HHS Public Access

Author manuscript

Annu Rev Vis Sci. Author manuscript; available in PMC 2020 April 06.

Published in final edited form as:

Annu Rev Vis Sci. 2019 September 15; 5: 201–221. doi:10.1146/annurev-vision-091718-014741.

The Importance of the Interaction Between Ocular Motor Function and Vision During Human Infancy

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Abstract

Numerous studies have demonstrated the impact of imposed abnormal visual experience on the postnatal development of the visual system. These studies have provided fundamental insights into the mechanisms underlying neuroplasticity and its role in clinical care. However, the ocular motor responses of postnatal human infants largely define their visual experience in dynamic three-dimensional environments. Thus, the immature visual system needs to control its own visual experience. This review explores the interaction between the developing motor and sensory/perceptual visual systems, together with its importance in both typical development and the development of forms of strabismus and amblyopia.

Keywords

visual development; accommodation; vergence; hyperopia; strabismus; amblyopia

1. INTRODUCTION

Typical postnatal development of vision in humans depends on adequate retinal image quality in both eyes and registration of neural images from the right and left eyes in the visual cortex. The visual system, therefore, controls its own postnatal development using accommodation responses to achieve focus and vergence responses to achieve alignment as stimulus distance changes. Although the development of spatial vision, accommodation, and vergence has been studied for more than 50 years, relatively little attention has been paid to the important interaction between sensory and motor visual processing (Aslin & Dumais 1980). The goal of this review is to ask how well the visual system controls its own visual experience during the first months after birth and what role this interaction may play in the development of strabismus and amblyopia when visual experience is disrupted.

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DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

1.1. Interventions Used to Study the Impact of Disrupted Visual Experience on Sensory Function

Studies of disrupted visual experience in animal models have typically examined the impact of experimentally degraded afferent sensory input. Some have revealed the impact of monocular visual deprivation on the development of the primary visual cortex (Wiesel 1982). Important clinical parallels to this intervention exist in humans (e.g., ptosis, cataract, or corneal opacity during infancy) (Rabin et al. 1981). Other studies of animal models have adopted analogues to the conditions more commonly associated with amblyopia in humans: strabismus and anisometropia. Misalignment of the eyes was introduced with surgery or prism-rearing (e.g., Kiorpes & Boothe 1980, Smith et al. 2017, Wiesel 1982), whereas anisometropia was introduced with unilateral atropine drops or by placing a defocusing lens before one eye (e.g., Movshon et al. 1987, Smith et al. 2017). Studies of disrupted visual experience now include behavioral visual responses, single-unit recordings, various forms of histological mapping, and examination of multiunit response properties in striate and extrastriate cortex (Arcaro et al. 2017, Bi et al. 2011, Hallum et al. 2017, Horton & Hocking 1997, Shooner et al. 2017, Tao et al. 2014, Wang et al. 2017).

1.2. The Consequences of Disrupted Visual Experience

These intervention studies of animal models in combination with behavioral studies of humans who experienced disrupted early visual experience have revealed a broad range of associated abnormalities, including reductions in acuity (the typical clinical definition of amblyopia) as well as contrast sensitivity at middle and high spatial frequencies, misperception of spatial position, failure to recognize form, and inability to detect motion in three dimensions. Reduced binocular function with habitual interocular suppression is also often observed (Gandhi et al. 2015, Maurer et al. 2007, McKee et al. 2003, McKyton et al. 2015, Meier & Giaschi 2017). Interestingly, a number of studies in which sensory input has been disrupted have also demonstrated abnormalities in motor function. Beyond issues related to eye alignment and vergence, studies of humans with amblyopia have revealed disruption of fixational, saccadic, and optokinetic nystagmus movements. The origins of these motor abnormalities could lie in afferent deficits or efferent motor processing (Chung et al. 2015, McKee et al. 2016, Niechwiej-Szwedo et al. 2010, Schor 1983). For example, in addition to studies of changes in the visual cortex, studies of monkeys raised with prisms or eyes surgically misaligned have revealed lasting disruption of motor circuitry (Das 2016, Walton et al. 2017).

The literature continues to reveal wide-ranging impacts of disrupted early visual experience on development of the visual system. It highlights the clinical complexities of fully restoring patients to normal visual function. For example, when considering the typical clinical metric used for amblyopia, approximately two lines of acuity difference between the eyes remain on average after prescribed treatment (e.g., Repka et al. 2005). Also, surgical procedures to restore eye alignment rarely result in fully normal alignment, and correction to within five degrees of alignment is viewed as a success (e.g., Wang & Wang 2014). Despite numerous proposed amblyopia treatments, including binocular stimulation, action video games, perceptual learning, darkness, transcranial magnetic stimulation, and pharmacological interventions (Stryker & Lowel 2018), the difficulty of and frequent failures in restoring normal vision for patients reveals the need for an alternative approach. Might experience-dependent disruption and its complex set of consequences be prevented? For a prevention approach to succeed, a clear understanding of the origins of strabismus and amblyopia and their associated risk factors must be developed.

Some forms of strabismus and amblyopia seem more amenable to prevention. For example, appealing candidates include forms with relatively late onset that may be related to refractive error (e.g., refractive esotropia and anisometropic amblyopia), as opposed to those that appear earlier (e.g., infantile esotropia) with as-yet poorly understood etiology (e.g., infantile esotropia or intermittent exotropia). Disappointingly, the first studies that provided glasses correction to hyperopic infants at risk for refractive esotropia had mixed success in the prevention of strabismus (Anker et al. 2004, Atkinson et al. 1996, Ingram et al. 1990, Jones-Jordan et al. 2014), suggesting that preventative approaches may need to be more complex (Babinsky & Candy 2013, Somer et al. 2018).

1.3. The Importance of Ocular Motor Responses

In studying the plastic visual system and the visual experience of infants in the first months and years after birth, much of the typical and atypical development literature has concentrated on afferent visual processing. In a three-dimensional dynamic environment, however, retinal image quality and neural image registration depend on the performance of the motor visual system. All evidence indicates that normal development relies on precisely matched right- and left-eye images. For example, although the focus of an object changes by 10 diopters (D) as it moves from a viewing distance of infinity to 10 cm, children with as little as 1 D of difference in refractive error between their eyes are at risk for amblyopia (Barrett et al. 2013). Similarly, each eye of a young infant must rotate by approximately 13° [23 prism diopters (pd)] to maintain registration of retinal images as targets approach from infinity to 10 cm, whereas a child with less than 3° (5 pd) of strabismic misalignment of the eyes can have permanently disrupted cortical function (e.g., Harwerth & Fredenburg 2003). Given these motor demands, how do infants create their own postnatal visual experience during this immature and plastic period? The purpose of this review is to explore this question in the contexts of understanding how typical function develops, how infants might derail into clinical abnormality, and how disrupted early visual experience impacts visual perception.

