misalignment. Finally, “none” was scored as no change in accommodation in excess of demand occurring during the misalignment.

In Figure 4, Infant A shows an example of both a fair (0.5 D target) and a poor (4-D target) link between convergence and accommodation. Infant B shows an example of no link between misalignment and accommodation. Here accommodation remains appropriate at the 2-MA target distance, at which the infant makes a large misalignment.

Figure 5 shows the results of this categorization. It is clear that most misalignments are not linked to equivalent accommodative errors. Thus, we can conclude that accommodative errors do not drive misalignments.

Do Misalignments Result from Poor Detection of Disparity?

To determine the relationship between misalignments and the detection of binocular disparity, we compared conditions in which this information was, and was not, available. A subgroup of the infants in this study were tested both binocularly and with remote monocular occlusion of one eye, enabling us to compare the prevalence of misalignments across these conditions. Because infants are thought to be unable to use retinal disparity before 4 months of age (the time at which these misalignments disappear in typical infants) we predicted that there should be no difference in the prevalence of misalignments between conditions.

Figure 6 shows the percentage of infants who showed misalignments in the binocular, in comparison to the monocular, condition. We found that infants showed approximately three times as many misalignments when one eye was occluded as when they had binocular vision. In addition, most misalignments that were still apparent at more than 8 weeks of age were observed in the monocular condition. In comparison, after this age, there were very few misalignments in the binocular condition. Thus, infants appear to be more likely to have misalignment when the stimulus is monocular and retinal disparity information is unavailable.

Are Misalignments Related to an Inappropriate Response to a Moving Target?

Because our studies used a pseudorandom order of target presentation, infants were photographed immediately after the target had moved both from near to far and from far to near. Although the target was stationary at the time of photography, fleeting misalignments appeared to be stimulated differentially by whether target movement was away from or toward the infant.

Figure 7 shows the proportion of misalignments associated with both near-to-far and far-to-near target movement. It is clear that significantly more misalignments occur when the infants are shifting from near to far viewing than from far to near. The overconvergence produced by a shift from a near to a far target is much greater than would be expected if the eyes had simply remained at the near vergence position and was always more than 2 MA greater than the previous demand. Because, in these cases, the infants are showing significant esotropic misalignments, it suggests that the infants are misinterpreting a signal.
was not within 1 D of the vergence response. With the 4-D target, the link between vergence and accommodation was poor because the overaccommodation was not 1 D greater than demand. Infant B shows an example of no link between accommodation and vergence during a misalignment—that is, overconvergence but not overaccommodation with the 2-D target.

to diverge the eyes and are instead producing an overconvergence of the eyes. They, therefore, fail to respond appropriately to a moving stimulus. Although the length of time the misalignment remained was not tested, the infants usually recovered within a few seconds, as observed through the video monitor.

A second situation in which infants are required to detect changes in target position in depth is when a base-out prism is placed in front of one eye. Placement of the prism produces a retinal shift identical with a far-to-near target movement down the axis of the eye without the prism. When the prism is removed again, movement of the retinal image produces the reverse target movement, from near to far. If infants’ ocular misalignments are related to asymmetries in target movement, then we should see errors when removing the prism (nasal-to-temporal target movement) but not when introducing it (temporal-to-nasal target movement). This would result in a convergent corrective eye movement when the prism is placed in front of one eye but failure to diverge when the prism is removed, with infants thus retaining overconvergence. We have reported this behavior previously, and refer to this behavior as getting “stuck.” To test for this, we used a χ² analysis to determine whether a misalignment was more likely to be found during the same visit as infants were seen to “get stuck” on the prism response. This showed a significant association between the two behaviors (χ² = 11.549, df = 1, P < 0.001). Thus, fleeting overconvergence detected on the prism response test was associated with misalignments, and both occurred in response to movement of the retinal image in the near-to-far direction only.

**DISCUSSION**

In this study, we investigated factors that may account for vergence misalignments in typical young infants. We chose to study the extremes of vergence error, because these are data that may have been discarded as outliers or may have become lost during averaging in other studies.

The use of digital photography and a rapidly responding motorized beam for moving the target monitor allowed simultaneous vergence and accommodation to be measured immediately after responses to an approaching or receding target. This novel technique, not used in previous studies, made it possible to determine which cues to vergence and accommodation were most often associated with misalignments. These misalignments are thought to be the result of a failure in the same mechanisms that result in infantile esotropia.

It must be stressed that the misalignments described in this study are not heterotropias or heterophorias in the conventional sense of the terms. It could be argued, for instance, that misalignments that were noted in the nonoccluded condition could represent a very short-lived, intermittent esotropia (heterotropia), but, if this were so, a basic convergent angle would be expected on cover test and on occlusion. Alternatively, if the deviations on occlusion were heterophorias, they should be expected on occlusion. Indeed, no infant included in the analysis showed any significant heterotropia or heterophoria on clinical examination or

**FIGURE 6.** Percentage of infants by age demonstrating misalignments with both eyes open and with one eye occluded. Data are only available in the one-eye-occluded condition between 6 and 14 weeks of age. The data show that misalignments with both eyes open were most frequent before 8 weeks of age and disappeared by 16 weeks. In the occluded condition, misalignments were more common than in the binocular condition, even in the oldest infants tested. This suggests that having both eyes open helps to prevent misalignments.
on analysis of the overall vergence position between occluded and nonoccluded conditions. Any infant with manifest strabismus seen on clinical examination or consistently on all photographs was excluded (four infants not described herein, two cases of manifest exotropia in the first weeks who subsequently showed the characteristics of intermittent distance exotropia). The infants generally maintained appropriate binocular alignment on the targets, only showing brief large convergent deviations that were “caught on camera” but resolved within a few seconds.