2. TYPICAL DEVELOPMENT

Maintaining the eye's image plane at the photoreceptors with change in target distance is typically achieved by adjusting the optical power of the eye's internal lens, a process called accommodation. Maintaining bifoveal fixation of targets at different distances is achieved by rotating the eyes in opposite directions using vergence eye movements. Early studies of the development of these motor responses indicated that human newborns are capable of both but that response accuracy increases significantly over the first months after birth (Aslin 1977, Banks 1980, Brookman 1983, Hainline & Riddell 1995, Haynes et al. 1965, Slater & Findlay 1975). Interestingly, this development occurs over a period during which infant stimulus demands are also changing.

2.1. Accommodation

In terms of the demand for accommodation, the newborn eye has an average axial length of approximately 17 mm, whereas the adult eye has an average length of approximately 23 mm (Larsen 1971, Mutti et al. 2018). Thus, eye length increases on the order of 35% between birth and approximately 10 years of age. If the eye is to maintain minimal refractive error during this period, its total optical power must weaken over time to form an image at the progressively increasing distance of the retina. Refractive error is defined by the mismatch in these distances.

At birth, infants typically have a hyperopic (farsighted) refractive error, i.e., the optical image would be formed behind the retina (Figure 1*a*), with a relatively wide distribution across individuals (a mean of approximately 2 D with a standard deviation of ±2 D) (Cook & Glasscock 1951, Mayer et al. 2001, Mutti et al. 2018). While the eye grows over the first year or so, its optical focus typically becomes more tightly matched to its physical length. Thus, the distribution of refractive error narrows and shifts to lower amounts of hyperopia, a process termed emmetropization (e.g., Mutti et al. 2018). Active elimination of refractive error during lengthening of the eye has been studied extensively in the context of abnormality in myopia (e.g., Smith et al. 2014). Regulation of this process is proposed to include both experience-dependent and genetic factors, raising questions of how both may affect image planes in the central and peripheral retina (Gawne et al. 2017, Harb & Wildsoet 2019, Rucker et al. 2015, Smith et al. 2014, Wojciechowski 2011).

In hyperopia, when the eye's optics are underpowered relative to its length, a retinal image may be focused on the retina with an accommodative response (Figure 1*a*). Increasing the power of the biological lens through this mechanism brings the image plane forward toward the photoreceptors. Young hyperopic infants without glasses must accommodate to focus at any distance, making this motor response central for their retinal image quality. The demand on accommodation should progressively decrease if an infant undergoes emmetropization over the first couple of years after birth. Early studies of the development of accommodation suggested that infants younger than 8 weeks or so were typically focusing at a viewing distance of approximately 30–50 cm, even though their underlying (cyclopleged) refractive error was hyperopic (e.g., Banks 1980, Haynes et al. 1965). After this age, infants increasingly modulate their accommodative response with changing stimulus distance.

2.2. Vergence

In terms of the vergence demand for bifoveal fixation on a target, the distance between the eyes (interpupillary distance) during infancy is two-thirds that of the adult value. This distance matures over a period of at least 10 years (MacLachlan & Howland 2002, Pryor 1969). Compared with adults, infants will need to rotate their eyes less for the same change in viewing distance to achieve image alignment on both foveas (Figure 1*b*). Further complicating the calibration process, the visual direction corresponding to many individual photoreceptors will change with their postnatal migration to form the densely packed fovea (Lee et al. 2015, Yuodelis & Hendrickson 1986). It is currently unclear how representation of visual direction in postreceptoral stages of neural processing matures over time, although maturation of spatial-resolving ability implies that representation of direction may become more precise (Aslin & Dumais 1980, Chino et al. 1997). Several studies have established that even newborn infants perform vergence movements (Aslin 1977, Hainline & Riddell 1995, Slater & Findlay 1975), although a typically developing infant can exhibit large but infrequent misalignment of their eyes until approximately 3 months after birth (Horwood 2003).

2.3. Accommodation and Vergence in Combination

Both accommodation and vergence demands as well as their relationship change during the first couple of years after birth. As an infant grows, accommodative demand typically decreases while vergence demand increases. Maturation may also require that the brain regions receiving copies of these motor signals, as either corollary discharge or efference copy, recalibrate interpretations with age. Such tuning or adaptation in ocular motor responses is typically attributed to the cerebellum (Kheradmand & Zee 2011, Nitta et al. 2008). Interestingly, prior to approximately 2 months after birth, any recalibration of the estimation of viewing distance would need to be achieved in the absence of feedback derived from reaching with hands (Cunha et al. 2015) or feet (Galloway & Thelen 2004); therefore, recalibration must rely heavily on sensory signals originating in the retina or from audition. This is an important developmental challenge with potential relevance to current approaches in robotics and machine learning (Lonini et al. 2013, Zhu et al. 2017). In addition, accommodation and vergence motor responses are neurally coupled, and each must incorporate an element driven by the other system in its response (Mays & Gamlin 1995). Despite these developmental challenges, accommodation and vergence responses can be produced with latencies of less than 1 s by 2 months after birth (Tondel & Candy 2008), typically without an extended series of error corrections.

This complex control and coordination of ocular motor behavior must be achieved while sensitivity to the spatial information available in the foveal retinal image is immature and limited. Beyond the impact of any defocus or astigmatism, the optical image formed at the infant retina is likely to be of relatively mature quality. Optical aberrations during early infancy are not dramatically greater than those in adulthood and, combined with infants' small pupils, appear capable of generating a well-focused retinal image in spite of poor neonatal acuity (Candy et al. 2009). Immaturities that may significantly limit performance are found from the first stages of neural processing (Banks & Bennett 1988, Brown et al. 1987, Candy & Banks 1999), and both electroencephalography responses recorded over the primary visual cortex and forced-choice preferential looking data both suggest further postreceptoral immaturity (Dobson & Teller 1978, Norcia et al. 1990, Skoczenski & Norcia 1998). Newborn human acuity and peak contrast sensitivity may be reduced by a factor of approximately 10 relative to adults (Norcia et al. 1990). These immaturities in spatial vision will limit the detection of blur and spatial position (Aslin & Dumais 1980, Brown et al. 1987, Schor 1985), key cues used by adults to drive accommodation and vergence responses. These interdependencies between motor and sensory signals highlight the challenges faced during the joint and simultaneous maturation of these systems (Aslin & Dumais 1980).