We did find, however, a significant proportion of infants (27.4%) who exhibited a large ocular misalignment at least once during testing. Because there was a significant positive correlation between the number of times infants showed misalignment in the laboratory and the parental report of misalignment, we believe that we are detecting the same behavior in the laboratory as is reported by parents from observation in the home.

We did not find the large numbers of exotropes found by Archer et al. and Sondhi et al. and feel that this serves to emphasize the necessity to account for angle λ when assessing alignment. In illustration of the effect that misinterpretation of angle λ can have, there were 68 individual photographs in this study that photograph scorers were sure, based on the position of the corneal reflections, showed definite exotropia. However, when vergence angle was corrected using an age appropriate value for angle λ, none of these was a divergent angle large enough to fulfill our criterion for genuine exodeviation (i.e., past orthotropia).

Our main interest was to determine the correlates of misalignments in infancy. We were able to rule out accommodative errors as a cause of these misalignments because there was little concomitant overaccommodation associated with the overconvergence. By comparing the frequency of misalignments in the monocular and binocular conditions, we were able to show that, when binocular information is available, the frequency of misalignments decreases. Finally, there was an asymmetry in the production of misalignments, with these occurring more often after near-to-far (nasal to temporal) target movement than after far-to-near (temporal to nasal) movement. We were able to demonstrate this asymmetry in two conditions: (1) in response to real target movement as targets moved to new positions during photorefraction; and (2) when a prism was removed from in front of one eye producing optical target motion away from the infant. Previous research has shown that responses to divergent disparity develop later than responses to convergent disparity. However, the responses measured in this study occur at a much younger age than reported by Birch and are present well before stereopsis is thought to be developed. We found that most misalignments occur in the first 2 months of life, and parents report them most frequently during the first month. Incomplete development of the motion-detection system, which is known to be present from birth, may provide a more plausible explanation for these misalignments.

Motion processing has been implicated in the etiology of esotropia. Tychsen argued that the asymmetric OKN, smooth pursuit, and perception of motion in patients with infantile esotropia demonstrate a deficit in motion processing. This asymmetry results in stronger responses to targets moving nasally in each eye (movement towards the infant) than targets moving temporally in each eye (movement away from the head). This could result in a convergence bias, with the result that most vergence errors are convergent, leading to a higher prevalence of esotropia. In typical infants, this asymmetry is overcome by the development of cortical systems that provide symmetric motion sensitivity to both nasally and temporally directed targets. If mature binocularity does not develop or there is a failure in motion processing, this convergence bias may become habitual and lead to constant and increasing esotropia.

Day and Norcia discuss the interrelevance of vergence, stereopsis, and symmetric motion processing. To use retinal disparity information appropriately, it is necessary for the eyes to be aligned on the same target. This may result from a prestereoptic system in which information about the position of each eye is used separately to align the eyes on a salient, static target. As stereopsis develops, this information can then be used to correct small errors in eye alignment and improve vergence control. Similarly, the motion system is thought to require eye alignment to develop properly. This system may contribute to vergence control by adding a dynamic component and thus enable accurate tracking of targets moving in depth. In support of this, Thorn et al. have demonstrated that good dynamic vergence occurs after the development of stereopsis and therefore also symmetrical motion processing.

In this study, the asymmetry in motion processing with poor response to nasal-to-temporal movement can be used to explain the inappropriate response to stationary targets that have moved away from the infant to their current positions. The immature motion system may be insufficient to respond appropriately to such a target and thus any response would have to rely on other systems. Sensitivity to motion, regardless of its direction, may activate the eye movement system, which has become biased to temporal-to-nasal movement during the early weeks of life. This would trigger a reflexive, convergent eye movement in response to movement of the target in either direction, bringing the target onto the retina of each eye if the target is moving toward the infant. If the target is moving away from the infant, primitive motor fusional reflexes (either based on optimal summation in the developing layer 4 of the visual cortex or separate monocular fixations) are necessary to stop the convergence, to prevent overconvergence. This error would be overcome, for instance, by the maturation of cortical pathways that are tuned for both convergent and divergent retinal disparities.

Our results give further support to the motion deficit theory of esotropia by demonstrating misalignments in typical infants younger than 4 months of age that are not related to accommodation, but occur more frequently when the infants are...
viewing monocularly (thus unable to use binocular fusional mechanisms) and when targets are moving away from the infant (thus depending on the poorly developed temporal motion processing pathways). We suggest that these misalignments are therefore a good model in which to observe development of infantile esotropia. Further study of these misalignments may elucidate the mechanisms that cause this condition.

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