2.4. Sensitivity of Infants' Accommodation and Vergence Responses

Our lab has studied the sensitivity of infants' accommodation and vergence responses to understand the impact of sensory immaturities on motor performance. We have recorded motor responses to full-cue stimuli consisting of broadband naturalistic spatial targets presented on a screen moving in depth along a sinusoidal trajectory (Figure 2). After performing a Fourier transform of these data, we examined the response at the frequency of the target movement as evidence of a stimulus-driven response. Eccentric photorefraction was used to record accommodation responses (Wang & Candy 2010) and Purkinje image eye tracking was used to document simultaneous vergence performance from video images (Seemiller et al. 2016) (PowerRefractor 1, Multichannel Systems & PowerRef 3, Plusoptix). These studies have revealed tracking of sinusoidal amplitudes of 1 D for accommodation and 1° for vergence at 5–10 weeks of age, demonstrating a significant signal to noise ratio at the frequency of the target movement. These results reflect the performance of a relatively small group and do not address individual differences with their implications for clinical care. Of note, although the data shown in Figure 2 were not calibrated for the individual infants, the fact that the infants tracked the structure within these sinusoidal functions demonstrates sensitivity to even smaller stimulus changes.

These studies have demonstrated that the immature spatial vision of young infants supports motor responses to full-cue stimuli on a somewhat unexpectedly fine scale. Which cues or information in the stimulus might they be using? Several cues can drive adult accommodation and vergence responses, indicating potential redundancy when they are combined (e.g., Schor et al. 1992). For example, blur in the retinal image can provide fine-scale feedback about errors of accommodation. Yet, the characteristics of blur used to provide feedback about direction and magnitude of focus error remain an open question (e.g., Del Aguila-Carrasco et al. 2017). Candidates include longitudinal chromatic aberration, higher-order monochromatic aberrations, and fluctuations in accommodation. While the spatial vision of infants is immature (Norcia et al. 1990), responses to full-cue stimulus changes of less than 1 D indicate this level of sensitivity to blur, proximity, motion in depth, or disparity, or a combination thereof, within the first 3 months after birth.

In adults, retinal disparity provides feedback about small errors of vergence (Schor et al. 1992). Previous literature has suggested that the number of infants demonstrating sensitivity to disparity increases rapidly from approximately 20% at around 3 months of age to close to 100% at 6 months (see Teller 1997, figure 17; see also Birch et al. 1982, Fox et al. 1980, Petrig et al. 1981). Because the vergence system may track targets moving on the order of only 1° at 1–2 months after birth, it seems reasonable to ask whether the brain is using retinal disparity to achieve this task. Chino and colleagues (Chino et al. 1997, Maruko et al. 2008) have documented single-unit responses to disparity in areas V1 and V2 in infant macaques from days after birth. Aslin & Dumais (1980), Schor (1985), and Brown and colleagues (2007) have also suggested that infants' sensitivity to disparity may be limited by front-end immaturities in their spatial vision (their contrast sensitivity function) rather than by their binocular function. Recent evidence from our lab using a large field of large high-contrast random elements on a rear-projection screen (80° × 60°) has revealed vergence tracking to dichoptically presented sinusoidal oscillations in horizontal disparity over an amplitude of 2° at 0.1 Hz for 30 s (Seemiller et al. 2018a). The three youngest individual infants who could be tested, at 35–44 days after birth, generated a significant vergence response in tracking this stimulus, and 12 of 16 individuals between 35 and 65 days postpartum provided significant responses. While previous literature using forced-choice preferential looking and visual-evoked potential responses has consistently demonstrated that responses to disparity are not common until weeks later, Seemiller et al. (2018a) suggested that disparity in isolated competition with other cues could drive a vergence response by 1 month of age in numerous infants (blur and proximity cues indicated the stimulus remained in the plane of the rear-projection screen).

2.5. Stability of Accommodation and Vergence

Because maintaining fixation is an active task as opposed to a passive absence of innervation (Krauzlis et al. 2017), we also examined the stability of infants' accommodation and vergence responses to a static stimulus. An inability to hold the eyes in stable fixation could lead to increased retinal image motion with smearing and an accompanying reduced sensitivity to changes in blur or spatial position. In our measurements, true response variability combined with measurement noise indicated that accommodation responses were stable by 2 months of age: root-mean-square errors on the order of 0.3 D versus 0.1 D for adults. These data were collected using eccentric photorefraction at 25 Hz (Candy & Bharadwaj 2007). Vergence responses in some infants are stable to a root-mean-square error of 0.1° both horizontally and vertically by 1 month of age when measured with a video-based eye tracker at 250 Hz (Seemiller et al. 2018b). This level of vergence performance was not significantly different from that of adults for the short recordings included in the analysis. How much waking time infants spend performing at this level remains to be determined. The dynamics of fluctuations in accommodation will modify the retinal image quality of the infant eye (Candy et al. 2009), whereas fluctuations in vergence may impact the registration of representations in the visual cortex.

2.6. Cue Combination

Neural coupling between the accommodation and vergence motor systems has been observed as soon as it has been tested after birth (Aslin & Jackson 1979, Bobier et al. 2000, Turner et al. 2002). This coupling could lead to a potential conflict between responding to the typically increased accommodative demand and reduced vergence demand of infants relative to those of adults. In addition, a simple sum of the different cues available in a full-cue stimulus would likely result in excessive responses. As the cues may be considered redundant, the weighting assigned to them in a final response becomes important. Differences in relative cue weighting in the final motor responses of infants could play a significant role in the development of strabismus. The reliability of cues such as perspective, looming, familiar size, blur, and disparity are likely to change with development and differ between individuals (Horwood & Riddell 2013, 2014; Kavsek et al. 2012). The role such changes play in different developmental and clinical outcomes remains to be determined.

2.7. Summary

Studies of typical infants have documented responses to binocular correlation at approximately 8 weeks (Braddick 1996) and interocular disparity at approximately 10 weeks of age (Birch et al. 1982, Fox et al. 1980, Petrig et al. 1981; see also Norcia et al. 2017). By contrast, the vergence system appears surprisingly sensitive, responding to disparity within 5 weeks or so after birth. Although the accommodation system appears initially less responsive, it is sensitive to less than 1 D of change in defocus by approximately 8 weeks. The sensitivity of these two motor systems provides an infant with the potential to exert significant control over their retinal visual experience during the first months after birth. This experience defines the input to mechanisms responsible for all visual aspects of learning and function in the environment.

With eccentric photorefraction and video-based Purkinje image eye tracking, the dynamic accommodation and vergence responses of infants and young children can be measured simultaneously. Even though these techniques can be difficult to calibrate and contribute significant measurement noise, researchers are developing a clearer understanding of retinal image quality and alignment during early development through their use. The next section addresses how the developing visual system aligns and focuses the eyes in the presence of challenges that could lead to strabismus and amblyopia.

3. ATYPICAL DEVELOPMENT

How might some young patients derail into strabismus and amblyopia during the first months or years after birth? Some forms of strabismus appear related to poorly understood neural abnormalities, for example, infantile esotropia, intermittent exotropia, or an esotropia driven by a high accommodative convergence gain. Others appear associated with optical characteristics of the eye, for example, refractive esotropia associated with significant hyperopia, sensory strabismus that develops after a congenital cataract, or perhaps microstrabismus associated with anisometropia. Although the latter forms could also have a more central neural component, an exciting task for basic and clinical vision science is to determine whether visual experience can be manipulated during infancy and early childhood to encourage both emmetropization and the prevention of some forms of strabismus and amblyopia (Abrahamsson & Sjostrand 1996, Anker et al. 2004, Atkinson et al. 1996, Ingram et al. 1990, Jones-Jordan et al. 2014, Smith et al. 2017, Somer et al. 2018).

The first large-scale studies providing spectacle correction to hyperopic infants in an attempt to prevent strabismus and amblyopia generated mixed results (Anker et al. 2004, Atkinson et al. 1996, Babinsky & Candy 2013, Ingram et al. 1990). Whereas the incidence of strabismus and amount of emmetropization varied (Atkinson et al. 2000, Ingram et al. 1991), the prevalence of amblyopia was generally lower at 4 years of age for children who were prescribed glasses versus those who were not, even with no direct monitoring of compliance with spectacle wear. Although meta-analysis of this literature suggests possible limitations in these studies (Jones-Jordan et al. 2014), one clear point emerges: Only approximately 20% of moderate to significant hyperopes developed strabismus even in the absence of glasses. The typical age of onset of the deviation in these patients is between 2 and 3 years of age, with a range from approximately 6 months to 6 years (e.g., Parks 1958). What is different about the children who develop strabismus compared with the 80% who remain aligned (Babinsky & Candy 2013)? Perhaps, those who accommodate to overcome their hyperopia also drive excessive accommodative convergence and become misaligned. If so, then those who did not accommodate to focus their retinal images would remain aligned. Data collected to date have consistently suggested the reverse (Ingram et al. 1994, Somer et al. 2018). Children with significant hyperopia who accommodate more accurately tend to remain aligned, whereas those who underaccommodate are more likely to develop strabismus. Evidence indicates that infants who accommodate more accurately also tend to emmetropize and those who experience their hyperopic defocus do not (Ingram et al. 1994, Mutti et al. 2009). These findings counter a prediction based on results from animal models of experience-dependent regulation of eye growth, where hyperopic defocus drives growth of the eye toward emmetropia (Smith et al. 2014).

3.1. Bias Toward Clear Vision or Single Vision?

Might aligned hyperopes who are not accommodating accurately already be struggling to remain aligned? If children with low amounts of hyperopia typically underaccommodate by only ~0.50–1 D for targets at 57 cm, lags of on the order of 3 D observed in moderate hyperopes could be considered abnormal (e.g., Mutti et al. 2009). To determine whether typical young children from birth to 12 years of age exhibit a bias toward clear vision (accurate accommodation) or single vision (accurate vergence) in the presence of an imposed conflict between their accommodation and vergence systems, we placed –2 D lenses or corresponding 2 meter angles of base out prism before their eyes and found no consistent group bias toward accurate accommodation or vergence in full-cue conditions (Bharadwaj & Candy 2009). However, the importance of the noted individual differences in bias toward alignment or retinal focus remains to be determined. Horwood & Riddell (2014) have also documented variations in bias toward accurate accommodation or vergence across individuals. If hyperopes who are underaccommodating are sacrificing retinal image quality to remain aligned in the presence of their conflict, then why would they develop a deviation at 2 or 3 years after birth? Their interpupillary distance would have been the narrowest in the newborn period, which is also when their vergence demand would have been lowest (approximately two-thirds of the adult value). Depending on their accommodative effort, they would have been at most risk for overconverging during early infancy rather than after their interpupillary distance had increased. Viewing distances of 2- or 3-year-olds are not overly different from those at the end of the first year after birth, yet the peak age of onset of refractive esotropia falls within the later age range.

3.2. Maintaining Alignment of the Eyes

Numerous studies have examined risk factors for the more common forms of childhood strabismus, which usually include the presence of a family history, hyperopia, and/or anisometropia (Babinsky & Candy 2013, Birch et al. 2005, Maconachie et al. 2013, Reddy et al. 2009). For children to decompensate into a misalignment in binocular conditions, however, they must also have an alignment demand (for fusional vergence) that they are unable to overcome. The alignment demand placed on the vergence system is often characterized as the difference between alignment at the stimulus and the underlying misalignment when viewing the target with only one eye (see Figure 3) (dissociated heterophoria in clinical terms). Little is known about this fusional alignment demand for typically developing infants. We, therefore, used Purkinje image tracking to look at eye alignment when one eye is occluded at 3–5 months of age and compared findings with those of 2.5–5-year-old children and naive young functionally emmetropic adults (Sreenivasan et al. 2016). On average, the 3–5-month-old infants had 2.5 D of hyperopia, so if they accommodated accurately and drove adult-like amounts of accommodative convergence, they should be more converged than an adult emmetrope. This could present as a latent convergent misalignment of the eyes in monocular viewing conditions, when fusional vergence movements have been prevented, termed an esophoria (center-left side of Figure 3). An esophoria would require a fusional divergence movement to achieve bifoveal fixation in binocular viewing conditions. Alignment of the participants viewing a target at 80 cm with an infrared filter over one eye (objective dissociated heterophoria measurements) indicated that, on average, they all needed to converge by approximately 1° (2 pd) to achieve binocular alignment at the stimulus, with no effect of age (Figure 3). The only outlier infant, who needed to diverge by approximately 3° (6 pd) to achieve binocular alignment, had a refractive error of 6.5 D of hyperopia in both eyes.

How much latent misalignment in monocular conditions can infants and young children typically overcome to achieve motor fusion in binocular conditions? They are at risk for strabismic misalignment when they are no longer able to generate enough fusional vergence to achieve binocular alignment. In a clinical situation, this fusional range is estimated by asking a patient viewing binocularly to maintain single and clear vision through progressively increasing amounts of prism. When they can no longer align their eyes, they report double vision. Infants and small children are not able to follow instructions, and so data collected from them can reflect only reflex behavior. We recorded reflex alignment responses in the presence of prism driving convergence and divergence while uninstructed naive participants aged 3–5 months, 2.5–5 years, or 20–32 years viewed a naturalistic cartoon image subtending 6° vertically by 2.5° horizontally at an 80-cm viewing distance (Sreenivasan et al. 2016). Recordings of realignment responses to prism indicated that, on average, the three naive groups had matched reflex fusional vergence ranges that compared well with adults from previous findings in the literature (Figure 3). The groups achieved approximately 9° (15 pd) of convergence and 6° (10 pd) of divergence before their eyes no longer realigned to maintain fixation at the 80-cm viewing distance. Hence, these participants could converge from their diverged position in monocular conditions to achieve alignment in binocular conditions and then converge even further to remain aligned. Young children become strabismic when they cannot generate enough fusional vergence to overcome their demand.

Adults demonstrate adaptation of their eye alignment in response to a period of increased convergent or divergent demand experimentally introduced with prisms (e.g., Carter 1965, Henson & North 1980). For example, four adults viewing binocularly through horizontal (6 pd/3.5°) or vertical (2 pd/1°) prisms for 3 min demonstrated adaptation in monocular viewing alignment that compensated for 60–80% of the demand (Henson & North 1980). Do young children also exhibit this tonic adjustment to increased demand? A typical increase in interpupillary distance with growth, from approximately 40 mm to 60 mm by 16 years of age (MacLachlan & Howland 2002), provides progressively increasing convergent demand over time. Alternatively, excessive accommodative convergence associated with hyperopia generates the need to diverge the eyes to achieve motor fusion. Can slower-acting tonic integration components of the vergence system adapt to compensate for these demands and thereby reduce the demand on the fast-acting disparity-driven fusional vergence system (Schor 1979)? We asked 3–5-year-old children to view a naturalistic movie binocularly through 6 pd (3.5°) of prism for a total binocular period of 2.5 min. We recorded their alignment in monocular conditions (objective dissociated heterophoria) after every 15 s of binocular viewing (Wu et al. 2016). On average, their monocular alignment adapted by 56% SD ±28% and 75% SD ±23% for convergent and divergent demands, respectively, toward their new required binocular alignment through the prism. Naive young adults achieved 48% SD ±26% and 85% SD ±21% for convergent and divergent directions, respectively, for the same prism-induced shift in apparent viewing distance.

These studies demonstrated that typical infants and children have robust motor alignment from within months after birth. Most are, therefore, equipped with tools to overcome their developmental alignment challenges and exhibit relatively adult-like performance despite their immature combination of accommodation and vergence demands. A key next step is to understand the factors involved in the development of a strabismus that disrupts this performance. Are some infants born with disrupted fusional vergence potential or ability to undergo adaptation? This question is not trivial to address, as prospective studies of the development of strabismus involve recruiting and tracking many infant participants (the combined prevalence of all forms of strabismus is approximately 2–3%) (Friedman et al. 2009). The ethics of providing interventions such as glasses designed to prevent strabismus are also ambiguous in the absence of a deep understanding of this condition that impacts only approximately 20% of significant hyperopes (Somer et al. 2018). Current clinical guidelines suggest providing optical correction for hyperopia greater than 4.50–6.00 D in the absence of strabismus during infancy and early childhood, but they are based solely on clinical consensus in the absence of definitive evidence (Wallace et al. 2018).

3.3. Anisometropia

Anisometropic or refractive amblyopia, the other common form of amblyopia, is even harder to study than strabismus during its development in humans (Barrett et al. 2013). However, preventing this form of amblyopia is even more appealing because the refractive difference between the eyes is entirely correctable with spectacles. Animal models have been used to demonstrate that blurring the retinal image in one eye can induce abnormality resembling human anisometropic amblyopia (e.g., Movshon et al. 1987, Smith et al. 2017). Unfortunately, compared with strabismus, anisometropia in infants and children is harder to detect. There is minimal if any external sign of abnormality, and the difference in the refractive errors of the eyes routinely goes undetected while the patient develops a bias toward the function of their dominant eye. Anisometropia is routinely not discovered in children until they fail a visual acuity screening and are diagnosed with amblyopia associated with anisometropia (Barrett et al. 2013). The amount of anisometropia they had at the onset of the amblyopia is unknown, and the age at which amblyopia first developed is also not clearly understood.

These issues limit the precision of potential preventative measures. For example, Abrahamsson & Sjostrand (1996) noted a range of clinical outcomes in young patients who had anisometropia of between 3 D and 5.5 D at 1 year of age and who had then been provided with full optical correction at 2 to 3 years of age. Following 20 consecutive cases until the age of 10 years, they noted that 6 developed more anisometropia and amblyopia (3 also with strabismus), 7 experienced a reduction in anisometropia with no amblyopia or strabismus, and the remaining 7 developed amblyopia or strabismus with no increase in anisometropia. Interestingly, reported spectacle use did not differ between the groups.

A current movement toward screening for risk factors for amblyopia in young populations holds promise for discovering and helping these patients. Some evidence, however, suggests that anisometropia can resolve while uncorrected (Almeder et al. 1990, Barrett et al. 2013), providing a note of caution and suggesting that deeper understanding is still needed to assess the associated risks (Smith et al. 2017). How much is too much anisometropia during the development of spatial vision? What is the role of pupil size in increasing depth of focus during early childhood? How do anisometropes coordinate their accommodation and vergence performance (Bharadwaj & Candy 2011)? How does hyperopia interact with anisometropia in the development of refractive esotropia? Once again, current clinical guidelines for the optical correction of anisometropia during infancy and early childhood are based on clinical consensus rather than definitive evidence (Wallace et al. 2018).

4. THE IMPACT OF DISRUPTED VISUAL EXPERIENCE ON VISUAL PERCEPTION

The primary goal of vision is presumably to provide a stable unified percept of the world, enabling individuals to interact more efficiently with their environments. How does perception adapt to the presence of disrupted visual experience during early childhood? With strabismus, the brain must resolve the misregistration of the neural images in the visual cortex, together with any accompanying double vision (diplopia) and competing information in the same visual direction (confusion). To examine an object using their fovea, children with strabismus need to fixate the object with one eye while managing misalignment of the other eye. In this situation, it would be beneficial to ignore or suppress part of or all the information from the misaligned eye to eliminate diplopia and confusion. This suppression of influence in perception can be demonstrated routinely when older patients with strabismus are in binocular viewing conditions (Babu et al. 2017, Campos 1982, Sireteanu 1982). The developmental and clinical challenge presented by these patients is that this form of suppression during early childhood may lead to permanent loss of perceptual binocular function including stereopsis (Banks et al. 1975, Fawcett et al. 2005, Sengpiel et al. 1994).

Amblyopia is also frequently considered an unfortunate by-product of the adaptive suppression process. If a child is able to maintain equal preference for fixating with either eye, or maintain alignment for much of the time with only intermittent strabismus, they may have permanently reduced perceptual binocular function but not develop amblyopia to the same degree as a patient with a strong preference for viewing with a dominant eye (Sireteanu 1982). Our limited understanding of the neural adaptations involved in this suppression process significantly impacts the management or treatment of children who exhibit this behavior.

A recent body of work has started to explore in more detail the significance of binocular interactions in older patients with amblyopia and to test binocular forms of therapy (Barrett et al. 2012, Birch 2013, Ding & Levi 2014, Economides et al. 2012, Hess & Thompson 2015, Kwon et al. 2014, Ooi et al. 2013, Spiegel et al. 2016). In particular, binocular interactions are used to study the balance between excitatory and inhibitory processes. Emphasis on the role of binocular processes in amblyopic vision reinforces the importance of ocular motor responses in defining binocular input to the afferent visual system. Recent studies have demonstrated how eye movements may be planned to align either eye with a desired target in strabismic visual systems as well as how the likelihood of one eye taking up fixation can depend on the location of the target within the visual field (Agaoglu et al. 2014, Economides et al. 2014). Although the simplest hypothesis suggests that the entire image from a deviated eye should be suppressed in perception to avoid diplopia and confusion, a large body of evidence now suggests that this is not common. We are only beginning to understand in more detail the unstable and varied forms of binocular function that have been described clinically (e.g., Bagolini 1976, Campos 1982). Is the strabismic brain performing some form of dynamic probability-based computation to infer the most likely structure of the environment in each situation? Accumulating evidence suggests more subtle adaptations involving both perceptual and motor components are being established, rather than complete suppression of all information from one eye.

The percepts of typically developed visual systems also involve various forms of image suppression and distortion. Percepts during saccadic eye movements (e.g., Binda & Morrone 2018) or continuous flash suppression (e.g., Yang et al. 2014), for example, may be relevant to disruptions in spatial and temporal binocular relationships. Of recent note, Christiansen et al. (2017) demonstrated complex interactions among color, interocular switching of information, and perception. When a target was presented simultaneously in a different color to each eye and then the colors were exchanged rapidly between the eyes, subjects perceived the target to be one of the two colors over stable intervals that spanned many color exchanges. This result reveals color-based rivalry between stimulus features rather than rivalry between the eyes (see also Blake & Logothetis 2002).

As a management strategy for presbyopia, implementation of anisometropia provides an interesting test of its visual effects. By focusing one eye for distance and the other for near, adults achieve simultaneous focus at a range of distances. Termed monovision, this approach is implemented using contact lenses, refractive surgery, or intraocular lenses. Studies have examined its effect on, for example, acuity, stereopsis, blur suppression, or motor fusional reserves as a function of add power (amount of anisometropia), position in the visual field, stimulus contrast, and sighting ocular dominance. Findings have been variable, again suggesting a significant influence of differing motor and visual stimulus conditions (e.g., Evans 2007). However, up to approximately 60% of preexisting contact lens wearers tolerate this form of presbyopic correction, especially when the difference in focus is 1.50 D or less. Yet, reports (e.g., Pollard et al. 2011) indicate patients can decompensate into eye misalignment and diplopia in binocular conditions when given monovision correction, presumably owing to the mismatch in sensory input to the two eyes of a fragile binocular visual system. As a result, some patients require surgical realignment of this strabismus.

Given current difficulties in identifying anisometropic patients during infancy (unlike when parents seek clinical care after noticing their infant's eyes are misaligned), relatively little is known about the natural history of anisometropia or its perceptual effects during infancy and early childhood when amblyopia is likely develop (Barrett et al. 2013, Birch & Holmes 2010). Even though adults can tolerate anisometropic visual experience, monovision studies have provided ample evidence of its persistent subtle effects on acuity and stereopsis as well as its impact on patients with fragile motor function. Currently, we tend to make inferences about the ongoing impact of anisometropia on perception during human infancy only on the basis of animal models and the adult monovision literature. We have just begun to understand the subtle interaction between maturation of the eye's optics and the role of only 1 D of anisometropia in disrupting neural development and perception, and yet, this could be the easiest form of amblyopia to prevent.

5. WHAT COMES NEXT?

As discussed in Section 2, the accommodation and vergence motor systems are interdependent during postnatal development of vision. These systems are responsible for providing adequately focused and aligned visual experience despite immature spatial vision, hyperopia, and a narrow interpupillary distance. Section 3 addresses the development of disrupted visual experience when ocular motor systems can no longer provide adequately focused and aligned images, and Section 4 briefly considers adaptations required to achieve unified and stable percepts of the world during disrupted visual experience.

Numerous key questions still need to be addressed to understand how the ocular motor systems coordinate visual experience during development. Do the human motor and sensory visual systems develop iteratively in an interdependent manner while the spatial resolution of the visual system matures? How can human visual development inform machine learning and robotics (e.g., Vogelsang et al. 2018, Zhu et al. 2017)? How do accommodation and vergence motor responses interact with other eye movements during development (e.g., Dysli & Abegg 2016, Oohira et al. 1991)? How does development of the first stages of visual processing impact higher-order extrastriate function, and what is the influence of top-down processes on basic sensory and motor visual development? When might an infant's vision be sensitive enough to be vulnerable to different forms of abnormal visual experience (e.g., Birch & Stager 1985, Hartmann et al. 2018, Maurer et al. 2007)? When do secondary adaptations start to develop? Which young patients are at highest risk of developing strabismus, and why? Finally, if they are identified, can we modify their visual experience to prevent deviation and amblyopia?

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health/National Eye Institute (R01 EY014460, P30 EY019008) and by Fight for Sight postdoctoral fellowships to Shrikant Bharadwaj and Vidhyapriya Sreenivasan. I am also particularly grateful to members of our lab and Arthur Bradley for their insightful discussions.

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SUMMARY POINTS

1. Our typical inability to fully restore vision when treating strabismic and amblyopic patients reveals the need for an alternative approach. Might experience-dependent disruption of vision and its complex set of consequences be prevented?
2. This review asks how well the visual system controls its own visual experience during infancy and early childhood, and what role the interaction between sensory and motor processing may play in the development of strabismus and amblyopia.
3. Both accommodation and vergence demands, as well as their relationship, change during the first couple of years after birth, potentially impacting both retinal image quality and alignment. As an infant grows, accommodative demand typically decreases, while vergence demand increases.
4. Despite these developmental challenges and immature spatial vision, accommodation and vergence responses can be produced with latencies of less than 1 s by 2 months after birth, typically without an extended series of error corrections. Infants can also track sinusoidal amplitudes of 1 D for accommodation and 1° for vergence at 5–10 weeks of age.
5. Children with significant hyperopia who accommodate more accurately tend to emmetropize and remain aligned, whereas those who underaccommodate are more likely to remain hyperopic and to develop strabismus. These findings counter a prediction based on results from animal models of experience-dependent regulation of eye growth, where hyperopic defocus drives growth of the eye toward emmetropia.
6. For children to develop a strabismic misalignment in binocular conditions, they must have an alignment demand that they are unable to overcome with fusional vergence. Typical 3–5-month-old infants were found to have a mean fusional demand of approximately 1° with the mean capacity to overcome approximately 8° of convergent and 6° of divergent misalignment at an 80-cm viewing distance.
7. Once an infant or child becomes strabismic, accumulating evidence suggests more subtle adaptations involving both perceptual and motor components are being established, rather than complete suppression of all information from one eye.

FUTURE ISSUES

1. Anisometropia is routinely not discovered in children until they fail a visual acuity screening and are diagnosed with amblyopia associated with anisometropia. The amount of anisometropia they had at the onset of the amblyopia is typically unknown, and the age at which amblyopia first developed is also not clearly understood. How much is too much anisometropia during the development of spatial vision?
2. How do the apparently redundant cues to accommodation and vergence motor responses interact during development such that only approximately 20% of moderate hyperopes develop strabismus?
3. Our limited understanding of the neural adaptations involved in overcoming strabismic diplopia and visual confusion significantly impacts the management or treatment of children who exhibit this behavior. Is the strabismic brain performing some form of dynamic probability-based computation to infer the most likely structure of the environment?
4. When might an infant's vision be sensitive enough to be vulnerable to different forms of abnormal visual experience?
5. Which young patients are at highest risk of developing strabismus, and why?
6. Can we modify visual experience during infancy and early childhood to prevent some forms of strabismus and amblyopia?

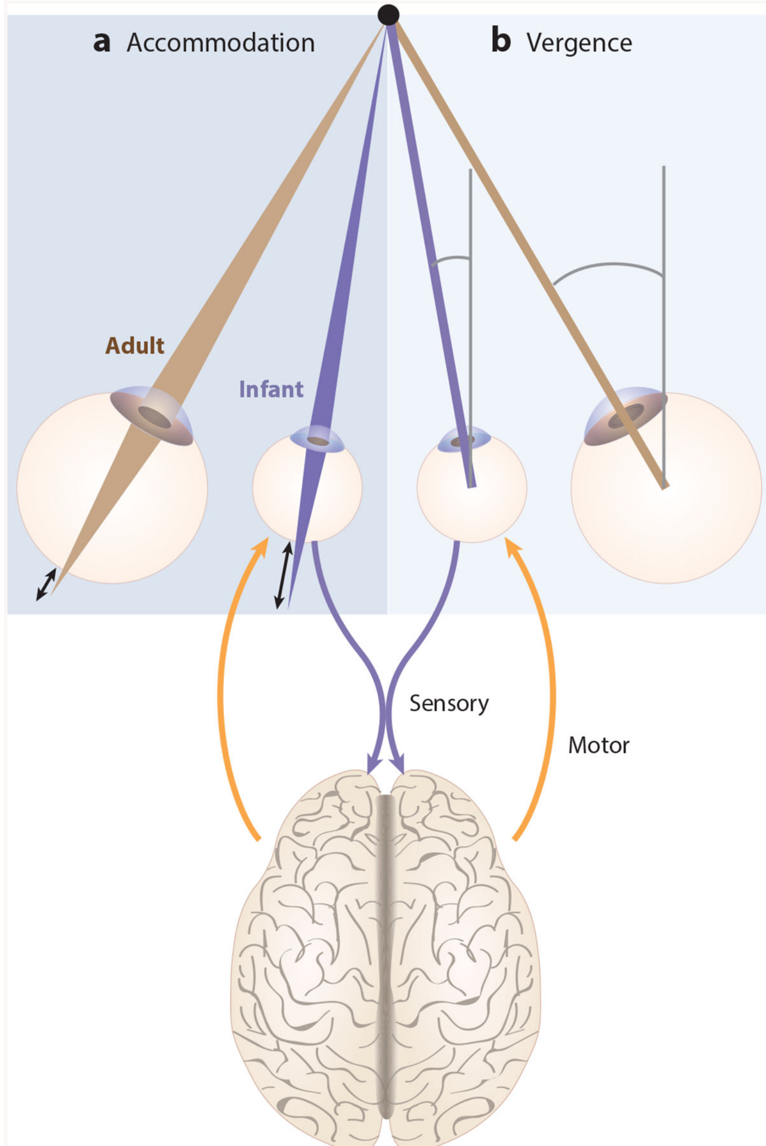

Figure 1.
An illustration of the accommodation and vergence motor demands of the developing human visual system and the ways in which infants control their own postnatal visual experience. (*a*) Compared with adults, infants are typically more hyperopic. By increasing the optical power of their eyes via accommodation, they can move an image forward into focus on the retina. (*b*) Compared with adults, infants also have a narrower interpupillary distance and therefore need to rotate their eyes through a smaller angle to align both eyes at a target.

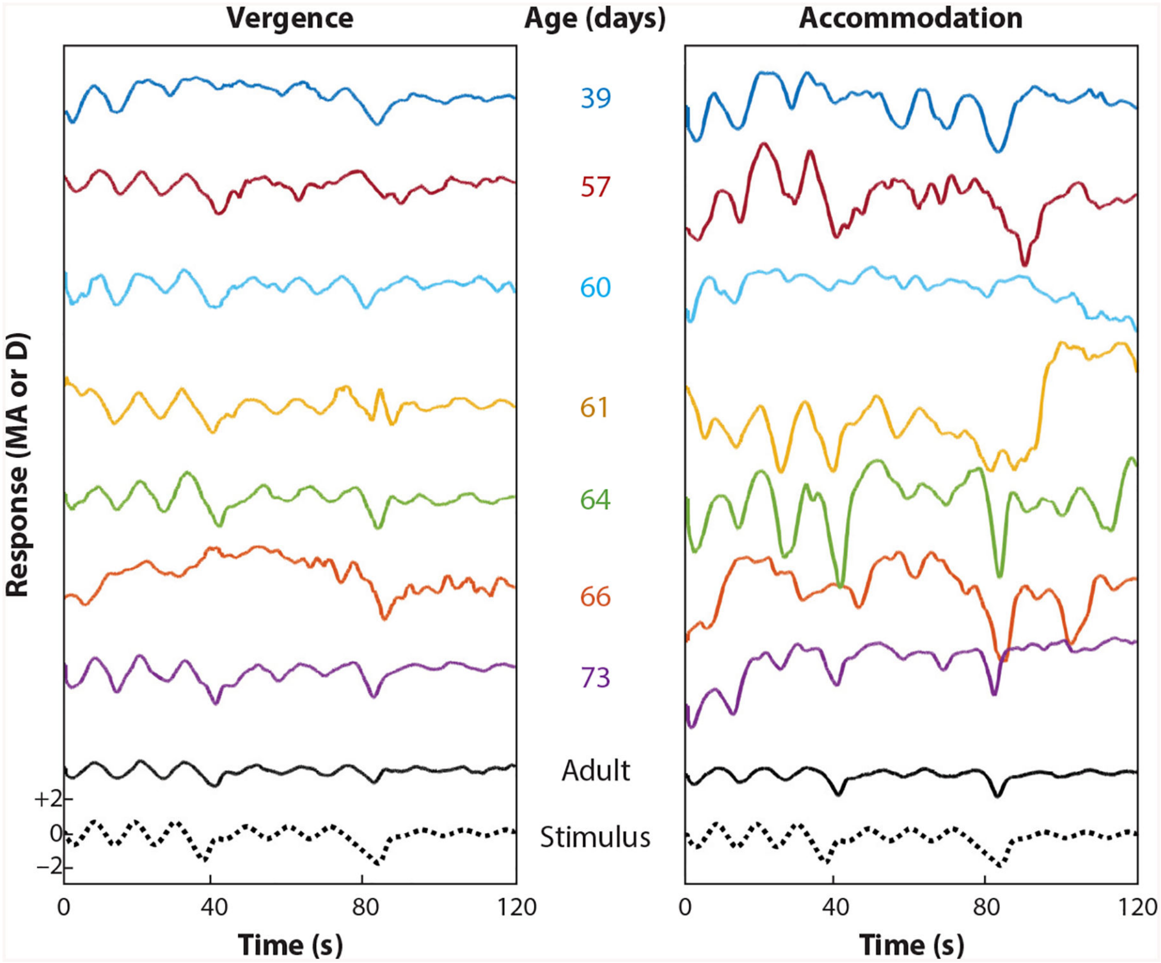

Figure 2.

Individual trials collected from eight participants viewing a cartoon movie on a screen moving back and forth around a viewing distance of 50 cm on a motorized track (Seemiller et al. 2016). Uncalibrated vergence and accommodation responses were collected simultaneously at 50 Hz (PowerRef 3, Plusoptix). Data are smoothed over a 1-s window, and stimulus profiles are provided at the bottom of each panel for comparison. Abbreviations: D, diopter; MA, meter angle.

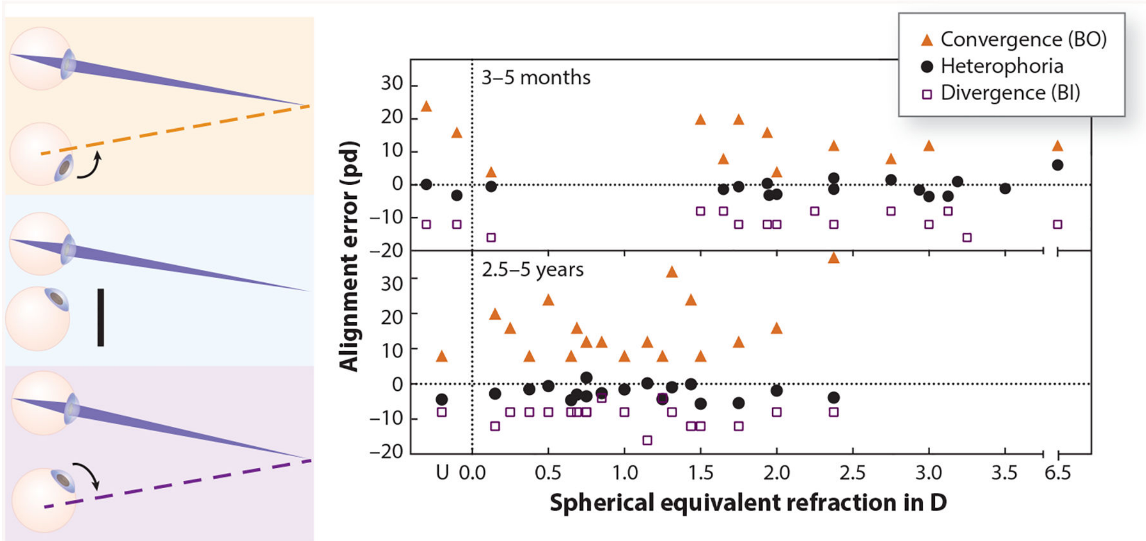

Figure 3.

The role of fusional vergence in maintaining binocular eye alignment during typical development. The two graphs show alignment error as a function of hyperopic refractive error of individual participants aged (*top*) 3–5 months and (*bottom*) 2.5–5 years. The alignment error in pd is plotted for a target at an 80-cm viewing distance (1 pd is approximately 0.57°). Black circles indicate latent alignment error revealed when one eye was occluded (heterophoria), as shown in the center-left illustration. These participants typically have a small adult-like exophoria (divergent alignment error). Orange triangles indicate the maximum amount of convergent prism demand that was overcome to maintain reflex alignment in binocular conditions, as shown in the top-left illustration. Purple squares indicate the maximum amount of divergent prism demand that was overcome to maintain reflex alignment in binocular conditions, as shown in the bottom-left illustration. The distance between the triangles and squares indicates the range of errors the participant overcame to achieve alignment. Positive errors indicate convergent error, whereas negative errors indicate divergent error. U symbol indicates participants whose refractive errors were unknown (Sreenivasan et al. 2016). Abbreviations: BI, base in prism; BO, base out prism; D, diopter; pd, prism diopter.